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Evidence-based Series 6-14 EDUCATION AND INFORMATION 2013

Treatment of Acute Myeloid Leukemia in Older Patients

Y. Zaretsky, M. Crump, A.E. Haynes, A. Stevens, K. Imrie, R.M. Meyer, and the Hematology Disease Site Group

A Quality Initiative of the
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Evidence-based Series (EBS) 6-14, consists of three sections:

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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Evidence-based Series 6-14: Section 1

Treatment of Acute Myeloid Leukemia in Older Patients: Guideline Recommendations

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QUESTIONS

1. What is the relative efficacy of aggressive induction chemotherapy as compared with less aggressive treatments used in the treatment of older patients (> 55 years) with newly diagnosed acute myeloid leukemia (AML)?
2. What is the optimum induction regimen for older patients with AML?
3. What is the optimum post-remission therapy?
4. What are the roles of granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) in conjunction with chemotherapy in this group of patients?
5. What disease and patient-related parameters can be used to identify patients age > 55 years who are more likely to benefit from aggressive induction therapy?

Outcomes of interest include survival, response rate, response duration, and toxicity.

TARGET POPULATION

The recommendations apply to adult patients over the age of 55 years with newly diagnosed, previously untreated, AML.

RECOMMENDATIONS

- **Based on the consensus of the Hematology Disease Site Group (DSG), intensive induction chemotherapy is recommended for patients with good performance status and minimal organ dysfunction or comorbidity. Intensive induction treatment has resulted in superior outcomes (remission rates, remission duration, and survival) without an increase in toxicity, in comparison with therapy that includes reduced doses or is of palliative intent.**

Key Evidence

- Buchner et al (1) compared two doses of daunorubicin (60 mg/m^2 versus [vs.] 30 mg/m^2) in patients aged 60 years or older. More intensive therapy resulted in fewer early deaths and a superior remission rate, and because the duration of remission was similar in both groups, the superior remission rate in the more intensively treated patients translated into superior overall survival.

- **Comparative data fail to demonstrate superior outcomes associated with use of a specific anthracycline or anthracenedione agent in induction. No consistent differences in treatment-related toxicities were observed. Thus, the decision as to which agent to use may be determined by other factors, such as drug acquisition costs, that may vary among institutions. For those reasons, each individual institution should determine their specific policies regarding the agent of choice.**

Key Evidence

- The Hematology DSG conducted separate meta-analyses for the categories of comparisons (daunorubicin [DNR] vs. idarubicin [IDR], DNR vs. mitoxantrone [MXT], and IDR vs. MXT), and all failed to detect statistically significant differences between the agents with respect to response rate or overall survival.

- **There is insufficient evidence to make a firm recommendation regarding the administration of consolidation therapy to older patients who have achieved a complete remission. Based on DSG consensus, it is recommended that patients in complete remission with a good performance status who have recovered from any toxicity receive at least one cycle of consolidation with conventional or intermediate dose cytarabine with or without anthracycline.**

Key Evidence

- No randomized trials of consolidation therapy compared to placebo or observation were identified.
- The decision that patients with a good performance status who have recovered from toxicity should receive at least one cycle (and up to two) of consolidation therapy with conventional or intermediate dose cytarabine with or without anthracycline was based on an extrapolation of the evidence from younger patients (age < 55 years) (2) and on the consensus of the Hematology DSG.

- **There is no role for maintenance therapy for patients in first complete remission.**

Key Evidence

- Four randomized trials of maintenance therapy showed no significant differences in relapse-free or overall survival compared to the control (3-6).

- **For patients with important comorbidities who are deemed ineligible for induction chemotherapy by their physicians or whose personal preferences are for a palliative approach, treatment with low-dose cytarabine is recommended to optimize disease control while avoiding serious treatment-related toxicities.**

Key Evidence

- Burnett et al (7) demonstrated that, in older AML patients deemed unfit for intensive chemotherapy, low-dose cytarabine was associated with higher remission rates and longer survival compared to hydroxyurea, with no difference in toxicities.

➢ **The routine use of myeloid growth factors (G-CSF or GM-CSF) as an adjunct to intensive chemotherapy in older patients with AML is not recommended.**

Key Evidence

- An aggregate data meta-analysis pooling results of the published studies of GM-CSF or G-CSF was performed by the Hematology DSG. The meta-analysis did not detect a difference between groups who did or did not receive growth factors with respect to complete response rate, mortality or disease recurrence, overall survival, infection rates, or infectious death. Toxicity data were inconsistently reported and therefore not pooled.

➢ **There is insufficient evidence to guide a recommendation on the use of specific prognostic factors to guide treatment decisions in older patients.**

Key Evidence

- To date there are no prospective trials investigating the use of specific prognostic factors to guide treatment decisions in older patients.

QUALIFYING STATEMENTS

- ➢ Treatment decisions in older patients with AML are complex and often influenced by comorbid illnesses, consideration of quality of life, and patient preferences. Thus, treatment recommendations described in this evidence-based series may require alteration after discussions with patients and their families.
- ➢ The Hematology DSG recognizes that the trials reviewed for the creation of this guideline included a broad range of patients, from those where currently the use of aggressive attempts at remission might routinely be considered (e.g., those age 56-65) as well as those where only a minority of patients would be treated aggressively (e.g., those age 66 or greater). In the absence of significant weight of evidence to provide recommendations specific to the latter group, the DSG concluded that patient preferences and attention to co-morbidities (physiologic age) remain important considerations in treating elderly patients with AML.

FUTURE RESEARCH

The outcome of conventional cytotoxic chemotherapy in older patients remains extremely poor despite advances in supportive care; thus, several novel therapies are being developed and investigated in clinical trials in this patient population. These include multidrug reversal agents, immunomodulatory therapies, and signal transduction targeting (e.g., PSC-833, UCN-01, gemtuzamab ozogamicin, PS-341, decitabine, ATRA, flt-3 tyrosine kinase inhibitors).

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Evidence-based Series 6-14: Section 2

Treatment of Acute Myeloid Leukemia in Older Patients: Evidentiary Base

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Outcomes of interest include survival, response rate, response duration, and toxicity.

INTRODUCTION

AML is an uncommon cancer with an estimated incidence of 3-5/100,000 (National Cancer Institute Surveillance Epidemiology and End Results [SEER] http://seer.cancer.gov). The incidence of acute myeloid leukemia rises significantly with age, with a median age at diagnosis of 65–70 years (1). Age is known to be a powerful independent prognostic factor for outcome in these patients. Comorbid diseases, decreased tolerance of the side effects of therapy, and adverse disease biology all contribute to the poor outcome. With standard induction treatment, the complete remission rate is approximately 40–50% compared with 70–80% in younger patients. Treatment-related mortality is as high as 25–30% in older patients, and long-term disease-free survival (DFS) is only 10% (2). Despite the fact that they represent the majority of patients with this disease, many trials of new therapies have specifically excluded older patients, and thus their optimal treatment is not clear. Given their poor

response rates and the high treatment-related mortality, the routine administration of intensive chemotherapy to all older patients with AML may not be appropriate.

The proportion of people older than 65 years of age in Western populations is expected to double during the next 40 years. As this demographic shifts, the incidence of this disease will likely increase, and physicians will be faced with these complex treatment decisions more frequently. The Hematology Cancer Disease Site Group (Hematology DSG) considered the topic for development as an evidence-based series because of the uncertainties around treating older patients with AML and the observed variation in treating these patients across Ontario.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (3). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Hematology DSG and a methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on the treatment of older patients with AML. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence is the basis for clinical recommendations developed by the Hematology DSG and presented in a practice guideline as part of this evidence-based series (Section 1). The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE (OVID) (1980 through February 16, 2006), EMBASE (OVID) (1980 through Week 6, 2006 [February 16]), and the Cochrane Library (2006, Issue 1) databases were searched with the term combinations shown in Appendix 1. In addition, the American Society of Clinical Oncology (ASCO) (1997 to 2005) and the American Society of Hematology (ASH) (1997 to 2005) conference proceedings were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov/) databases were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers for the original literature search and by one reviewer for subsequent searches. The reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. Personal files were also searched.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of evidence-based guidelines, reviews, randomized controlled trials (RCTs), or meta-analyses of RCTs in newly diagnosed, previously untreated patients with AML > 55 years of age. Studies that enrolled patients of all ages were also included if they contained well-described subgroup analyses according to age. The outcome measures of interest included response rate, overall survival, disease-free survival (DFS), toxicity, quality of life, and economic outcomes. During guideline development, the age of criterion for inclusion was changed from > 60 years of age to > 55 years of age to reflect the age of inclusion for trials evaluating elderly patients in the literature.

Exclusion Criteria

The following were not considered:

1. Studies of patients with relapsed or refractory AML.
2. Studies of patients with acute promyelocytic leukemia (APL).
3. Letters and editorials.
4. Articles published in a language other than English.

Study Quality Assessment

The methodologic assessment of full report articles was examined by using the published validated quality assessment tool of Jadad et al for RCTs (4), but the score was not used to explicitly weight study results or to exclude studies from the analysis. The literature has shown that studies scoring ≤ 2 points are more likely to produce treatment effects which are on average 35% larger than those produced by trials scoring ≥ 3 points (5). Fully published articles are generally required for a confident methodological assessment, whereas because abstracts describe preliminary information with less description of the study methodology, they may provide less confidence in making treatment recommendations. Subset analyses may be useful for the generation of hypotheses but may be misleading and should not, on their own, be used to make treatment recommendations (6). Therefore, conclusions about the use of chemotherapy and growth factors are most influenced by the full paper publications. In addition to the Jadad scale, other study quality parameters are summarized below.

Synthesizing the Evidence

To determine the role of growth factors as an inducer of more rapid granulocyte recovery and primary prophylaxis of infection in the treatment of older patients with AML, an aggregrate data meta-analysis was performed pooling results of published studies, using Review Manager 4.2 (RevMan Analyses © The Cochrane Collaboration (7)) statistical software, available through the Cochrane Collaboration. For the analyses of DFS and overall survival, the hazard ratio (HR) was used to pool the data. If the hazard ratio was not reported, it was estimated using the methods described by Parmar et al (8). The meta-analyses were performed using the random effects and model. Data extraction of key outcomes was performed by one reviewer and verified by a second reviewer. Intention-to-treat (all randomized patients) or evaluable (patients who were included in the analysis) data were used in the meta-analyses, according to how data were presented in the trial reports. The weighting of trials was based on the inverse variance; quality scores were not used to determine weight. The meta-analyses were performed with outcomes expressed as relative risks (RR) for dichotomous outcomes or as HRs for survival outcomes, with 95% confidence intervals (CI). The x^2 and I^2 tests were used to assess for heterogeneity of results across the trials. A probability level for the x^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% were considered indicative of statistical heterogeneity. The z-test is used by Review Manager for the test of significance for treatment effect.

RESULTS AND DISCUSSION BY QUESTION

In order to organize the material, we will answer each question individually, addressing the following:

1. The results of the search
2. The feasibility of meta-analysis
3. Outcomes
4. Discussion

1. INTENSIVE VERSUS NONINTENSIVE THERAPY

Question

What is the relative efficacy of aggressive induction chemotherapy as compared with less aggressive treatments used in the treatment of older patients (age > 55 years) with newly diagnosed AML?

Results

Literature Search Results

Nine publications were identified that met eligibility criteria (9-18). The included publications were categorized as:

1. Three full publications investigating the use of intensive versus (vs.) non-intensive induction therapy (9-11);
2. Six full publications investigating the dose of induction agent (12-17) and;
3. One abstract publication investigating palliative treatments (18).

Aggregate Data Meta-analysis

Due to clinical heterogeneity among the trials assessing non-intensive vs. intensive therapy, no statistical pooling of the studies was performed.

Trials Investigating the Use of Intensive versus Non-intensive Induction Therapy

Quality assessment

All three trials were multicentred. No trials stated their method of randomization. Allocation concealment was used in at least two trials (10,11) and was unclear in the third trial (9). Even though blinding of the regimens to outcome assessors and patients was not possible due to the nature of the administration of those regimens, trials did not mention the use of other forms of blinding (e.g., data analysts). The number and reasons for withdrawals and dropouts in each arm after randomization were reported in two trials (10,11). Two trials scored two points on the Jadad quality assessment tool (9,10) while one trial scored one point (11). In one trial (10), authors did not state whether there were differences between arms in baseline characteristics. Arms were balanced for a list of characteristics in the other trials (9,11). There did not appear to be pharmaceutical authorship or sponsorship in the included trials. Authors did not state that a power calculation was used in any of the trials. One trial used an intention-to-treat (ITT: all randomized patients analyzed according to treatment allocation) analysis for all outcomes (9). In the trial by Ruutu et al (11), patients were crossed over to the other arm if there was an increase in leukemic cells after one cycle or no reduction after the second cycle; it is not clear whether an ITT analysis was used for outcomes other than complete response (CR).

Outcomes

Trial results

This category consists of three trials (9-11) published as full papers, all of which were restricted to older patients. Those trials are summarized in Table 1.

Tilly et al (9) compared low-dose cytarabine with intensive chemotherapy consisting of rubidazone (a semisynthetic derivative of daunorubicin) and cytarabine in 87 patients 65 years of age and older. Patients with prior myelodysplastic syndrome (MDS) were not included. Although the CR rate was significantly higher in the intensively treated group (Table 1), induction treatment toxicity, including infectious complications (including fatal) (89% vs. 56%, $p<0.01$) and severe granulocytopenia (100% vs. 71%, $p<0.01$) and thrombocytopenia (100% vs. 83%, $p<0.05$), were also higher in the intensively treated group (Table 1). Platelet and red blood cell transfusions were given to all patients in the intensively

treated arm but to fewer patients in the cytarabine arm (80% and 71%, respectively); the mean number of transfusions types was greater in the intensively treated arm ($p<0.01$ and $p<0.02$, respectively). Mean hospital stay was longer in the intensively treated arm (33.6 vs. 27.5 days, $p<0.01$). No differences in median overall survival were detected (Table 1).

Löwenberg et al (10) compared intensive chemotherapy (daunorubicin, vincristine, and cytarabine) with supportive care only (transfusions and antibiotics plus mild cytoreductive treatment with hydroxyurea or subcutaneous cytarabine for palliation of symptoms) in 60 patients aged 65 years and older. Twenty-one of 29 patients in the palliative arm received cytoreductive treatment. The median survival of patients treated intensively was significantly longer than the group receiving palliative treatment only (21 weeks vs. 11 weeks, $p=0.015$). The palliative strategy appeared to be similar to the intensive treatment in terms of the need for hospitalization (median nights spent in hospital, 50% vs. 54%, no p-value reported) (Table 1).

Ruutu et al (11) compared two cycles of moderate intensity five-day TAD (thioguanine, cytarabine, and daunorubicin) with a less intensive oral regimen, ETI (etoposide, thioguanine, and idarubicin) in 51 patients aged 65 years and older with de novo or secondary AML. All patients received oral mercaptopurine and methotrexate maintenance. Patients included in this study were those judged by their physicians to be not fit enough to tolerate fully intensive standard induction and consolidation but fit enough to receive moderately intensive treatment aimed at achieving a remission. One patient randomized to ETI and six randomized to TAD died during the first induction treatment, although the cause of death was not specified. The CR rate and median overall survival were superior with ETI (Table 1). No differences were detected between the groups for time spent in hospital, numbers of red blood cells, or platelet transfusions or for toxicities in the first induction cycle.

Table 1. Studies evaluating active versus palliative therapy in elderly patients with acute myeloid leukemia.

Author, year	Intervention	Sample size	Overall survival	Disease-free survival	Complete remission	Toxic death
Tilly, 1990 (9) age>65y (range 65-83y)	induction: intensive (rubidazone 100mg, ARA-C 200mg) vs. LDAC 20 mg sc	intensive:46[A] vs. LDAC: 41[A] de novo AML (no APL)	median 12.8 vs. 8.8 mo p>0.12[B]	NR median CR duration: 13.8 vs. 8.3 mo p>0.31	52% vs. 32%[C] p<0.001	early deaths 31% vs. 10% p<0.001
Löwenberg, 1989 (10) age>65 (range 65-85y)	induction: DAV: DNR 30mg/ ARA-C 200 mg/ VCR 1 mg vs. palliative treatment[D]	DAV:31[E] vs. palliative: 29[E] de novo AML (no APL)	median[F]: 21 vs. 11 wk p=0.015[G]	median: 16 wk vs. N/A [H]	58% vs. 0% p=NR	Early death: 1 vs. 1 pt p=NR Death in hypoplasia: 2 vs. 9 pt p=NR Death before chemo: 8 pts (palliative)
Ruutu, 1994 (11) age>65 (range 65-87y)	induction/ consolidation[I]: DAT: DNR 60mg/ ARA-C 200mg/ TG 200mg po vs. ETI: IDR 15mg/ TG 200 mg/ VP-16 160 mg (all po)	DAT: 26[A] vs ETI: 25[A] $1^0/2^0$ AML (1 APL, prior MDS incl)	median[J,K]: 3.7 vs. 9.9 mo p=0.042[L]	median RFS[J]: 2.7 vs. 7.2 mo p=NS[L]	induction: 23% vs. 60% p=0.007	Deaths during first induction cycle: 6 vs. 1 pt. p=NR

Note: 1^o=primary; 2^o=secondary; 1st=first; AML=acute myeloid leukemia; APL=acute promyelocytic leukemia; ARA-C=cytarabine arabinoside; chemo=chemotherapy; CR=complete response/remission; DNR=daunorubicin; IDR=idarubicin; LDAC=low-dose ARA-C; MDS=myelodysplasia; mo=month; N/A=not applicable; NR=not reported; po=orally; pt=patient; RFS=relapse-free survival; rubidazone=semisynthetic derivative of DNR; sc=subcutaneous; TG=thioguanine; VCR=vincristine; VP-16=etoposide; vs.=versus; wk=week; y=year;

[A]Patients randomized.

[B]Mantel-Haenszel test.

[C]Response evaluated at different times: 2 wk after the end of LDAC treatment and 4 wk after the end of intensive treatment.

[D]Hematologic and antibiotic supportive care and mild cytoreductive chemotherapy (hydroxyurea or cytarabine) for palliation of leukemia-related symptoms.

[E]Evaluable patients.

[F]Duration of survival determined from time of diagnosis or from CR for those with a CR.

[G]Log-rank analysis.

[H]No patients in this arm achieve complete remission.

[I]If increase in leukemic cells after one cycle or no reduction after second cycle, patients were crossed over to the other arm.

[J]Authors do not indicate whether all randomized patients included in these analyses.

[K]Survival determined from date of diagnostic bone marrow aspirate or biopsy.

[L]Generalized Wilcoxon test.

Discussion

The three studies comparing palliative or low-dose strategies to more intensive therapy for older patients show conflicting results. Only one randomized study (10) compared standard induction treatment to no-induction treatment, using hydroxyurea and/or cytarabine only for palliation of symptoms. This study demonstrated a significant difference in survival in favour of the intensively treated group, with no difference in need for hospital admission between the treatment arms. This study had significant limitations as it included only 60 patients. In the study by Tilly et al (9), the remission rate was significantly higher in the intensively treated group compared with the group treated with low-dose chemotherapy, at the cost of increased treatment-related mortality, resulting in similar overall survival. This trial included only 87 patients and had limited power to exclude a clinically meaningful difference in survival. In contrast, in the study by Ruutu et al (11), the group receiving the oral regimen had significantly improved remission and survival rates, with no difference in toxicities compared with daunorubicin, cytarabine, and thioguanine in doses considerably lower than standard induction with 7+3 (ARA-C/DNR). The oral ETI regimen is difficult to compare with the other regimen that included daunorubicin and cytarabine but was at least as toxic, as judged by the need for hospitalization and transfusions.

While the quality of the data is relatively weak, and given the fact that no further data comparing currently available therapies are expected, it is the opinion of the Hematology DSG that intensive induction chemotherapy can produce an increase in response rate and survival in older patients as compared with low-dose, symptomatic, or palliative treatment.

Trials Investigating the Dose of Induction Agent

Quality assessment

Six trials were identified that investigated the dose of induction agent in adult patients with AML (12-17); one trial was published in abstract form (14), and the rest were fully published. Quality assessment of the trial published in abstract form was difficult (14). The method of randomization was not reported nor was the use of blinding. No mention of withdrawals or dropouts was made, and no sample size requirement was reported. Of the remaining five trials, none scored more than two points using the Jadad quality assessment tool. All the trials were randomized, but only three trials reported the method of randomization (13,16,17). None of the trials reported on the use of blinding, on withdrawals or dropouts, or on a sample size requirement. Only Kahn et al (13) and Rees et al (17) used an ITT analysis. Three trials reported that the treatment and control arms were balanced with respect to a list of patient characteristics (12,13,16).

Outcomes

Trial results

Three of the studies (13-15) were restricted to older adults, and three studies (12,16,17) evaluated a subset of older patients. Trials are summarized in Table 2.

Buchner et al (14) compared two doses of daunorubicin (60 mg/m^2 vs. 30 mg/m^2) as part of a TAD regimen in 340 patients aged 60 years or older. More intensive therapy resulted in fewer early deaths or deaths in hypoplasia (20% vs. 31%, p=0.031), a superior remission rate (38% vs. 20%, p=0.001), and because duration of remission was similar in both groups, the superior remission rate in the more intensively treated patients translated into superior overall survival (14% vs. 5%, p=0.002).

Yates et al (12) compared two doses of daunorubicin, (30 or 45 mg/m^2) with doxorubicin (30 mg/m^2), all in combination with Ara-C (100 mg/m^2, days 1 – 7) in 226 patients; no advantages were detected with the higher dose of daunorubicin. This trial was discussed in further detail in the "Choice of Anthracycline or Anthracenedione in Induction Therapy" section.

Khan et al (13) compared full-dose DAT (daunorubicin 60 mg/m^2, days 1 – 3; Ara-C 200 mg/m^2, days 1 – 5; and thioguanine 100 mg/m^2 po, twice daily [bid] days 1 – 5) with attenuated-dose DAT (daunorubicin 50 mg/m^2, day 1; Ara-C 100 mg/m^2 sc, bid days 1 - 5; and thioguanine 100 mg/m^2 po, bid days 1 – 5) in 40 patients 70 years of age and older. There was no significant difference in CR rates between the two arms; however, early deaths, mainly from hemorrhage or sepsis, were significantly more common in the more intensively treated group (55% vs. 15%, p=0.05), which translated into longer median survival for the group receiving attenuated therapy (159 days vs. 29 days, p=0.02).

Dillman et al (16) compared differing doses of Ara-C (200 mg/m^2 vs. 100 mg/m^2, days 1 - 7) in combination with daunorubicin 30 mg/m^2 days 1 – 3 in 100 patients aged 60 years or older. An interim analysis indicated that Ara-C 200 mg/m^2 could not be superior in this age group, and subsequently, older patients were assigned to the cytarabine 100 mg/m^2 arm. Complete remission was not different between the two arms (44% vs. 38%, p=0.68) nor was median overall survival (11 weeks vs. 9.6 weeks, p=0.227) or the incidence of therapy-related deaths.

In the Medical Research Council (MRC) AML 9 study (17), intensification of induction and consolidation and the need for maintenance therapy were evaluated in 335 patients. There were three randomizations: initially patients were randomized between DAT 3+10 (DNR 50 mg/m^2, days 1, 3, 5; cytarabine 100 mg/m^2 bid, days 1 – 10; 6TG 100 mg/m^2 po, bid days 1 – 10) and DAT 1+5 (DNR day 1; cytarabine days 1 – 5; 6TG days 1 – 10). Patients in CR were then randomized to two cycles of DAT 2+7 consolidation alternating with two courses of MAZE (m-AMSA, 5-azacytidine, and etoposide) or COAP (cyclophosphamide, vincristine, Ara-C, and prednisone). Lastly, patients were randomized between a year of monthly maintenance (eight courses of cytarabine and thioguanine followed by four courses of COAP) or to no further treatment. In the subgroup of patients, aged 60 years of older, CR rates were similar (46% vs. 45%). Though induction deaths were higher for DAT 3+10, this was outweighed by the lower incidence of resistant disease. Overall survival appeared to be higher in the intensively treated group (12% vs. 5%); however, no p-value was reported.

Feldman et al (15) compared high-dose mitoxantrone (80 mg/m^2) with standard dose mitoxantrone (36 mg/m^2) in combination with a fixed dose of cytarabine (3 g/m^2, days 1 – 5) in 54 patients aged 60 years and older. Early death (prior to day 14) or death during hypoplasia occurred in 31% of patients in the lower dose arm and 11% in the higher dose arm. Ten of the 11 deaths were due to sepsis and/or pneumonia. Non-infectious complications were not different between the two groups. Similarly, response rates (57% vs. 41%) and median survivals (nine months vs. six months) were not significantly different.

Discussion

Studies comparing more chemotherapy to less chemotherapy during induction have shown contradictory results. The trials by Yates et al, Dillman et al, and Feldman et al are older and have limited power to detect differences in CR or overall survival (12,15,16). Conversely, the more recent trial by Buchner et al (14) is much larger, suggesting that standard doses of 7+3, when applied to the study patient population, provide the best outcome in terms of CR and overall survival.

Table 2. Outcomes for trials investigating the dose of induction agent.

Author, year (ref)	Intervention	N	OS	DFS	CR	Toxic death
Kahn, 1989 (13)	full (DNR 60 mg, Ara-C 200 mg, 6TG 100 mg)	20	Mdn 29 d	NR	25%	60%
	low (DNR 50 mg, Ara-C 100 mg, 6TG 100 mg)	20	159 d p<0.02		30% p=NS	25% p=0.05
Feldman, 1997 (15)	high MTZ 80 mg, Ara-C 3 g	28	Mdn 9 mo	Mdn 5 mo	57%	NR
	standard MTZ 36 mg, Ara-c 3 g	26	6 mo p=NS	3 mo p=NS	42% p=NS	NR
Yates, 1982 (12)[A]	7+3 DNR 45, Ara-C 100	68	NR	NR	31%*	NR
	7+3 DNR 30, Ara-C 100	73			47%*,† *p<0.05	
	7+3 DOX 30, Ara-C 100	85			35%† †p=NS	
Rees, 1996 (17)[B]	DAT 3+10 (DNR 50 mg/m^2 d1,3,5; Ara-C 100 mg/m^2 bid d1-10, 6TG 100 mg/m^2 po bid d1-10)	167	10 yr 12%	NR	47%	33%[C]
	DAT 3+5 (DNR d1, Ara-C d1-5, 6TG d1-10)	168	5%		45% p=NS	28%[C] p=NS
Dillman, 1991 (16)	DNR 30 mg/m^2, Ara-C 200 mg/m^2 d1-7	50	Mdn 9.6 wk	NR	38%	NR
	DNR 30 mg/m^2, Ara-C 100 mg/m^2 d1-7	50	11 wk p=NS		44% p=0.68	
Büchner, 1997 (14)	TAD (DNR 30 mg/m^2)	340	NR	17%	45%	31%
	TAD (DNR 60 mg/m^2)			22% p=NS	52% p=0.026	20% p=0.031

Notes: 6TG=thioguanine; Ara-C=cytarabine; CR=complete response; d=day(s); DFS=disease-free survival; DNR=daunorubicin; DOX=doxorubicin; Mdn=median; mo=month(s); MTZ=mitoxantrone; N=number of patients; NR=not reported; NS=not statistically significant; OS=overall survival; ref=reference; wk=week(s); yr=year(s).
[A]The induction regimen was followed by maintenance with TG/pred + VCR/IND anthracycline q4 or 8 wks x 2-3 yrs.
[B]The induction regimen was followed by randomization to consolidation therapy with either DAT 2+7/MAZE vs. COAP; consolidation was followed by randomization to maintenance with Ara-C and thioguanine x 9 vs. no further treatment.
[C]Induction deaths.

Trials Investigating Palliative Treatments

Quality assessment

One trial investigating palliative treatments was identified (18). When this section of the report was initially drafted, this trial had been reported in abstract form only. When the report was completed, a full article publication became available and is therefore included. The method of randomization was reported but not the use of blinding. Numbers and reasons for withdrawals and dropouts were not reported. The authors reported that a sample size of 200 patients per arm would be required to detect a difference of 10% in overall survival (10% vs. 20% at two years) with 90% power. The trial arms were balanced with respect to age, sex, disease type, white blood cell count, and performance status. The final analyses were ITT.

Outcomes

Trial results

As part of the NCRI (formerly MRC) AML 14 Trial, patients over 60 years of age were randomized to low-dose (LD) Ara-C (20 mg sc bid for 10 days every 4 – 6 weeks) or to hydroxyurea (HU) (18). Patients were also randomized to receive all-trans retinoic acid (ATRA) 45 mg/m^2 daily for 60 days. Two hundred seventeen patients were enrolled: 148 had a WHO performance score < 2; 193 patients were 65 years of age or older; 126 had de novo AML, 57 had secondary disease, and 29 had high-risk MDS (blasts > 10%). Two hundred two patients were randomized to HU vs. LD-Ara-C, and 207 patients were randomized to ATRA vs. no ATRA. Complete remission was seen in one of 99 (1%) patients in the HU arm and 18 of 102

(18%) in the LD-Ara-C (p=0.00006) arm. Overall survival was considerably improved in the LD-Ara-C arm (HR 0.60; 95% CI, 0.44 to 0.81; p=0.0009). Toxicity and supportive care requirements were similar between the two groups. There were no significant differences in overall or within treatment arm outcomes between patients who received ATRA and patients who did not receive ATRA.

Discussion

There is only one trial in which palliative regimens are compared. Burnett et al (18) demonstrated that in older AML patients deemed unfit for intensive chemotherapy, low-dose cytarabine was associated with higher remission rates and longer survival compared to hydroxyurea, with no difference in toxicities. One of the limitations of this study is that important information is lacking, such as the definition of "unfit for chemotherapy," without which the findings cannot be reliably generalized.

2. THE CHOICE OF ANTHRACYCLINE OR ANTHRACENEDIONE IN INDUCTION THERAPY

Question

What is the optimum induction regimen for older patients (age > 55 years) with newly diagnosed AML?

Results

Literature Search Results

The literature search identified 13 published randomized trials comparing different anthracycline or anthracenedione agents as part of induction treatment. Those trials were divided into five categories:

1. Daunorubicin (DNR) vs. idarubicin (IDR): five trials (19-23).
2. DNR vs. mitoxantrone (MXT): three trials (24-26).
3. DNR vs. IDR vs. MXT: one trial (27),
4. DNR vs. other (doxorubicin, amsacrine, aclarubicin): one trial each (12,28,29).
5. IDR vs. MXT: one trial (30).

Two reports (23,30) were published in abstract form and the rest as full papers. Nine studies were restricted to older adults (20,21,23,25-30), and four (12,19,22,24) reported results in a subset of older patients.

One study, reported by Linkesch et al (31), was excluded as it contained only 25 elderly patients randomized unequally between each arm. One review, with a meta-analysis, that compared IDR with another anthracycline was identified for inclusion (32).

Quality Assessment

Two studies scored two points, and all remaining studies scored one point on the Jadad quality assessment tool. Twelve trials were multicentred, and one abstract did not provide this information (30). No trials stated their method of randomization, but allocation concealment was used in two trials (20,26). Even though blinding of the regimens to outcome assessors and patients was not possible due to the nature of the administration of those regimens, trials did not mention the use of other forms of blinding (e.g., data analysts). The number and reasons for withdrawals and dropouts in each arm after randomization were reported in three trials (12,19,22), which were subgroup trials providing this information for the study group as a whole. In two subgroup trials, authors state a baseline imbalance between arms for platelet count (19) and previous hematologic disorder (19), respectively, for the entire study group. Two trials reported in abstract form did not provide baseline information (23,30), and one trial did not state whether there were differences among arms (25). Arms were balanced for all or a list of characteristics in remaining trials, of which two subgroup trials (12,24) reported information for the entire study group only. Pharmaceutical authorship or sponsorship was noted in five trials (19,20,22,24,27). Three trials reported the use of power calculation (20,26,27). Two trials used an ITT analysis for efficacy outcomes (20,21), while one trial (22) reported ITT data for one outcome only. Two trials provided minimal methodologic information as they were abstracts (23,30).

Goldstone et al (25) published a three-arm trial that randomized patients in a 1:1:2 fashion but did pair-wise comparisons for their analyses. They increased their age criterion part way through the study, but 12 patients less than 56 years of age were included in the study. In addition, some patients were concurrently enrolled in up to two other trials, and a small amount of patients (1%) did not have AML. Six trials, including the Goldstone et al trial, were factorial in design (12,25-29); in only one trial the factorial design may have been accounted for in one outcome (27).

Outcomes

Review

The AML Collaborative Group conducted a review, with a meta-analysis (32), comparing IDR with another anthracycline in seven trials (19-22,33-35). The authors provided the sources searched for retrieving trials but did not explicitly state the inclusion and exclusion criteria for the review and used a pooling method different than that used in this systematic review. The meta-analyses were conducted with patients of all ages, but trend analyses (method not provided) for age subgroups detected no significant trend for early ($p=0.06$) or late induction deaths ($p=0.20$), although a significant trend for decreasing CR rates with increasing age ($p=0.006$) was detected, **with no difference between the arms in the subgroup of patients over the age of 60. Overall survival was not reported in the elderly subgroup.**

Trial results

Where pooling of data has permitted a meta-analysis, the results of specific trials are shown in the figures in the section below describing Meta-Analysis. Additional data from those trials are in Table 3; no significant difference was detected for most outcomes. Only those reports not included in the meta-analyses are described below (i.e., the trials of DNR vs. other).

Oberg et al (28) compared DNR, cytarabine, and thioguanine with a combination substituting aclarubicin for DNR for induction and consolidation in 90 patients aged 60 years and older with untreated de novo AML. No differences in CR rate or cause-specific survival were detected (Table 3).

Stein et al (29) evaluated 299 patients aged ≥ 51 years who were randomized to receive cytarabine plus either DNR or amsacrine. Those in CR received three cycles of consolidation with DNR, cytarabine, and thioguanine and were then randomized to maintenance with DNR and cytarabine or observation. No difference in response rate was observed (Table 3).

Yates et al (12) compared two doses of DNR (45 mg/m^2 and 30 mg/m^2) with doxorubicin (30 mg/m^2), all in combination with cytarabine in patients aged 1–84 years. In patients older than 60 years, the CR rate with DNR 30 mg/m^2 was superior to DNR 45 mg/m^2 ($p<0.05$; Table I); no difference was detected for either DNR dose compared to doxorubicin (Table 3).

Table 3. Additional outcomes reported for trials evaluating anthracyclines or anthracenediones in elderly patients with acute myeloid leukemia.

Author, year	Patient population	Induction therapy (sample size)	Additional outcomes
		DNR vs. IDR	
Mandelli, 1991, full paper (20)	1°/2° AML not stated (no prior Rx for leukemia) 7 pts APL Age 55 to 80y	IDR/ARA-C (124) vs. DNR/ARA-C (125)	Median OS: 87 vs. 169 d p=NS Median RFS: 299 vs. 284 d p=NS
Reiffers, 1996, full paper (21)	1° AML 9 pts. APL Age 55-75y	DNR/ARA-C (108) vs. IDR/ARA-C (112)	Median OS: 273 vs. 328 d p=0.3 3y DFS[A]: 15% vs. 19% p=0.22
Vogler, 1992, full paper (19)	1°/2° AML not stated APL included. Age >60y (subgroup)	DNR/ARA-C (59) vs. IDR/ARA-C (52)	Median OS: 209 vs. 235 d[B] p=0.58
Wiernik, 1992, full paper (22)	1° AML APL included. Age >60y (subgroup)	DNR/ARA-C (45) vs. IDR/ARA-C (38)	Median OS: 3.2 vs. 3.4 mo[C] p=NR
Mori, 2003, abstract (23)	1°/2° AML APL not mentioned. Age range 65-75y	DNR/Behenoyl-ARA-C/6-MP (65) vs. IDR/Behenoyl-ARA-C (63)	2y OS: 43% vs. 37% p=NR 2y DFS: 48% vs. 48% p=NR
		DNR vs. MXT	
Lowenberg, 1998, full paper (26)	1°/2° AML 8 pts. APL Age>60y (range 60-88y)	DNR/ARA-C (242) vs. MXT/ARA-C (247)	5y OS: 6% vs. 9% Median OS: 36 vs. 39 wk p=0.23 5y DFS: 8% vs. 8% Median DFS: 39 vs. 39 wk p=0.73
Arlin, 1990, full paper (24)	1° AML APL included Age ≥60y (subgroup)	MXT/ARA-C (48) vs. DNR/ARA-C (51)	Median OS: 98 vs. 51 d p=NR
Goldstone, 2001, full paper (25)	1°/2° AML 59 pts. APL Age ≥56[D] (range 44-91y; 2% <56y)) Some pts in ATRA trial; 226 pts in G-CSF trial	DAT (DNR/ARA-C/6-TG) (328) vs. ADE (DNR/ARA-C/VP-16) (327) vs. MAC (MXT/ARA-C) (656)	5y OS: 12% vs. 8% vs. 10% DAT vs. ADE p=0.02 DAT vs. MAC p=0.10 ADE vs. MAC p=0.20 5y DFS: 18% vs. 15% vs. 16% p=NS[E]

Table 3 (continued). Additional outcomes reported for trials evaluating anthracyclines or anthracenediones in elderly patients with acute myeloid leukemia.

Author, year	Patient population	Induction therapy (sample size)	Additional outcomes
		DNR vs. IDR vs. MXT	
Rowe, 2004, full paper (27)	1° AML Age >55y	DNR/ARA-C (116) vs. IDR/ARA-C (118) vs. MXT/ARA-C (114)	Median OS: 7.7 vs. 7.5 vs. 7.2 mo p=NS Median DFS: 5.7 vs. 9.4 vs. 7.1 mo p=0.68 DNR vs. IDR
		DNR vs. other	
Stein, 1990, full paper (29)	1° AML Age≥51y APL included.	DNR/ARA-C (159) vs. m-AMSA/ARA-C (140)	CR: 47% vs. 42%[F] p=0.45
Oberg, 2002, full paper (28)	De novo AML APL 2 pts Age >60y	ARA-C/6-TG/DNR (43) vs. ARA-C/6-TG/ACLA (47)	Cause-specific survival (death due to leukemia): median 345 vs. 77 d p=NS CR: 51% vs. 47% p=NS
Yates, 1982, full paper (12)	Untreated AML APL included. Age >60y (subgroup)	DNR 45/ ARA-C (68) vs. DNR 30/ARA-C (73) vs. ADM/ARA-C (85)	CR: 31% vs. 47% vs. 35% DNR 30 vs. DNR 45 p<0.05 DNR 30 vs. ADM p=0.14 DNR 45 vs. ADM p=0.60
		IDR vs. MXT	
Archimbaud, 1997, abstract (30)	1°/2° AML APL not mentioned. Age range 60-83y	ARA-C/VP-16/IDR vs. ARA-C/VP-16/MXT n=154 pts[G]	Median[H] OS: p=NS[I] for non-transplanted pts Median DFS: p=NS[I] for non-transplanted pts.

Note: 1^0=primary, 2^0=secondary; AML=acute myelogenous leukemia; APL=acute promyelocytic leukemia; ARA-C=cytarabine arabinoside; de novo, previously untreated; mo=month; y=year; DNR=daunorubicin; MXT=mitoxantrone; OS=overall survival; DFS=disease-free survival; wk=week; IDA=idarubicin; vs.=versus; chemo=chemotherapy; 6-TG=thioguanine; d=day; pt(s)=patient(s); m-AMSA=amsacrine; ACLA=aclarubicin; CR=complete response; ADM=doxorubicin;VP-16=etoposide.
[A]Data interpolated from published curves.
[B]Data reported in article.
[C]Order of data unclear in the article.
[D]Changed partway through study to ≥60y but patients <60y could be included if not considered suitable for more intensive treatment in other concurrent trials.
[E]Unclear if pairwise comparisons conducted for analyses.
[F]79% of patients evaluated.
[G]Numbers for each group not given.
[H]Assumed based on information provided.
[I]Data in each arm not provided.

Aggregate data meta-analysis

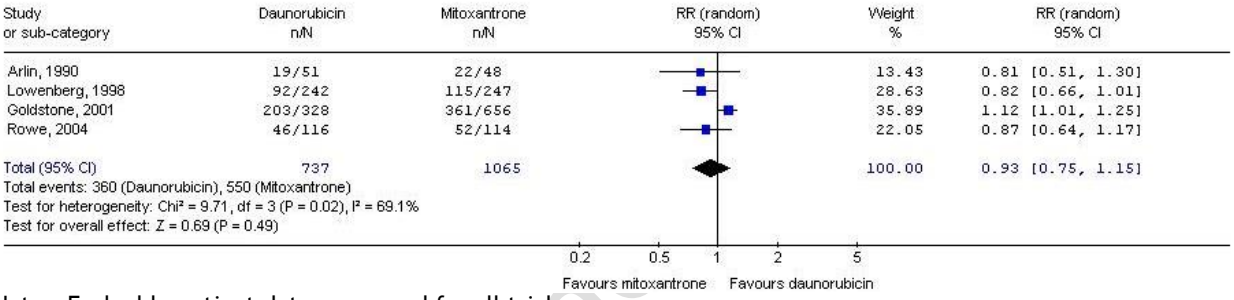
An overall meta-analysis was not conducted because the investigative arms were considered too clinically heterogeneous to justify a combined analysis. Thus, meta-analyses were conducted separately for the categories of comparisons (DNR vs. IDR, DNR vs. MXT). A meta-analysis of IDR vs. MXT was not conducted as only one trial reported sufficient data for inclusion in a meta-analysis (27). Early in the development of this report, before the meta-analyses were conducted, the following factors were examined for heterogeneity among trials: prior MDL (whether included or excluded in trials), age, performance status, and baseline cytogenetics. An analysis of outcome according to baseline cytogenetics was

planned, but lack of assessable outcome data for these subgroups precluded this analysis. Abstract data were included in the meta-analyses.

No statistically significant differences were detected in the comparison of MXT to DNR with respect to CR rates (RR, 0.93; 95% CI, 0.75 to 1.15; p=0.49) (Figure 1) or overall survival (HR, 0.94; 95% CI, 0.74 to 1.19; p=0.60) (Figure 2). These comparisons exhibited a high degree of statistical heterogeneity (I^2>50%). This may be partially explained by the lower doses of daunorubicin and mitoxantrone used in the Lowenberg (26) trial (30 mg DNR and 8 mg MXT compared to 45-50 mg of DNR and 12 mg MXT used in the other two trials).

Meta-analyses comparing IDR to DNR did not detect statistically significant differences with respect to CR rates (RR, 0.91; 95% CI, 0.81 to 1.03; p=0.12) (Figure 3) or overall survival (HR, 0.98; 95% CI, 0.80 to 1.21; p=0.87) (Figure 4). As survival was not uniformly reported, the results of only three studies (19-21) could be pooled. No statistical heterogeneity was observed for pooled CR data, and only low degree of statistical heterogeneity was exhibited for the overall survival data (I^2=27.2%).

Figure 1. Meta-analysis of complete remission for mitoxantrone versus daunorubicin in induction.



Note: Evaluable patient data were used for all trials.

Figure 2. Meta-analysis of overall survival for mitoxantrone versus daunorubicin in induction.

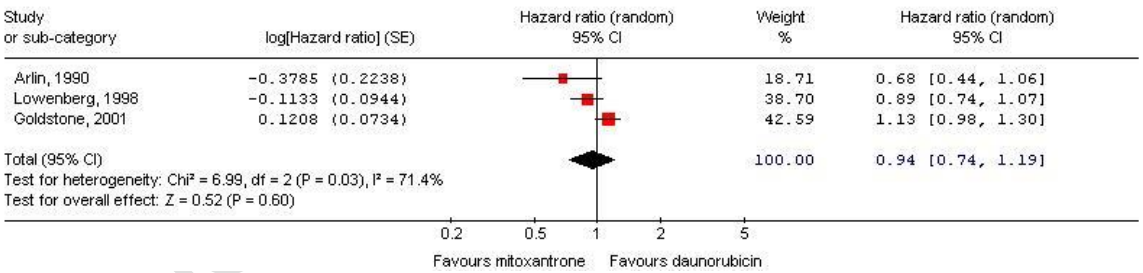
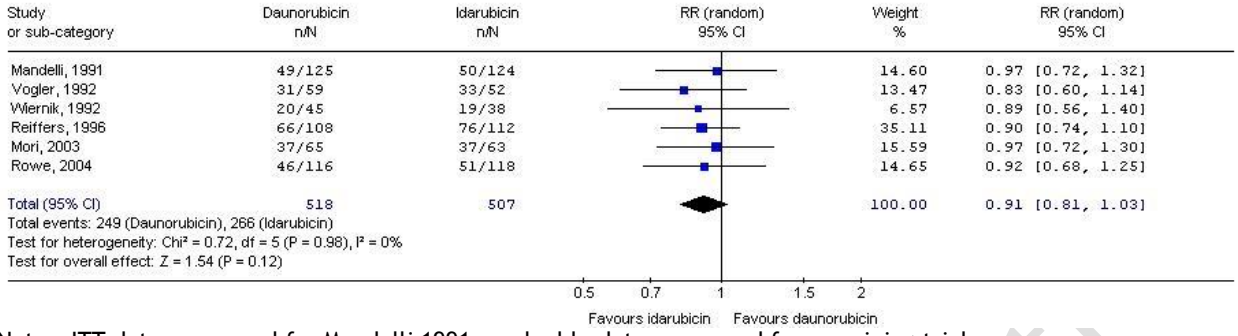
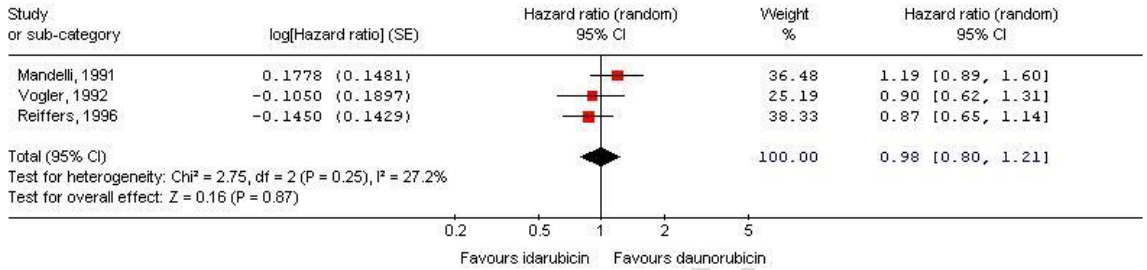


Figure 3. Meta-analysis of complete remission for idarubicin versus daunorubicin in induction.



Note: ITT data were used for Mandelli 1991; evaluable data were used for remaining trials.

Figure 4. Meta-analysis of overall survival for idarubicin versus daunorubicin in induction.



Toxicity

The relative toxicities of these agents were compared within trials; data are summarized in Appendix 2. These toxicity data do not contribute to the decision about the preferred choice of agent.

Discussion

Substitution of IDR or MXT for DNR was hypothesized to provide therapy that would be associated with a superior anti-leukemic effect and/or less treatment-related toxicity. While differences in response rates were reported in one study (25), a meta-analyses failed to detect any statistically significant differences with respect to response rate or overall survival at one or two years. No consistent differences in treatment-related toxicity, and specifically cardiac toxicity, were observed.

The DSG recognized that no advantages of one anthracycline or anthracenedione agent over another were detected. The DSG thus concluded that these agents were interchangeable and that the decision of which agent to use may be determined by factors other than treatment effectiveness, such as drug acquisition costs, that may vary among institutions. For these reasons, each individual institution should determine their specific policies regarding the agent of choice.

3. OPTIMUM POST-REMISSION THERAPY

Question

What is the optimum postremission therapy for older patients (age > 55 years) with newly diagnosed AML?

Literature Search Results

Seven studies were identified that examined postremission therapy for elderly patients with AML (25,26,29,36-39). Those trials were divided into two categories: consolidation therapy (25,36-38) and maintenance therapy (25,26,29,39). Goldstone et al (25) reported the results of a trial that included three randomized comparisons; induction, consolidation, and maintenance. The consolidation and maintenance comparisons are reported in this section of the guideline. The trial reported by Jehn et al (38) was designed to evaluate the use of myeloid colony-stimulating growth factors as well as compare two consolidation regimens. That abstract reported data for the consolidation regimens, whereas the data for the growth factor randomization part of the trial were reported in a publication by Amadori et al (40). Although Amadori et al (40) did not report data on the consolidation regimens, the authors provided details on the overall trial design that were not reported in the abstract by Jehn et al (38). Amadori et al (40) stated that a later publication would detail the final results of the consolidation phase of the trial. Büchner et al (39) reported the results of a trial that randomized patients to maintenance therapy or to intensive consolidation therapy. For the purposes of this systematic review, that trial was included in the maintenance therapy section.

Quality Assessment

A proper quality assessment of the consolidation randomization of the AML-13 trial could not be done as that part of the trial was reported in abstract form only, by Jehn et al (38). However, Amadori et al (40) provided details of the overall design of the AML-13 trial that were used, where applicable, to assess the quality of the consolidation randomization part of the trial. Only one trial (39) scored two points on the Jadad quality assessment tool; the remaining trials scored only one point. All the identified trials were multicentred. Two trials reported the method of randomization (central) (36,39). One trial did not use blinding (40), and the remaining six trials did not report on the use of blinding. Three trials compared maintenance therapy to no further treatment, and did not report the use of a placebo (25,26,29). Four trials compared consolidation therapy to either the same regimen with an additional drug or the same regimen on a different schedule and dose (25,36-38). One trial compared maintenance therapy to intensive consolidation therapy (39). The number and reasons for withdrawals and dropouts in each arm after randomization were provided in five trials (26,29,36,37,39). Patient characteristics were balanced between treatment arms for all trials. Four trials stated that a power calculation was used to determine the required sample size (26,37,39,40); however, one trial (26) did not accrue the required number of patients (of the required 208 patients only 151 were randomized to maintenance or to no further treatment). Four trials conducted an ITT analysis (25,36,37,39).

Aggregate Data Meta-analysis

Due to clinical heterogeneity among the trials assessing optimum postremission therapy, no statistical pooling of the studies was performed.

Consolidation Therapy

Outcomes

Results for the four trials of consolidation therapy can be found in Table 4.

Mayer et al (36) tested three different doses of cytarabine as consolidation (100 mg/m^2 x 5 days vs. 400 mg/m^2 x 5 days vs. 3 g/m^2 every 12 hours on days 1, 3, and 5; each for four courses) after patients achieved CR with standard daunorubicin and cytarabine induction. In the older age cohort (129 patients older than 60 years of age), the DFS after four years was similar in all three arms (p=0.19); however, the number of patients in each arm was small. Due to significant toxicity in the high-dose group, only 29% of patients older than 60 years received all four cycles of planned treatment compared to 71% and 66% in the low-dose and intermediate-dose groups, respectively. Severe central nervous system toxicity was reported in this group and was especially common in patients older than 60 years. Because of this, after 31 patients had received high-dose cytarabine, randomization to the high-dose arm was restricted to patients 60 years old and younger.

Stone et al (37) tested the addition of mitoxantrone (5 mg/m^2 bid x 3 days) to intermediate dose cytarabine (500 mg/m^2 bid x 3 days) for two courses compared with standard dose cytarabine (100 mg/m^2 x 5 days) alone for four monthly courses as postremission therapy after standard 7+3 induction. No difference was observed in DFS (cytarabine+mitoxantrone vs. cytarabine alone: median, 10 months vs. 11 months), relapse rate (82% vs. 77%, respectively), or median overall survival from the second randomization (1.3 years vs. 1.6 years, respectively). Patients who received the cytarabine plus mitoxantrone combination experienced more toxicity (hemorrhage, p=0.03; diarrhea, p=0.005; dysrhythmias, p=0.03; and malaise, p=0.01) but not more deaths.

Goldstone et al (25) tested short versus long consolidation in an effort to maintain remission. Short consolidation consisted of one cycle of DAT; long consolidation consisted of one cycle of DAT followed by two cycles of COAP and one cycle of DAT. Death while in remission, mainly from infection, while not significantly different between arms, was considerable and appeared somewhat higher in the arm receiving the long consolidation (8% vs. 3%). Relapse risk (81% vs. 73%), DFS (16% vs. 23%), and overall survival at five years (23% vs. 22%) did not differ between the short and long consolidation arms.

Jehn et al (38) compared oral versus intravenous (IV) consolidation therapy after induction with one or two cycles of mitoxantrone, cytarabine, and etoposide (MICE) in 346 (of an initial 757) patients aged 61 – 80 years. Patients in CR after induction were randomized to two cycles of IV idarubicin, cytarabine, and etoposide (mini-ICE) or oral mini-ICE (cytarabine given subcutaneously [sc]). Rates of grade 3/4 nausea were 9% versus 4%, vomiting 11% versus 2%, and infection 20% versus 27%, in the oral versus IV arm, respectively. DFS (median 0.75 years vs. 0.89 years, p=0.22) and overall survival (median 1.31 years vs. 1.48 years, p=0.33) were not significantly different between the two arms.

Discussion

In the three fully published trials comparing two or more different consolidation approaches, there was increased toxicity from the escalation of the dose of cytarabine, the addition of mitoxantrone to intermediate dose cytarabine, and from longer duration of treatment (four cycles vs. a single cycle of consolidation), with no improvement in relapse-free or overall survival. Jehn et al (38) showed that oral therapy was not less toxic than IV therapy. Importantly, there are no trials comparing consolidation therapy with observation alone after achieving CR in elderly patients with AML. Given the lack of evidence, the routine use of consolidation therapy in older patients is not recommended. Extrapolating from evidence in younger patients (age < 55 years) (36), the DSG concluded that in patients with a

good performance status who have recovered from toxicity should receive at least one (and up to two) cycles of consolidation therapy with conventional or intermediate dose cytarabine with or without anthracycline.

Table 4. Randomized trials of consolidation therapy.

Author, year (ref)	Consolidation regimen	N	OS	DFS	CR	Toxic deaths
Mayer, 1994 (36)[A]	LD Ara-C (100mg)	48	4 yr 9%	3 yr 17.0%[B]	NR	NR
	ID Ara-C (400mg)	50		23.9%[B]		
	HD Ara-C (3g)	31		16.2%[B] p=0.19[B]		
Stone, 2001 (37)	Ara-C 500mg + MTZ 5mg	87	Median 1.3 yr	Median 10 mos	NR	NR
	Ara-C 100mg	82	1.6 yr p=NS	11 mos p=0.67		
Goldstone, 2001 (25)	DAT	150	5 yr 23%	5 yr 16%	NR	NR
	DATx2/COAPx2	152	22%	23%		
Jehn, 2002 (38) (abstract)	iv mini-ICE (8/100/100)	172	Median 1.48 yr	Median 0.89 yr	NR	NR
	po mini-ICE (20/200/100 sc)	174	1.31 yr HR 1.14 95% CI: 0.88 to 1.49	0.75 yr HR 1.17 95% CI: 0.91 to 1.50		

Notes: Ara-C=cytarabine; COAP=cyclophosphamide, vincristine, cytarabine, prednisolone; CI=confidence interval; CR=complete response; DAT=daunorubicin, cytarabine, thioguanine ; DFS=disease-free survival; HD=high-dose; HR=hazard ratio; ID=intermediate-dose; iv=intravenous; LD=low-dose; mini-ICE=idarubicin, cytarabine, etoposide; mos=months; MTZ=mitoxantrone; N=number of patients randomized; NR=not reported; NS=not statistically significant; OS=overall survival; po=oral; ref=reference; yr=year(s).
[A]Only data for patients over 60 years of age are included in this table for the trial reported by Mayer et al (36).
[B]Comparison was made between all three groups.

Maintenance Therapy

Outcomes

Results for the four trials of maintenance therapy can be found in Table 5.

Büchner et al (39) compared prolonged maintenance treatment to intensive consolidation without maintenance therapy in 197 patients aged ≥ 60 years. All patients received induction with TAD (cytarabine 100 mg/m^2 days 1 and 2, then 100 mg IV every 12 hours days 3 – 8; daunorubicin 60 mg/m^2 days 3 – 5; 6-thioguanine 100 mg/m^2 po every 12 hours days 3 – 9). If patients did not enter remission (defined as bone marrow blasts ≥ 5%), they received a second induction with HAM (cytarabine 1 g/m^2 IV every 12 hours days 1 - 3; mitoxantrone 10 mg/m^2 IV days 3 – 5). Patients in remission after the first or second induction received consolidation with TAD (as above). After TAD, patients were given either maintenance chemotherapy or one course of intensive consolidation according to their initial randomization. Maintenance chemotherapy consisted of monthly courses of cytarabine 100 mg/m^2 sc every 12 hours for five days combined with a second drug: daunorubicin 45 mg/m^2 days 3,4 (course 1); 6-thioguanine 100 mg/m^2 po every 12 hours days 1 – 5 (course 2); cyclophosphamide 1 g/m^2 day 3 (course 3); or 6-thioguanine as in course 2 (course 4), repeating at course 1 for three years. Intensive consolidation consisted of cytarabine 0.5 g/m^2 every 12 hours on days 1,2,8,9 and mitoxantrone 10 mg/m^2 on days 3,4,10,11. There was no significant difference in median relapse-free survival (11 months vs. 10 months,

p=0.1001) or median overall survival (11 months vs. 7 months, p=0.242) in the groups receiving maintenance therapy compared to intensive consolidation. Toxicity data were not available for the patients receiving maintenance chemotherapy because it was generally given on an outpatient basis.

Table 5. Randomized trials of maintenance therapy.

Author, year (ref)	Maintenance regimen	N	OS	DFS	CR after induction	Toxic deaths
Büchner, 2003 (39)[A]	Maint: Ara-C + second drug[B]	157	Median 11 mos	Median 14 mos	62%	4%
	IC: Ara-C + MXT[C]	140	8 mos p=0.242	11 mos p=0.0341	59%	7%
Goldstone, 2001 (25)	IFN	148	5 yr 21%	5 yr 20%	NR	NR
	No tx	146	20% p=NS	15% p=NS		
Löwenberg, 1998 (26)	Ara-C	74	5 yr 18%	5 yr 13%	NR	NR
	No tx	73	15% p=0.29	7% p=0.006		
Stein, 1990 (29)	DNR + Ara-C	23	Median 12 mos	3 yr 21%	NR	NR
	No tx	29	40 mos p=0.007	28% p=NS		

Notes: Ara-C=cytarabine; CR=complete response; DFS=disease-free survival; DNR=daunorubicin; IC=intensive consolidation; IFN=interferon; Maint=maintenance; mos=months; MXT=mitoxantrone; N=number of patients randomized; NR=not reported; NS=not statistically significant; OS=overall survival; ref=reference; tx=treatment; yr=year.
[A]Only data for patients over 60 years of age are included in this table for the trial reported by Büchner et al (39).
[B]Ara-C was combined with either daunorubicin (course 1), 6-thioguanine (course 2), Cyclophosphamide (course 3), or 6-thioguanine (course 4). After the fourth course, the sequence was repeated starting with course 1.
[C]The second arm of the Büchner trial consisted of intensive consolidation therapy.

Goldstone et al (25) compared 12-month maintenance treatment with interferon-α ($3x10^6$ units three times per week) with no treatment in 362 patients. No benefit was seen with respect to relapse risk (77% vs. 81%), DFS (20% vs. 15%) or overall survival (21% vs. 20%) at five years in patients receiving interferon maintenance therapy compared with those receiving no maintenance. Of 182 patients randomized to interferon, 41 did not start the treatment. These were mainly patients who received a long consolidation course (discussed in *Consolidation Therapy* section), of whom 55% started interferon compared with 94% in the short consolidation arm. Of note, only 42 of the 141 patients starting interferon actually completed the full 12 months of treatment.

Löwenberg et al (26) compared low-dose cytarabine (10 mg/m^2 sc every 12 hours for 12 days every six weeks for eight cycles) as maintenance treatment to no maintenance treatment in 151 patients. The DFS rate at five years for patients receiving maintenance therapy was significantly better than those receiving no treatment (13% vs. 7%, p=0.006); however, overall survival was not significantly different (18% vs. 15% at five years, p=0.29).

Stein et al (29) compared maintenance treatment (cytarabine 100 mg/m^2 for five days and daunorubicin 45 mg/m^2 for two days, repeated every 13 weeks for four cycles) with no maintenance in 52 patients. There was no difference in relapse-free survival (21% vs. 28%, p=not reported); however, overall survival was significantly greater (40 months vs. 12 months, p=0.007) for patients who received no maintenance compared to patients who received

maintenance treatment. There was considerable toxicity associated with maintenance therapy, with 91% of patients experiencing severe or life-threatening hematologic toxicity and 33% of patients experiencing serious infections.

Discussion

Comparisons of maintenance chemotherapy (26,39) or interferon (25) following consolidation with no treatment did not show an improvement in relapse-free or overall survival, with one study reporting inferior relapse-free and overall survival for patients that received maintenance chemotherapy (29). In addition, maintenance therapy was associated with significant toxicity. Although the power of the individual studies to detect a difference in outcome is limited, with currently available agents, maintenance therapy following consolidation cannot be recommended. There is insufficient data to make a firm recommendation regarding the role of maintenance chemotherapy in patients not eligible for intensive consolidation.

4. THE ROLE OF MYELOID COLONY-STIMULATING FACTORS

Question

What are the roles of granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor in conjunction with chemotherapy in older patients (age > 55 years) with newly diagnosed AML?

Results

Literature Search Results

Fifteen publications were identified that met the eligibility criteria (Table 6). Some trials included patients with APL. One study evaluating a growth and development factor as a thrombopoietic agent was excluded from the analysis. The included publications were categorized as:

1. Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) as an inducer or more rapid granulocyte recovery and primary prophylaxis of infection: evaluated in ten trials (25,41-49).
2. G-CSF as an initiator of cell cycling for chemotherapy sensitization: evaluated in one trial (27).
3. Both of the concepts identified in the above two categories: evaluated in one trial (40).
4. Quality of life and/or economic outcome measures: evaluated in three trials (50-52).

Quality Assessment

Of 12 trials evaluating myeloid colony-stimulating factors, two trials scored four points (44,46), two trials scored three points (45,48), and the remaining trials scored two or less points, using the Jadad quality assessment tool. All trials were multicentred. Two trials (40,44) stated their method of randomization, and treatment allocation was concealed in three (44,46,47). Seven trials stated that either the study drug was blinded or double-blinding was used (27,43-48), although only one double-blinded trial indicated who was blinded (44). Three studies were not placebo controlled (40-42). The number and reasons for withdrawals and dropouts in each arm after randomization were provided in three trials (40,48,49). An imbalance at baseline for age between arms was noted in one trial (45), minimal baseline comparison information was provided in another (42), and no information was provided in four trials (25,27,46,47). Arms were balanced for all or a list of characteristics in the remaining trials. Pharmaceutical authorship or sponsorship was noted in six trials (27,41-45). Ten trials stated a power calculation was used (27,40-46,48,49), although one study (43) was underpowered to detect CR. Five trials conducted a true ITT analysis for at least one outcome (excluding toxicity) of interest to this guideline (43,44,46,47,49); two trials (40,41) conducted ITT analyses for all outcomes (excluding toxicity). One trial was terminated because no benefit was shown for the primary outcome (49) and another because the study drug was no longer available (47). One trial changed their eligibility criteria part way through the study to exclude APL (44).

A factorial design was noted in six trials (25,27,40-43). One trial accounted for the factorial design when analyzing remission (25), and another trial may have also accounted for design in one outcome (27). A seventh trial may have also been factorial in design (44). One study used one-tailed p-values for statistical significance in favour of growth factor and included patients with prior myeloid growth factor treatment (48). Methodologic rigour was not assessed for the studies evaluating economics.

Table 6. Studies of myeloid colony-stimulating factors in patients with AML.

First author, Year, Type of publication (reference)	Patient population	Intervention	
		Induction	Randomized study drug
Growth factor: Inducer of granulocyte recovery and prophylaxis of infection			
Lowenberg et al, 1997, full paper (42)	1° and 2° AML. 3 pts APL included. Age ≥ 61y.	DNR and ARA-C	GM-CSF vs. no GM-CSF (d-1 to max 28 d). Included in consolidation therapy.
Witz et al, 1998, full paper (43)	1° AML. 7 pts APL included. Age 55-75y.	IDR and ARA-C	GM-CSF vs. placebo (d1 to max d28).
Stone et al, 1995, full paper (44)	1° AML. 15 pts APL included. Age ≥ 60y.	DNR and ARA-C	GM-CSF vs. placebo (day after ARA-C completed until a defined event).
Rowe et al, 1995, full paper (45)	1° AML. 6 pts APL included. Age 56-70 y.	DNR and ARA-C	GM-CSF vs. placebo (d11 to max 42d). Given after consolidation.
Heil et al, 1997, full paper, subgroup analysis (46)	1° AML. APL in subset NR. Age ≥ 50y subset.	DNR, ARA-C, and VP-16	G-CSF vs. placebo (24h after last chemotherapy dose to max 28d). Given after consolidation.
Heil et al, 1995, full paper, subgroup analysis (47)	1° AML. APL in subset NR. Age > 50y subset.	DNR, ARA-C, and VP-16	GM-CSF vs. placebo (48h before 2nd induction and subsequent courses until defined event).
Godwin et al, 1998, full paper (48)	1° and 2° AML. APL excluded. Age ≥ 56y.	DNR and ARA-C	G-CSF vs. placebo (d11 until defined event). Given after postremission chemotherapy.
Dombret et al, 1995, full paper (49)	1° AML. No APL included. Age ≥ 65y (age 64y included).	DNR and ARA-C	G-CSF vs. placebo (d9 to max 28d). Given after salvage therapy.
Löfgren et al, 2004, full paper (41)	1° AML. APL excluded. Age ≥ 60y.	MTX, ARA-C, and VP-16	GM-CSF vs. no GM-CSF (d-1 until defined event). Given with consolidation.
Goldstone et al, 2001, full paper, subgroup analysis (25)	1°/2° AML. Age of subset unknown. Unknown if APL included in subset.	DNR/ARA-C, IDR/ARA-C, or MXT/ARA-C	G-CSF vs. placebo (d8 after one course of chemotherapy for max 10d)
Growth factor: Initiator of cell cycling for chemotherapy sensitization			
Rowe et al, 2004, full paper (27)	1° AML. Age > 55y.	DNR and ARA-C vs. MTX and ARA-C vs. IDR and ARA-C	GM-CSF vs. placebo as of June 1994 (48h before induction until marrow free of residual leukemia). If marrow free of residual leukemia, open-label GM-CSF given until neutrophil recovery. GM-CSF given to all pts after consolidation.

Table 6 (continued). Studies of myeloid colony-stimulating factors in patients with AML.

First author, Year, Type of publication (reference)	Patient population	Intervention	
		Induction	Randomized study drug
Growth factor: Inducer, Prophylaxis of infection, Initiator of cell cycling			
Amadori et al, 2003, full paper (40)	1° AML. Age 61-80y.	MTX, ARA-C, VP-16	G-CSF d1-7 vs. G-CSF d8-28 vs. G-CSF d1-28 vs. no G-CSF
Quality of life and economic analyses of trials evaluating growth factors in elderly AML			
Uyl-de Groot et al, 1998, full report (50)	Based on Lowenberg et al 1997 (42) patient population	Uyl-de-Groot et al 1998, full report (50)	Based on Lowenberg et al 1997 (42) patient population
Bennett et al, 1999, full report (51)	Based on Rowe et al 1995 (45) patient population	Bennett et al 1999, full report (51)	Based on Rowe et al 1995 (45) patient population
Bennett et al, 2001, full report (52)	Based on Godwin et al 1998 (48) patient population	Bennett et al 2001, full report (52)	Based on Godwin et al 1998 (48) patient population

Note: 1°=de novo, newly diagnosed, primary, or previously untreated; 2°=secondary; AML=acute myeloid leukemia; APL=acute promyelocytic leukemia; ARA-C=cytosine arabinoside; d=day; DNR=daunorubicin; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte-macrophage colony-stimulating factor; h=hour; IDR=idarubicin; max=maximum; MTX=mitoxantrone; NR=not reported; pts=patients; VP-16=etoposide; y=year.

Myeloid Growth Factors as Inducers of Granulocyte Recovery and Primary Prophylaxis of Infection

Outcomes

Trial results

The literature search identified ten published randomized trials (41-49) (1888 patients) testing the role of growth factors during the induction phase of therapy in older patients with AML. Six trials tested GM-CSF (41-45,47) (1202 patients), and four tested G-CSF (25,46,48,49) (912 patients). Eight trials (25,43-49) (1686 patients) were placebo controlled, and two (41,42) (428 patients) were open labelled. Eight trials (25,41-45,48,49) included only older patients and two trials (46,47) reported results of a subset of older patients included in trials that also enrolled younger patients. The latter two trials reported limited data for the subset of older patients. One trial included a subset of patients from a larger factorial design study (25).

Seven trials (41-45,48,49) reported neutrophil recovery, and six trials (41-45,49) demonstrated significantly faster recovery with the use of growth factors; however, only in one trial (45), comparing GM-CSF to placebo, did this translate into a survival difference (Table 7). This trial also reported a reduced number of grade 4/5 infections (10% vs. 36%, p=0.002) and, of patients with pneumonia (n-14 and n=13, respectively), deaths due to pneumonia (14% vs. 54%, p=0.046) in the growth factor arm. One trial (49) demonstrated an improved CR rate in the growth factor group, but this did not translate into improved survival. A borderline significant reduction in infection rates (p=0.05) (41) and increased DFS (Table 7) (43) in the growth factor group were observed in one trial each. Infections were measured differently among trials. Two of these trials (41,42) were factorial in design. Overall survival was not reported in one trial (46), and DFS was not reported in four trials (25,44,46,49).

Table 7. Additional outcome data for trials evaluating myeloid growth factors as inducers of granulocyte recovery and primary prophylaxis of infection.

Author, year	Intervention	Additional outcome data
Lowenberg et al 1997 (42)[A]	GM-CSF vs. no GM-CSF	N/A
Witz et al 1998 (43)	GM-CSF vs. placebo	Median DFS: 23 vs. 11 mo, p=0.003 (adjusted p=0.007)
Stone et al 1995 (44)	GM-CSF vs. placebo	Median OS: 8.4 vs. 10.8 mo, p=0.10
Rowe et al 1995 (45)	GM-CSF vs. placebo	Median DFS: 8.5 vs. 9.6 mo, p=0.95 (adjusted p=0.47) Median OS: 10.6 vs. 4.8 mo, p=0.048 (adjusted p=0.021)
Heil et al 1997 (46) (subgroup)	G-CSF vs. placebo	N/A
Heil et al 1995 (47) (subgroup)	GM-CSF vs. placebo	DFS at 41 mo: 20% vs. 31%, p=0.28 OS at 43 mo: 24% vs. 50%, p=0.08
Godwin et al 1998 (48)	G-CSF vs. placebo	Median DFS: 8 vs. 9 mo, one-tailed p=0.38 Median OS: 6 vs. 9 mo, one-tailed p=0.71
Dombret et al 1995 (49)	GM-CSF vs. placebo	N/A
Löfgren et al 2004 (41)[A]	GM-CSF vs. no GM-CSF	Median OS: 9 vs. 14 mo, p=0.07
Goldstone et al 2001 (25) (subgroup)	G-CSF vs. placebo	3y OS: 15% vs. 18%, p=0.10

Note: DFS=disease-free survival; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte-macrophage colony-stimulating factor; mo=months; N/A=not applicable; OS=overall survival; vs.=versus.
[A]Factorial design trial not analyzed according to design.

Seven trials evaluated neutrophil recovery, five trials reported days in hospital, and three trials reported antibiotic use; reporting of median values of these endpoints precluded pooling of these data. Data ranges for these outcomes are shown in Table 8. Outcomes were assessed and analyzed differently among trials. Time to neutrophil recovery was significantly faster with growth factors in six trials (41-45,49), including one trial (41) that evaluated mean time to neutrophil recovery. The seventh trial (48) did not provide a p-value for the median data but reported a faster recovery using another analysis. Time in hospital was not statistically significant in any of the five trials that reported this outcome (42-45,48). Antibiotic use was significantly shorter in one trial (43) and borderline significant in another (one-tailed p=0.053) (48). Two of these trials (41,42) were factorial in design.

Table 8. Growth factor versus control for outcomes reported with median data.

Outcomes	Growth factor (range, median days)	Control (range, median days)
PMN recovery (n=6) (42-45,48,49)[A]	13 to 24	17 to 29
Days in hospital (n=5) (42-45,48)[B]	28 to 36	29 to 38
Antibiotic use (n=3) (42,43,48)	20 to 23	16 to 26

Note: PMN recovery=time to neutrophil recovery (polymorphonuclear recovery).
[A]In Lowenberg et al 1997, 74% evaluable patients. In Dombret et al 1995 (49), 51% evaluable (patients in CR) and cutpoint 1000 x10^6/L. All other trials evaluating neutrophil recovery at a cutpoint of 500 x 10^6/L.
[B]In Rowe 1995, 79% evaluable patients (45).

Aggregate data meta-analysis

An aggregate data meta-analysis pooling results of the published studies of GM-CSF or G-CSF was performed. Using a random effects model, a meta-analysis did not detect a difference between groups who did or did not receive growth factors with respect to complete response rate (RR, 1.03; 95% CI, 0.93 to 1.15; p=0.53) (Figure 5), DFS (HR, 0.84; 95% CI, 0.63 to 1.14; p=0.27) (Figure 6), overall survival (HR, 0.94; 95% CI, 0.79 to 1.13; p=0.52) (Figure 7), infection rates (RR, 0.96; 95% CI, 0.86 to 1.06; p=0.41) (Figure 8), or infectious death (RR, 0.97; 95% CI, 0.62 to 1.54; p=0.91) (Figure 9). A high level of statistical heterogeneity (I^2 > 50%) was observed for overall survival, a moderate level of heterogeneity (I^2 < 50%)_for DFS, complete response, and infection rates, and a low (I^2 < 25%) level of heterogeneity was observed for infectious death.

Figure 5. Meta-analysis of complete response for growth factor versus control in induction.

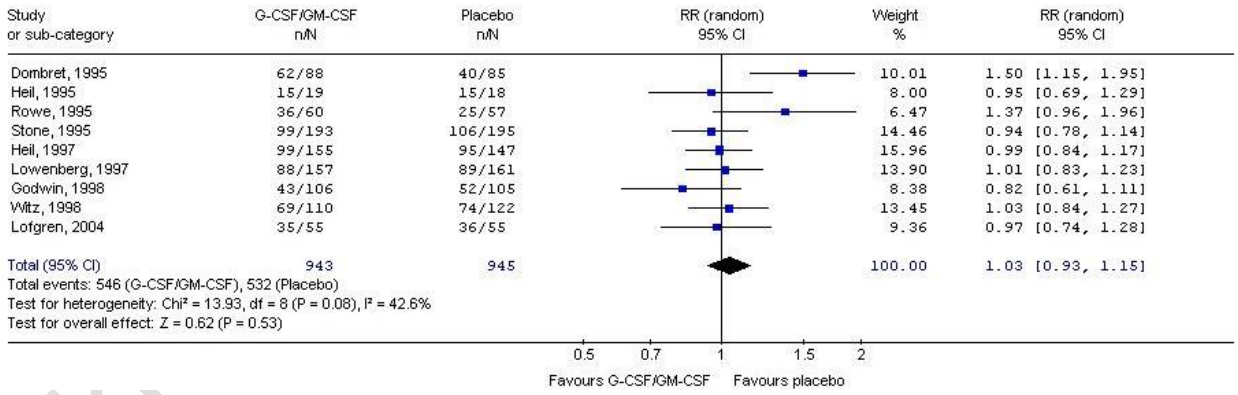
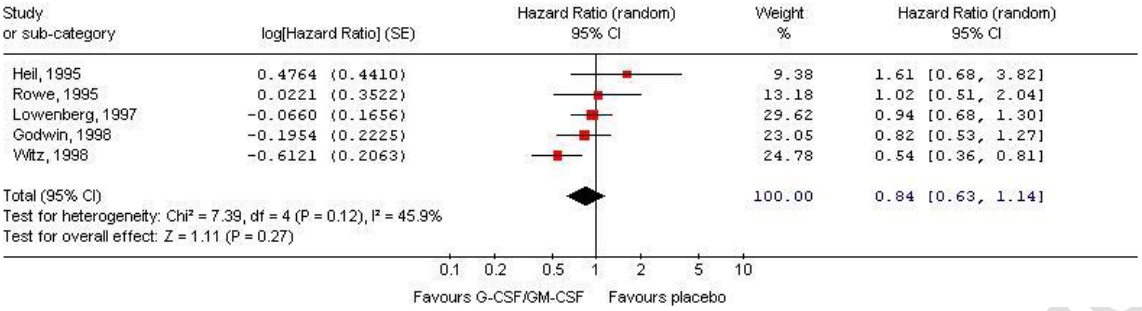


Figure 6. Meta-analysis of disease-free survival for growth factor versus control in induction.



Note: In Rowe 1995, authors did not indicate death as an endpoint in the analysis.

Figure 7. Meta-analysis of overall survival for growth factor versus control in induction.

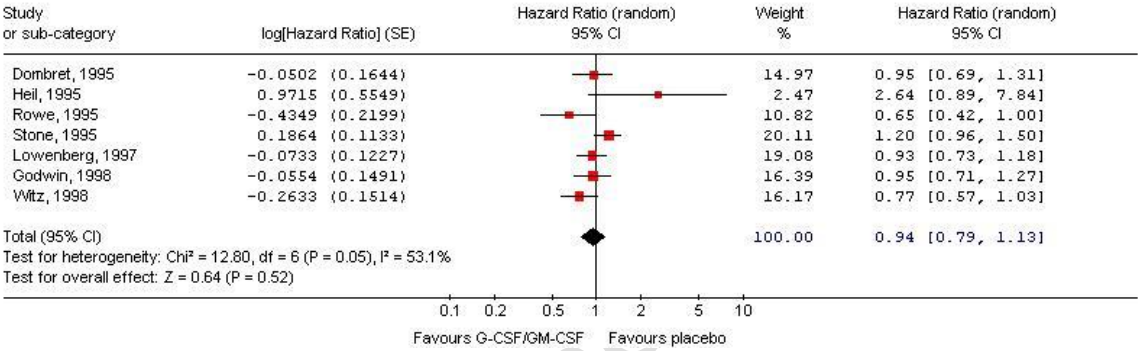


Figure 8. Meta-analysis of infection rates for growth factor versus control in induction.

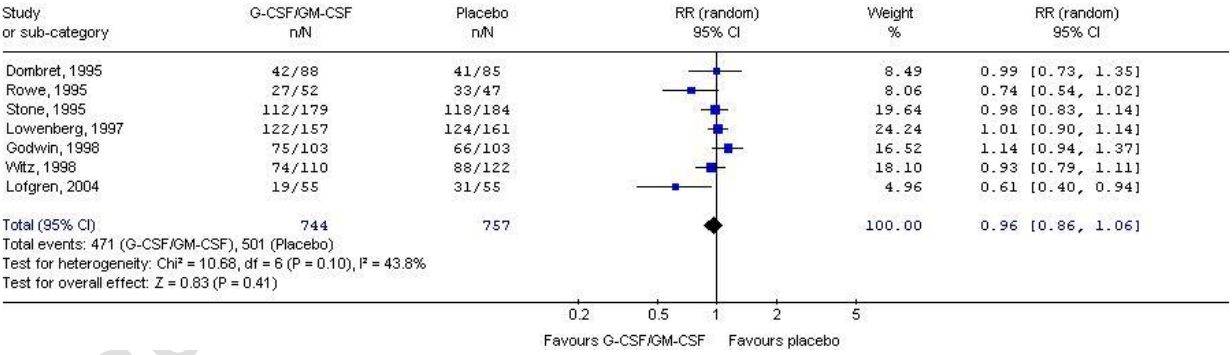
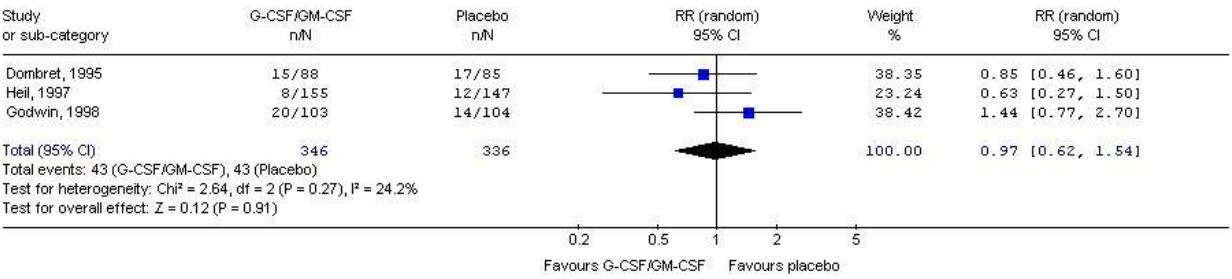


Figure 9. Meta-analysis of infectious death for growth factor versus control in induction.



Toxicity

Toxic death and early death and/or death in hypoplasia were each reported in three studies (Table 9). No studies reported a significant difference. Toxicities were inconsistently reported among the studies (Table 9). Two studies reported that some toxicities occurred more frequently with growth factor (42,47). One study reported some toxicities occurred more frequently with placebo or with growth factor (45). No difference between arms was observed in a majority of studies. Two studies did not provide toxicity information (25,46).

Discontinuation of the growth factor because of adverse events or intolerance in four studies occurred in the range of 4% to 40% (41-44). Two of the studies also reported 4% and 31% occurrence with placebo, respectively (43,44), which was significantly lower than growth factor in one (43). In one elderly subject study, authors state that one elderly patient refused further treatment after entering CR because of severe stomatitis, but no other information was specifically reported for the elderly subset population (47). One study reported that no withdrawals occurred because of toxicity (45). Remaining studies did not provide this information for the elderly population.

Table 9. Toxicity data for trials evaluating myeloid growth factors as inducers of granulocyte recovery and primary prophylaxis of infection.

Author, year, intervention	Toxic death	Toxicities
Lowenberg et al 1997 (42)[A] GM-CSF vs. no GM-CSF	NR early death/ death in hypoplasia: 14% vs. 13%, p=NR	*First induction cycle* Significantly more with GM-CSF: diarrhea, renal abnormalities, fever, cutaneous toxicity, hypotension, fluid retention, chills, phlebitis (p<0.05 for all) No difference between arms: hemorrhages, liver abnormalities, oral toxicity, nausea, cardiac rhythm abnormalities, neurotoxicity, bone pain, infections (no p provided).
Witz et al 1998 (43) GM-CSF vs. placebo	NR early death/death in hypoplasia: 18% vs. 15.5%, p=NR	No difference between arms for grade ≥3: hepatic toxicity, cardiac toxicity, oral mucositis, vomiting, intestinal toxicity.
Stone et al 1995 (44) GM-CSF vs. Placebo	Early deaths: 7% vs. 7%, p=NS Death in hypoplasia: 20% vs. 16%, p=NR	No difference between arms for nonhematologic toxicity.
Rowe et al 1995 (45) GM-CSF vs. Placebo	6% vs. 15%, p=0.18	Increase in placebo group: grade 3/4 hepatic and neurologic toxicity (no analysis provided). Significantly more with GM-CSF: grade 1/2 skin toxicity (p=0.002) No difference between arms for other toxicities.
Heil et al 1997 (46) (subgroup) G-CSF vs. Placebo	NR in SS	NR in SS
Heil et al 1995 (47) (subgroup) GM-CSF vs. Placebo	NR in SS	Duration of thrombocytopenia <25000/μL longer in GM-CSF after second induction for whole cohort, being more prominent in elderly subset (no analysis provided).
Godwin et al 1998 (48) G-CSF vs. Placebo	20% vs. 19% p=NR	Nonhematologic toxicities similar between arms. Bone pain: G-CSF, 1 pt vs. placebo, 5 pts; p=NR. No difference for duration of thrombocytopenia from start of chemotherapy (p=0.80).
Dombret et al 1995 (49) GM-CSF vs. Placebo	At 8 wk: 1.1% vs. 2.4%, p=NS	No marked side effects in either arm.
Löfgren et al 2004 (41)[A] GM-CSF vs. no GM-CSF	NR	Liver damage, renal failure, and heart failure in both arms at frequencies of 27% or less (no statistical analysis).
Goldstone et al 2001 (25) (subgroup) G-CSF vs. placebo	NR	NR

Note: G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte-macrophage colony-stimulating factor; NR=not reported; NS=not significant; pt(s)=patient(s); SS=elderly subset; vs.=versus; wk=week.
[A]Factorial design trial not analyzed according to design.

G-CSF as an Initiator of Cell Cycling for Chemotherapy Sensitization

Outcomes

Trial results

One (27) randomized trial of priming with GM-CSF in older adult patients (> 55 years) with AML was identified. Rowe et al (27) tested priming with GM-CSF (n=113) or placebo (n=125) starting 48 hours before induction therapy and continuing until the marrow was free of leukemia on day 10 of the first or second cycle of induction therapy, after which all patients with clear marrows received the study medication until neutrophil recovery (> $1.5x10^9$/L). Patients were also randomized to induction therapy, which was not accounted for in the analyses. Randomization to growth factor started part way through the enrollment period. The CR rate in the two groups was not significantly different nor was the therapy-related mortality, median DFS, or median overall survival (Table 10). This study may have been underpowered to detect CR and DFS.

Toxicity

No toxicity information was provided.

Combined Evaluation of Roles for Prophylaxis and Cell Cycle Sensitization

Outcomes

Trial results

In a prospective, randomized, multicentre trial, Amadori et al (40) investigated G-CSF administered during and/or after induction chemotherapy in patients aged 61–80 years with previously untreated AML. A total of 722 patients were randomized equally in four arms (Table 10). Complete remission, DFS, and overall survival were not significantly different between groups (Table 10).

Toxicity

The frequencies of grade 3/4 infection were similar between the four arms (Table 10). In addition, the frequencies of grade 3/4 adverse events were similar between each arm for the following: hemorrhage, hepatic, cardiovascular, hypotension, diarrhea, nausea, rigors/chills, bone pain, and rash/itch.

Table 10. Additional trials assessing growth factors.

Author, year (ref)	Intervention	N	CR	DFS	OS	Infectious death	Infections	Toxic death	Antibiotic use	Days in hospital	PMN recovery (>500 x 10^6/L)	Additional toxicities
Growth factor: Initiator of cell cycling for chemotherapy sensitization												
				median:	median:			death in induction:				
Rowe 2004 (27)[A]	GM-CSF vs.	113	36%	6.9 mos	5.3 mos	NR	NR	26%	NR	NR	NR	NR
	placebo	125	43%[B] p=NS	5.1 mos p=0.73[C]	8.5 mos p=0.11[C]			17% p=0.11[C]				
Growth factor: Inducer, Prophylaxis of infection, Initiator of cell cycling												
				3-yr:	3-yr:							
Amadori 2005 (40)	G-CSF d1-7 vs.	180	52.2%	17.6%	18.3%	NR	23.1%	NR	NR	NR	NR	NR
	G-CSF d8-28 vs.	180	48.3%	18.6%	14.4%		31.2%					
	G-CSF d1-28 vs.	180	64.4%	14.5%	7.6%		25.4%					
	no G-CSF	182	48.9% p=NR	21.5%	15.2%		27.0%					

Note: CR=complete response/remission; d=day; DFS=disease-free survival; G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte-macrophage colony-stimulating factor; mos=months; N=number of patients randomized; NR=not reported; NS=not significant; OS=overall survival; PMN=polymorphonuclear; ref=reference; vs.=versus; yr=year.

[A]Factorial design trial not analyzed according to design.

[B]Data provided in the text of article. Analysis based on n=235 patients.

[C]Evaluable patients not clear in the article.

Quality of Life / Economic Analyses

Analyses of the effect of growth factor use on quality of life or economic endpoints have been published (50-52) using data from growth factor trials in the elderly. All the economic analyses were retrospective and are several years out of date.

Uyl-de Groot et al (50) evaluated the cost effectiveness and quality of life of GM-CSF used as an adjunct to intensive remission induction chemotherapy in patients older than 60 years of age, using data from the trial by Lowenberg et al (42). No differences in CR, DFS, or overall survival were observed between the two arms. The cost effectiveness and a variety of quality of life assessments were performed in the subset of patients from the Netherlands. Compared with placebo-treated patients, the GM-CSF patients had more frequent problems with lack of energy, depressed mood, diarrhea, and rash/eczema (Table 10) during the period of hospitalization, but this was not apparent after hospitalization or after six months. No difference in quality-adjusted discounted survival was detected between the two groups. The average costs of initial (to the end of consolidation) treatment were higher in the GM-CSF treated group than in the control group (Table 11); costs during the follow-up period (two years maximum) were not significantly different between the groups (p-value not reported).

Bennett et al (51) performed an economic analysis of the trial of Rowe et al (45) evaluating GM-CSF in 117 older patients (56–70 years) with AML. Analyses using a decision analysis model were conducted on 88 patients (Table 11). GM-CSF patients had fewer grade 4/5 infections (9.6% vs. 36%, p=0.002) and, although not statistically significant, fewer grade 3 – 5 infections (52% vs. 70%, p=0.07) than placebo, which resulted in an estimated inpatient cost savings of $2310 (Table 11). This analysis is limited by its reliance on modeling rather than capturing actual resource utilization, and by the fact that it is from the only positive study for overall survival among those published to date. In addition, the model assumed that there were no differences in clinical outcomes between groups in the trial.

Bennett et al (52) performed an economic analysis of a randomized trial of G-CSF in 207 older patients (≥ 56 years) with AML using data from the study by Godwin et al (48). Again, a decision analysis model was used (Table 11), based on inpatient care and factoring in active infections requiring antibiotics during induction. Though G-CSF was found to hasten neutrophil recovery and patients receiving G-CSF required possibly fewer days of IV antibiotics (22 vs. 26 days, one-tailed p=0.05), the number of days in hospital was similar. The use of G-CSF did not result in cost savings (Table 11; no statistical analysis provided).

Table 11. Quality of life and economic analyses of trials evaluating growth factors in elderly patients with acute myeloid leukemia.

Study, year	Treatment	Quality of Life	Cost-effectiveness
Uyl-de-Groot et al 1998 (50) Based on Lowenberg et al 1997 (42)[A]	Induction: DNR/ARA-C At d-1, ± GM-CSF	• n≤30 for assessments • variety of questionnaires • Rotterdam Symptom Checklist[B]: p<0.05 for lack of energy, depressed mood, diarrhea, and rash/eczema during hospitalization • no differences in other questionnaires reported	• cost-effectiveness to the end of consolidation: GM-CSF: US $40782 vs. placebo: US$34465; p<0.01 • unclear number of patients in the analysis
Bennett et al 1999 (51) Based on Rowe et al 1995 (45)	Induction: DNR/ARA-C At d11, GM-CSF vs. placebo	NR	• Based on n=88 pts who received GM-CSF or placebo and survived induction treatment • Decision analysis model; factored in one or two cycles of induction and occurrence of grade 3-5 infections • Inpatient costs: GM-CSF: US $38412 placebo: US$40722 (no statistical analysis provided)
Bennett et al 2001 (52) Based on Godwin et al 1998 (48)	Induction: DNR/ARA-C At d11, G-CSF (n=104) vs. placebo (n=103)	NR	• Decision analysis model based on inpatient care factoring in active infections requiring antibiotics during induction • estimated costs: G-CSF: US$50593 placebo: US$49693 (no statistical analysis provided)

Note: ARA-C=cytosine arabinoside; d=day; DNR=daunorubicin; GM-CSF=granulocyte-macrophage colony stimulating factor; G-CSF=granulocyte colony-stimulating factor; n=number; pts=patients; y=year.
[A]Factorial design trial not analyzed according to design.
[B]Validated questionnaire (http://www.med.rug.nl/nch/rscl.pdf).

Discussion

Seven of 12 RCTs evaluating the use of growth factors in older patients undergoing intensive induction therapy for AML reported that treatment with G-CSF or GM-CSF with or following chemotherapy shortens the duration of neutropenia. However, an aggregate data meta-analysis of those trials did not detect differences in the more clinically important outcomes of infectious deaths, CR, DFS, or overall survival. There is, therefore, insufficient evidence to support the routine use of myeloid growth factors as an adjunct to intensive chemotherapy in older patients undergoing treatment for AML. Similarly, the use of G-CSF as an initiator of cell cycling for chemotherapy sensitization also did not result in detectable differences in DFS, overall survival, or CR. Thus, the use of G-CSF for this purpose is also not recommended.

The drug acquisition costs for growth factors are considerable. However, these costs could, in theory, be offset by a reduction in treatment-related toxicity and the associated costs of supportive care. Retrospective analyses have not shown a reduction in treatment costs or quality of life benefit attributable to growth factor use. More importantly, the generalizability of those analyses is limited, given that the data were retrospectively collected and that the analyses and supporting data are several years out of date. The DSG agreed that the quality of those analyses is limited and, therefore, so is their generalizability. Given the lack of evidence of a clinical benefit for growth factors and as the generalizability of the studies examining cost is limited, there is insufficient evidence to support a recommendation to use growth factors during the induction phase of chemotherapy for older patients with AML.

5. PROGNOSTIC FACTORS

Question

What disease and patient related parameters can be used to identify older patients (age > 55 years) who are more or less likely to benefit from aggressive induction therapy?

Results

Although the data reviewed suggest that standard-dose induction chemotherapy may be offered to patients with similar characteristics and performance status as those included in the randomized trials, it would be valuable to identify patients who are more likely to benefit from intensive, but potentially curable, treatment from those with a low likelihood of cure, for whom palliative treatment and a focus on quality of life may be most appropriate. Identifying host-related and disease-related prognostic factors may provide a more rational basis upon which to base those decisions.

Several prognostic factors, both clinical and biological, have been identified in the literature; however, due to the heterogeneity of these studies, the influence of any one of these factors is unclear. Of the 44 randomized trials reviewed in this guideline, 11 (2,15,25,26,29,37,42-44,48,53-55) evaluated specific factors that were thought to influence outcome specifically in older patients with AML (Tables 12 and 13).

Age has long been recognized as an important, independent prognostic factor in AML. Age-related declines in physiology and deterioration in organ function likely contribute. In four studies (2,25,29,44,53) increasing age was found to significantly affect remission rates, and in five (2,25,26,48,53,54) it was also found to affect survival. The age above which remission and survival rates appeared to decrease was variable across the studies that explored an age effect, and thus a clear age cut-off cannot be defined.

Cytogenetic abnormalities associated with treatment failure in younger patients are much more common in older patients and also likely contribute to their poor outcome. Conversely, the favourable cytogenetic abnormalities are more common in the younger patients and contribute to their improved survival.

Unfortunately, there is considerable variability in the risk categorization of cytogenetics in the studies, so that the results cannot be pooled. From the UK MRC AML 11 trial, Grimwade et al (53) identified three prognostic cytogenetic groups in older patients; (i) a favourable group (t(15,17), t(8,21) and inv(16)) that had a complete remission rate of 72% and a 2 year overall survival of 46%, (ii) an intermediate group (normal karyotype or non-complex karyotype, including trisomy 8 and 11q23 abnormalities) that had a CR rate of 63% and two-year overall survival of 26%, (iii) poor prognosis group (complex karyotypes [five or more], -5/7, del 5q or 3q) that had a CR rate of 26% and two-year overall survival of 5%. Anderson et al (2) grouped cytogenetic abnormalities using the Southwest Oncology Group (SWOG) criteria and similarly found that the group with unfavourable cytogenetics (complex, > 3 abnormalities, inv [3q], -5/5q, -7/7q, 11q or 17p, del [20q], +13, t (9,22)) had a CR rate of 34% as compared with 44% in the group with favourable/intermediate (fav/int) cytogenetics (p=0.0026) and a two-year overall survival of 7% compared with 22% (p=0.0056). Using the same classification system, the SWOG 9031 study (48,54) found a CR rate of 21% for the unfavourable group as compared to 55% for the fav/int group (p=0.0031). Overall survival was also significantly poorer for patients with unfavourable cytogenetics (p<0.0001). Rowe et al (27) assessed the prognostic value of the SWOG classification in a trial by the Eastern Cooperative Oncology Group (ECOG) that showed that patients with unfavourable cytogenetics had significantly inferior CR and median overall survival in comparison to those with intermediate or favourable cytogenetics.

Three (15,42,43) of four additional studies (15,37,42,43), using different cytogenetic risk categorizations found significantly inferior CR rates in the adverse cytogenetic risk groups

(13-42%). Three studies (15,42,43) also reported inferior survival for older patients with poor-risk cytogenetics.

Table 12. Prognostic factors for complete response (percent of patients).

Study (ref)	Age	Cytogenetic risk	Primary vs secondary	WBC	MDR status			Performance Status	CD34	
					+ bright	+ dim	-		+	-
Rowe, 2004 (27)	NR	Fav: 67% Int: 50% Unfav: 30% p=0.003	NR	NR	NR	NR	NR	NR	NR	NR
Goldstone, 2001 (25) Grimwade, 2001 (53)	CR rate ▼ as age ▲ *p=$2x10^{-5}$	Fav: 72% Int: 59% Adv: 26% *p=$2x10^{-14}$	Primary AML associated with CR *p=$5x10^{-7}$	▲ WBC associated with CR *p=$4x10^{-6}$	NR	NR	NR	CR rate ▼ in poorer performance status groups *p=$3x10^{-4}$	NR	NR
Godwin, 1998 (48) Leith, 1997 (54)	56-64: 47% ≥65: 44% p=0.59	Fav/Int: 55% Unfav: 21% p<0.0001	52% vs 24% p<0.0005	NS p=NR	34%	45% p=0.0019	67%	NR	38%	59% p=0.0027
Stone, 2001 (37)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Löwenberg, 1998 (26)	60-69: 44% 70-79: 43% 80-88: 14% p=0.074	NR[A]	44% vs 37% p=0.21	<$25x10^9$/L: 48% 25-$99x10^9$/L: 32% $100x10^9$/L: 36% p=0.006	NR	NR	NR	NR	NR	NR
Anderson, 2002 (2)	56-64: 47% ≥65: 33% *p=0.0026	Fav/Int: 44% Unfav: 34% *p=NS	42% vs 26% *p=0.018	<$10x10^9$/L: 41% ≥$10x10^9$/L: 35% *p=NS	37%	37% *p=NS	40%	0-1[B]: 40% 2-3[B]: 30% *p=NS	39%	37% *p=NS
Stein, 1990 (29)	51-60: 57% >60: 38% p=0.002	NR	43% vs 26% p=0.17	≤$10x10^9$/L: 49% >$10x10^9$/L: 41% p=0.27	NR	NR	NR	≤60[C]: 27% >60[C]: 47% p=0.06	NR	NR
Baer, 2002 (55)	<70: 48% ≥70: 38% p=0.28	Fav: 50% Int: 54% Adv: 13% p=0.04	43% vs 36% p=0.44	NR	NR	NR	NR	NR	NR	NR
Stone, 1995 (44)	CR rate ▼ as age ▲ *p=0.04	NR	NA	NS	NR	NR	NR	Normal activity: 60% Debilitated: 20% *p=0.001	NR	NR
Witz, 1998 (43)	55-64: 61% 65-75: 62% p=0.99	Fav: 77% Int/Unfav: 42% p=0.0003	NA	<$30x10^9$/L: 67% >$30x10^9$/L: 45% p=0.003	NR	NR	NR	0-1[D]: 65% 2-4[D]: 55% p=0.19	NR	NR
Löwenberg, 1997 (42)	61-69: 56% 70-79: 56% ≥80: 44% p=0.83	Fav: 75% Int: 54% Unfav: 36% p=0.008	56% vs 55% p=0.96	<$30x10^9$/L:	NR	NR	NR	0[D]: 66% 1[D]: 54% 2[D]: 43% 3[D]: 50% p=0.008	NR	NR
Feldman, 1997 (15)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Notes: Adv=adverse; AML=acute myeloid leukemia; CR=complete response; Fav=favourable; Int=intermediate; MDR=multi-drug resistance; NA=not applicable; NR=not reported; NS=not significant; ref=reference; Unfav=unfavourable; vs=versus; WBC=white blood count; ▲=increased or higher; ▼=decreased or lower.
[A]Authors reported an uninterpretable classification.
[B]Performance status by Southwest Oncology Group (SWOG) criteria.
[C]Karnofsky performance status.
[D]Performance status by World Health Organization (WHO) criteria.
*Multivariate analysis.

Table 13. Prognostic factors for overall survival (percent of patients).

Study (ref)	Age	Cytogenetic risk	Primary vs secondary	WBC	MDR status			Performance status	CD34 status	
					+ bright	+ dim	-		+	-
Rowe, 2004 (27)	NR	Mdn Fav: 15.1 mos Int: 10.1 mos Unfav: 5.1 mos p=0.002	NR	NR	NR	NR	NR	NR	NR	NR
Goldstone, 2001 (25) Grimwade, 2001 (53)	5-yr <70: 16% ≥70: 11% *p=0.0001	5-yr Fav: 34%* Int: 13% Adv: 2% *p=$8x10^{-11}$	Secondary AML had poorer OS *p=$2x10^{-6}$	5-yr >$100x10^9$/L: 7% <$100x10^9$/L: 15% *p=$6x10^{-13}$	NR	NR	NR	OS ▼ in poorer performance status groups *p=$2x10^{-6}$	NR	NR
Godwin, 1998 (48) Leith, 1997 (54)	OS ▼ as Age ▲ *p=0.014	Fav/Int: NR Unfav: NR *p<0.0001	Mdn 8 mos vs 7 mos *p=0.29	OS ▼ as WBC ▲ *p=0.029		NS *p=0.93		NR	NS *p=0.45	
Stone, 2001 (37)	Mdn 60-69: 20 mos ≥70: 19 mos p=0.52	Mdn CBF: 11 mos abnormal: 19 mos normal: 16 mos p=NS	NR	Mdn <$30x10^9$/L: 21 mos ≥$30x10^9$/L: 13 mos p=0.001	NR	NR	NR	NR	NR	NR
Löwenberg, 1998 (26)	OS ▼ as Age ▲ p=0.01	NR[A]	Secondary AML had poorer OS p=0.02	OS ▼ as WBC ▲ p=0.001	NR	NR	NR	OS ▼ in poorer performance status groups p<0.001	NR	NR
Anderson, 2002 (2)	OS ▼ as Age ▲ *p=0.024	2-yr Fav/Int: 22% Unfav: 7% *p=0.0001	2-yr 16% vs 10% *p=NS	OS ▼ as WBC ▲ *p=0.053	11%	2-yr 7% *p=NS	14%	2-yr 0-1: 15% 2-3: 12% *p=0.029	2-yr 20% 12% *p=NS	
Stein, 1990 (29)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baer, 2002 (55)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stone, 1995 (44)	NR	NR	NA	NR	NR	NR	NR	NR	NR	NR
Witz, 1998 (43)	NS	OS ▼ in poorer cytogenetic risk groups *p=0.0001	NA	OS ▼ as WBC ▲ *p=0.0002	NR	NR	NR	NS	NR	NR
Löwenberg, 1997 (42)	NS	OS ▼ in poorer cytogenetic risk groups p<0.001	NR	NR	NR	NR	NR	NR	NR	NR
Feldman, 1997 (15)	2-yr <69: 24% >70: 20% p=NS	10-mos Fav: 75% Int: 50% Unfav: 8% Sig diff, p=NR	NS	NR	NR	NR	NR	18-mos 0-1[C]: 27% >1[C]: 8% Sig diff, p=NR	NR	NR

Notes: Adv=adverse; AML=acute myeloid leukemia; CBF=core binding factor; Fav=favourable; Int=intermediate; MDR=multi-drug resistance; mos=months; NA=not applicable, NR=not reported; NS=not significant; OS=overall survival; ref=reference; sig diff=significant difference; Unfav=unfavourable; vs=versus; WBC=white blood count; yr-year(s); ▲, increased or higher; ▼, decreased or lower.

[A]Authors reported an uninterpretable classification.

[B]Performance status by Southwest Oncology Group (SWOG) criteria.

[C]Performance status by Eastern Cooperative Oncology Group (ECOG) criteria.

*Multivariate analysis.

Prior myelodysplastic disorders are present in up to 40% of older patients with AML (56). Eight (2,15,25,26,29,42,48,53-55) of the 11 studies evaluated the impact of antecedent hematological disorders on outcome, and four (2,25,26,48,53,54) detected a negative impact of secondary AML on remission rates or survival. Generally, remission rates in such patients are 20 - 30% lower than for elderly patients with de novo AML. For example in the study by Godwin et al (48) the CR rates were 24% and 53%, respectively (p=0.0035).

Patients with a poor performance status may not tolerate the rigours of chemotherapy and its ensuing complications. Eight (2,15,25,26,29,42-44,53) of the ten studies evaluated the impact of performance status, and in all but the SWOG (48,54) study, it was found to be predictive of lower remission rates and overall survival.

The prognostic value of presenting white cell count was evaluated in all but two (15,55) of the 11 studies, and in seven (2,25,26,37,43,44,48,53,54), an increasing white cell count had independent prognostic significance in terms of remission rates and/or overall survival.

Another potentially important biologic feature contributing to poor outcome is the intrinsic drug resistance of leukemic cells, partially mediated by expression of the multidrug resistance glycoprotein-MDR1. In the study by Leith et al (54), 71% of older patients enrolled in the SWOG 9031 trial (48,54) were MDR1-positive, compared with 30% of younger patients. These patients were less likely to achieve a CR (34-45% vs. 67%, p<0.0019) and more likely to have resistant disease. The significance of this is still unclear since additional studies have not confirmed this result (2).

FLT3 mutations and CD34 expression have variably been found to portend a poor prognosis in younger patients with AML but their prognostic significance in older patients is unknown, and larger prospective analyses will be needed to clarify their clinical significance.

Discussion

Although age is a significant predictor of outcome with conventional dose induction treatment, results have not been consistent across studies. Most reported trials have limited power to explore differences in remission rate and overall survival according to age strata. Patients enrolled in clinical trials are carefully chosen, and the remission rates and survival reported likely represent the best results that can be achieved at a particular age. Physicians should discuss with patients that the benefits of therapy decrease with increasing age and increasing comorbidity.

Patients with high-risk cytogenetics by any criteria and those with AML after a prior myelodysplastic syndrome have consistently lower rates of complete remission, shorter median survival, and a probability of survival at two years of < 10%, using currently available regimens. The presence of high-risk cytogenetic abnormalities at diagnosis should inform the discussion as to whether aggressive induction chemotherapy should be used. Such patients may prefer supportive care only, with attention to quality of life, but should also be considered appropriate candidates for clinical trials evaluating new treatment approaches at diagnosis.

Patients with impaired performance status also have a worse outcome with standard induction and consolidation treatment, independent of cytogenetic risk category. These patients are at greater risk of treatment-related toxicity and death during treatment and benefit less from standard induction therapy, in terms of overall survival. Conservative treatment with supportive and symptomatic care is an appropriate treatment consideration for those with performance status 2 or more.

There is currently insufficient information available to define the role of assessment of CD34 and pgp/MDR1 expression on leukemic blasts in aiding treatment decisions.

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (http://clinicaltrials.gov/) were searched for reports of new or ongoing randomized trials that included older patients with newly diagnosed AML. Six ongoing randomized trials were identified that enrolled patients with ages up to 60-70 years of age. Details of those trials can be found in Appendix 3. In addition, the following trials were ongoing as of November 27, 2007 and included older patients exclusively or had no age restrictions:

Protocol ID	Title and details of trial
DACO-016 NCT00260832	Trial of Decitabine in Patients with Acute Myeloid Leukemia. Age: ≥ 65 years. Outcomes: Not reported. Projected accrual: Not reported. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/viewclinicaltrials.aspx?cdrid=460099&version=healthprofessional&protocolsearchid=3902299&print=1.
C18477/3059/ AM/US-CA NCT00513305	Study of Low-Dose Cytarabine in Combination with Arsenic Trioxide, Compared with Low-Dose Cytarabine Alone, for the Treatment of Elderly Patients with Acute Myeloid Leukemia. Age: > 60 years. Outcomes: Not reported. Projected accrual: Not reported. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=565833&version=HealthProfessional&protocolsearchid=3902389.
AMLSG06-04 NCT00151255	All-Trans Retinoic Acid in Combination with Standard Induction and Consolidation Therapy in Older Patients with Newly Diagnosed Acute Myeloid Leukemia. Age: ≥ 61 years. Outcomes: Not reported. Projected accrual: Not reported. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=561080&version=HealthProfessional&protocolsearchid=3902393.
NCT00199147	Efficacy of G-CSF-Priming in Elderly AML Patients. Age: > 60 years. Outcomes: Remission rate after induction, remission duration, disease-free survival, overall survival, toxicity. Projected accrual: 250 patients. Accessed: November 27, 2007. Available at: http://clinicaltrials.gov/ct2/show/NCT00199147?term=NCT00199147&rank=1.
NCT00373373	Efficacy of Sorafenib Added to Standard Primary Therapy in Elderly Patients with Newly Diagnosed AML. Age: ≥ 61 years. Outcomes: Event-free survival, overall survival, response, toxicity. Projected accrual: 200 patients. Accessed: November 27, 2007. Available at: http://clinicaltrials.gov/ct2/show/NCT00373373?term=NCT00373373&rank=1.
EORTC-06012 AML-17 NCT00052299 GIMEMA-AML-17	Phase III Randomized Study of Standard Induction Chemotherapy with or without Gemtuzumab Ozogamicin in Elderly Patients with Previously Untreated Acute Myeloid Leukemia. Age: 61 - 75 years. Outcomes: Overall survival, response, disease-free survival, toxicity. Projected accrual: 450 patients. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=258151&version

	=HealthProfessional&protocolsearchid=3902471.
UHW-AML16 EU-20677 ISRCTN11036523 EUDRACT-2005-002846-14 MREC-CU106 NCT00454480	Phase II/III Randomized Study of Combination Chemotherapy with or without Gemtuzumab Ozogamicin or Tipifarnib in Patients with Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndromes. Age: Any age. Outcomes: Overall survival, response, toxicity. Projected accrual: 2000 patients. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=526121&version=HealthProfessional&protocolsearchid=3902493.
AMLCG 99 NCT00266136 BMBF 01 GI 02070	Biology and Treatment Strategy of AML in its Subgroups: Multicenter Randomized Trial by the German Acute Myeloid Leukemia Cooperative Group (AMLCG). Age: ≥ 16 years. Outcomes: Not reported. Projected accrual: Not reported. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=462327&version=HealthProfessional&protocolsearchid=3902513.
SWOG-S0521 NCT00492856 S0521	Phase III Randomized Study of Induction and Consolidation Combination Chemotherapy with or without Gemtuzumab Ozogamicin Followed by Maintenance Therapy Comprising Tretinoin, Mercaptopurine, and Methotrexate Versus Observation in Patients with Previously Untreated Low- or Intermediate-Risk Acute Promyelocytic Leukemia. Age: ≥ 18 years. Outcomes: Disease-free survival, overall survival, toxicity. Projected accrual: 500. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=553210&version=HealthProfessional&protocolsearchid=3902528.

CONCLUSIONS

Treatment decisions in older patients are complex and often influenced by comorbid illnesses, consideration of quality of life and patient preferences. The treatment recommendations described throughout this EBS may require alteration after discussion with patients and their families.

For patients with newly diagnosed, previously untreated AML with good performance status and minimal organ dysfunction or comorbidity who are aged 55 years and older, the Hematology DSG recommends full-dose induction (i.e., three days of an anthracycline and cytarabine 100-200 mg/m^2 as a seven-day continuous infusion). Full-dose induction treatment has resulted in superior outcomes (remission rates and survival) in comparison with therapy that includes reduced doses or is of palliative intent. Details of the analysis leading to this conclusion are presented in the section entitled "INTENSIVE vs. NONINTENSIVE THERAPY." Comparative data fail to demonstrate superior outcomes associated with the use of a specific anthracycline or anthracenedione agent, the details of which are discussed in the section entitled "THE CHOICE OF ANTHRACYCLINE OR ANTHRACENEDIONE IN INDUCTION THERAPY." Thus, the decision of which agent to use may be determined by factors other than treatment efficacy, such as drug acquisition costs, that may vary among institutions. For these reasons, each individual institution should determine their specific policies regarding the agent of choice. There is insufficient evidence to make a firm recommendation regarding the administration of consolidation therapy to older patients who have achieved a complete

remission. Based on DSG consensus, it is recommended that patients in complete remission with good performance status and who have recovered from any toxicity receive at least one cycle of consolidation with conventional or intermediate dose cytarabine with or without anthracycline. There is no role for maintenance therapy for patients in first complete remission. The routine use of myeloid growth factors as an adjunct to intensive chemotherapy in older patients is not recommended.

CONFLICT OF INTEREST

The members of the Hematology DSG were asked to disclose potential conflicts of interest relating to the topic of this systematic review. No conflicts were declared.

JOURNAL REFERENCES

When completed, the systematic review will be submitted to a peer-reviewed journal for consideration for publication.

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For a complete list of the Hematology DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/

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Appendix 1. Literature search strategy used in MEDLINE (OVID).

1. leukemia, myelocytic, acute/
2. acute myeloid leukemia.mp.
3. acute myelogenous leukemia.mp.
4. exp leukemia, nonlymphocytic, acute/
5. acute nonlymphocytic leukemia.mp.
6. or/1-5
7. (first line or induction or front line or initial therapy or previous: untreated or untreated).mp.
8. 6 and 7
9. limit 8 to ("all aged <65 and over>" or "aged <80 and over>" or "aging <65 to 79 years>")
10. exp guidelines/
11. exp practice guidelines/
12. 10 or 11
13. random:.tw,sh,pt.
14. exp meta-analysis/
15. meta-analy:.tw,sh,pt.
16. metaanaly:.tw.
17. (systematic overview: or systematic review:).tw.
18. or/14-17
19. exp clinical trials/
20. clinical trial.pt.
21. controlled clinical trial.pt.
22. multicenter study.pt.
23. comparative study/
24. or/19-23
25. 24 or 13
26. 9 and 12
27. 9 and 18
28. 9 and 25
29. or/26-28
30. limit 29 to english language

Appendix 2. Toxicities reported among trials evaluating anthracyclines or anthracenediones in elderly patients with acute myeloid leukemia.

Author, year	Toxic death	Induction Toxicities
	DNR vs. IDR	
Mandelli, 1991 (20) IDR/ARA-C vs. DNR/ARA-C	Toxic deaths (liver and cardiac): 3 pts vs. 2 pts Early deaths: 8% vs. 7.2%, p=NR Hypoplastic deaths: 29% vs. 14.4%, p=NR	p=0.01 median WBC nadir lower with IDR[A]; p=NS for median platelet nadir[A], p=0.06 for infections (more frequent with IDR) Non-heme toxicity: increase in serum bilirubin (p=0.009), BUN (p=0.034), serum creatinine (p<0.001) in IDA arm. For transaminases, p=NS. Cardiac toxicity: 5 pts (2 fatal, 3 reversible CHF) vs. 3 pts. (1 fatal, 1 cardiogenic shock, 1 reversible CHF), p=NR. Cardiac postmortem in 2 pts detected that not associated with anthracycline. Two pts with reversible CHF in IDR had pre-existing cardiopathy.
Reiffers, 1996 (21) DNR/ARA-C vs. IDR/ARA-C	DNR: 2pts fatal cardiac toxicity Early death: 5 vs. 7 pts, p=NR Hypoplastic death: 11 vs. 16 pts, p=0.35	p=NS for hematologic (duration of neutropenia or thrombocytopenia, febrile episodes, platelet transfusions) or non-hematologic (nausea/vomiting, stomatitis, hypersensitivity, hepatic, renal, neurological, alopecia). More diarrhea with DNR (p=0.009). Cardiac toxicity: p=NS for grade 1 toxicity; grade ≥2 in 4 pts. in DNR arm (2 fatal).
Vogler, 1992 (19) DNR/ARA-C vs. IDR/ARA-C	NR	NR
Wiernik, 1992 (22) DNR/ARA-C vs. IDR/ARA-C	NR	NR
Mori, 2003 (23) DNR/Behonyl-ARA-C/6-MP vs. IDR/Behonyl-ARA-C	Infectious death during hypoplasia: 8% vs. 5%; p=NR	Data NR for arms.
	DNR vs. MXT	
Lowenberg, 1998 (26) DNR/ARA-C vs. MXT/ARA-C	Deaths during chemotherapy (6% vs. 6%) and postinduction death (9% vs. 15%): 14.9% vs. 21.1% p=0.079	Severe infection: 18.6% vs. 25.1%, p=0.036 After first induction cycle: p=NS: hemorrhages (mild, gross, or debilitating), serious infections, liver function abnormalities, renal toxicity, vomiting and nausea, severe intractable diarrhea, severe oral toxicity requiring food intake or parenteral nutrition, fever.
Arlin, 1990 (24) MXT/ARA-C vs. DNR/ARA-C	NR	NR
Goldstone, 2001 (25) DAT vs. ADE vs. MAC	NR Induction death: 16% vs. 26% vs. 17%, p=NR	No difference between groups for hematologic toxicity (time to neutrophil and platelet recoveries) or non-hematologic toxicities (nausea/vomiting, alopecia, oral toxicity, diarrhea, and cardiac function).

Appendix 2 (continued). Toxicities reported among trials evaluating anthracyclines or anthracenediones in elderly patients with acute myeloid leukemia.

Author, year	Toxic death	Induction Toxicities
	DNR vs. IDR vs. MXT	
Rowe, 2004 (27) DNR/ARA-C vs. IDR/ARA-C vs. MXT/ARA-C	induction death: 16% vs. 22% vs. 14% DNR vs. IDR p=0.31 IDR vs. MXT p=0.12	No toxicity info provided.
	DNR vs. other	
Stein, 1990 (29) DNR/ARA-C vs. m-AMSA/ARA-C	NR Induction death: 25% vs. 38% p=0.018	Hepatic toxicity (increased bilirubin [4% vs. 10%, p<0.05] and ALP ≥5 times normal [1.3% vs. 6%, p=0.06]) greater in MXT arm. No differences between groups for renal and bladder toxicity, hepatic precoma or coma, nausea/vomiting, severe stomatitis, severe diarrhea, pulmonary toxicity, or cardiac toxicity.[B]
Oberg, 2002 (28) ARA-C/6-TG/DNR vs. ARA-C/6-TG/ACLA	early death: 7 vs. 17 pts.	p=NS for granulocytopenia and thrombocytopenia severity and duration (both occurred in all patients). Groups similar for nausea, oral mucositis, diarrhea, alopecia. Number of patients with cardiac toxicity too small for conclusions.
Yates, 1982 (12) DNR 45/ARA-C vs. DNR 30/ARA-C vs. ADM/ARA-C	Induction death: 54% vs. 41% vs. 56% p=NR	Severe toxicities (p=NR for all): Infections: 66% vs. 41% vs. 54% Hemorrhage: 21% vs. 21% vs. 32% Hepatic: 3% vs. 1% vs. 1% Renal: 10% vs. 15% vs. 7% Gastrointestinal: 4% vs. 3% vs. 13% Cardiac: 6% vs. 8% vs. 7% Necrotizing colitis: 1.5% vs. 0% vs. 7%
	IDR vs. MXT	
Archimbaud, 1997 (30) ARA-C/VP-16/IDR vs. ARA-C/VP-16/MXT	Toxic death in 15 pts (n for arms not provided)	p=NS severe toxicities, including sepsis, diarrhea, hyperbilirubinemia, hemorrhage, and vomiting

Note: ACLA=aclarubicin; ADE=DNR, ARA-C, VP-16; ADM=doxorubicin; ALP=alkaline phosphatase ARA-C=cytarabine; BUN=blood urea and nitrogen; CHF=congestive heart failure; CR=complete response; DAT= DNR/ARA-C/6-TG; DNR=daunorubicin; IDR=idarubicin; MAC=MXT, ARA-C; m-AMSA=amsacrine; MXT=mitoxantrone; NR=not reported; NS=not significant; pts=patients; VP-16=etoposide; vs.=versus; WBC=neutrophil count;.

[A]40% of patients included in these analyses.

[B]Evaluated patients ranged from 60%-82% among toxicity patients.

Appendix 3. Ongoing randomized trials with patients aged 16-70 years.

Protocol ID	Title and details of trial
NILG-AML 02/06 NCT00495287	A Remission Induction Therapy and Risk-Oriented Postremission Strategy for Adult Acute Myelogenous Leukemia (AML). Age: 16 - 65 years. Outcomes: Not reported. Projected Accrual: Not reported. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=559280&version=HealthProfessional&protocolsearchid=3907829.
AMLSG07-04 NCT00151242	Study on All-Trans Retinoic Acid, Induction and Consolidation Therapy, and Pegfilgrastim After Consolidation Therapy in Younger Patients with Newly Diagnosed Acute Myeloid Leukemia. Age: 18 - 60 years. Outcomes: Not reported. Projected Accrual: Not reported. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=447327&version=HealthProfessional&protocolsearchid=3907839.
EORTC-06991 NCT00004128 GIMEMA-EORTC-06991	Phase III Randomized Study of High-Dose Versus Standard-Dose Cytarabine During Induction and Interleukin-2 Following Intensive Consolidation and Autologous Peripheral Blood Stem Cell Transplantation in Patients with Acute Myeloid Leukemia. Age: 15-60 years. Outcomes: Overall survival, disease-free survival, response, toxicity. Projected accrual: 2000 patients (first randomization), 577 patients (second randomization). Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=67356&version=HealthProfessional&protocolsearchid=3907852.
ECOG-1900 NCT00049517	Phase III Randomized Study of Daunorubicin and Cytarabine with or without Gemtuzumab Ozogamicin Followed by Autologous Hematopoietic Stem Cell Transplantation in Patients with Acute Myeloid Leukemia (Autologous Transplantation Arm II Closed to Accrual as of 10/4/2007). Age: 16 - 60 years. Outcomes: Disease-free survival, overall survival, response. Projected accrual: 830 patients. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=258113&version=HealthProfessional&protocolsearchid=3907857.
SWOG-S0106 NCT00085709	Phase III Randomized Study of Induction Therapy Comprising Cytarabine and Daunorubicin with Versus without Gemtuzumab Ozogamicin Followed by Consolidation Therapy Comprising High-Dose Cytarabine and Post-Consolidation Therapy Comprising Gemtuzumab Ozogamicin Versus No Additional Therapy in Patients with Previously Untreated De Novo Acute Myeloid Leukemia. Age: 18 - 60 years. Outcomes: Disease-free survival, complete response. Projected accrual: 684 patients. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=360812&version=HealthProfessional&protocolsearchid=3907855.
P060504 NCT00428558 EudraCT N°:2006-005163026	Timed-Sequential Induction in CBF-AML. Age: 18 - 60 years. Outcomes: Not reported. Projected accrual: Not reported. Accessed: November 27, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=535726&version=HealthProfessional&protocolsearchid=3907885.

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Evidence-based Series 6-14: Section 3

Treatment of Acute Myeloid Leukemia in Older Patients: EBS Development Methods and External Review Process

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A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

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THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its

interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Hematology DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the treatment of acute myeloid leukemia (AML) in older patients, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

Prior to submission of this Evidence-based Series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, with expertise in methodological issues. Key issues raised by the Panel included:

1. Both reviewers commented on the quality of the evidence as it related to the first recommendation in favour of intensive induction therapy. The reviewers noted that one trial appeared to be the determining factor for that recommendation even though it has only been published in abstract form in 1997.

   DSG Response:

   The DSG agreed that the evidence regarding intensive induction therapy is limited; however, further trials of intensive induction therapy are not expected to be forthcoming in this patient population. Given that fact and the limited evidence available, the DSG came to the consensus opinion that intensive induction therapy for patients with good performance status and minimal organ dysfunction or comorbidity can produce an increase in response and survival in older patients compared to low-dose, symptomatic, or palliative treatment and should be recommended. The fact that this recommendation was consensus based has since been added to the guideline.

2. Both reviewers commented on the inclusion of studies with small sample sizes and the fact that studies that could be considered relatively old (mid-1990s) were included in the evidentiary base.

   DSG Response

   AML in the elderly is a disease for which limited evidence is available. Very few new trials including this patient population exist, which necessitated the need to include all randomized trials with this patient population. In addition, the DSG was required to use a consensus-based approach to form certain recommendations when the evidence was of lower quality. No changes were made.

3. One reviewer questioned whether the economic analyses included in the growth factors section would be generalizable to the contemporary context.

DSG Response

The DSG did consider the generalizability of the economic analyses to the present context when the original recommendations were drafted; however, this was not clear in the original discussion of the "Myeloid Colony-Stimulating Factors" section. The discussion has now been reworded to indicate that the analyses were retrospective, and the data on costs were several years out of date and, therefore, the generalizability of the economic analyses was limited. The original recommendation was not changed, as there is a lack of evidence for either a clinical benefit or a reduction in costs.

4. One reviewer commented that although the questions guiding this evidence-based series included response duration and toxicity as outcomes of interest, these were not mentioned in the first recommendation for intensive induction therapy.

DSG Response

Both response duration and toxicity were considered in the drafting of the recommendations. The authors agreed that the fact that these outcomes were considered should be explicitly stated; therefore, statements regarding response duration and toxicity were included in the first recommendation.

5. One reviewer commented that the key evidence for the fifth recommendation is a trial that has only been reported in abstract form. The reviewer noted that no information on the trial's quality was available and questioned how the study informed the recommendation.

DSG Response

The Hematology DSG agreed that the reviewer's comment was valid regarding the fact that important information on trial quality was missing. In addition, the DSG considered the reviewer's comments regarding the use of an abstract as the basis of a recommendation; however, during the course of discussion, one author (RM) noted that the trial was fully published in 2007. The group agreed that as that trial presented the only available evidence investigating palliative treatments in this patient population, the full publication should be obtained and included in the systematic review. The group agreed that the literature search should not be redone but should be a one-time event. The full report was obtained and the results and quality information were extracted: no major differences between the abstract and full publication were noted. As the DSG based the recommendation on the results of the abstract and given that the results are consistent between the abstract and the full publication, no changes were made to the recommendation.

6. One reviewer suggested that within the discussion section of question three (optimum postremission therapy) a reference be included to support the statement that "[e]xtrapolating from evidence in younger patients (age < 55 years), the DSG concluded that patients with a good performance status and who have recovered from toxicity should receive at least one (and up to two) cycles of consolidation therapy with conventional or intermediate dose cytarabine with or without anthracycline."

DSG Response

The reference to which this statement alludes has been added.

7. One reviewer noted that as toxicity was an outcome of interest, and that older patients may wish to weigh the costs and benefits of treatment with respect to these outcomes, statements regarding toxicity should be added to the "Section 1: Guideline Recommendations". Specifically, if no data on toxicity were available, this should be stated in the key evidence for the appropriate recommendations.

   DSG Response

   The authors have added statements regarding toxicity to the recommendations and the key evidence (where appropriate).

8. One reviewer commented that there is no recommendation addressing the last guideline question regarding prognostic factors.

   DSG Response

   No recommendation addressing prognostic factors was originally included as there were insufficient data to make a recommendation to use specific prognostic factors to guide treatment decisions in older patients. The authors have added a statement to the guideline addressing the lack of evidence on prognostic factors.

External Review by Ontario Clinicians

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, the Hematology DSG circulated Sections 1 and 2 to external review participants in Ontario for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Hematology DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review July 2, 2008)

QUESTIONS

1. What is the relative efficacy of aggressive induction chemotherapy as compared with less aggressive treatments used in the treatment of older patients (> 55 years) with newly diagnosed acute myeloid leukemia?
2. What is the optimum induction regimen for older patients with acute myeloid leukemia?
3. What is the optimum post-remission therapy?
4. What are the roles of granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor in conjunction with chemotherapy in this group of patients?
5. What disease and patient-related parameters can be used to identify patients age > 55 years who are more likely to benefit from aggressive induction therapy?

Outcomes of interest include survival, response rate, response duration, and toxicity.

TARGET POPULATION

The recommendations apply to adult patients over the age of 55 years with newly diagnosed, previously untreated, acute myeloid leukemia.

DRAFT RECOMMENDATIONS

- **Based on the consensus of the Hematology DSG, intensive induction chemotherapy is recommended for patients with good performance status and minimal organ dysfunction or comorbidity. Intensive induction treatment has resulted in superior outcomes (remission rates, remission duration, and survival) without an increase in toxicity, in comparison with therapy that includes reduced doses or is of palliative intent.**

  Key Evidence

  - Buchner et al (3) compared two doses of daunorubicin (60 mg/m^2 versus [vs.] 30 mg/m^2) in patients aged 60 years or older. More intensive therapy resulted in fewer early deaths and a superior remission rate, and because the duration of remission was similar in both groups, the superior remission rate in the more intensively treated patients translated into superior overall survival.

- **Comparative data fail to demonstrate superior outcomes associated with use of a specific anthracycline or anthracenedione agent in induction. No consistent differences in treatment-related toxicities were observed. Thus, the decision as to which agent to use may be determined by other factors, such as drug acquisition costs, that may vary among institutions. For those reasons, each individual institution should determine their specific policies regarding the agent of choice.**

  Key Evidence

  - The Hematology Cancer Disease Site Group (Hematology DSG) conducted separate meta-analyses for the categories of comparisons (daunorubicin [DNR] vs. idarubicin [IDR], DNR vs. mitoxantrone [MXT], and IDR vs. MXT), and all failed to detect statistically significant differences between the agents with respect to response rate or overall survival.

- **There is insufficient evidence to make a firm recommendation regarding the administration of consolidation therapy to older patients who have achieved a complete remission. Based on DSG consensus, it is recommended that patients in complete remission with a good performance status who have recovered from any toxicity receive at least one cycle of consolidation with conventional or intermediate dose cytarabine with or without anthracycline.**

  Key Evidence

  - No randomized trials of consolidation therapy compared to placebo or observation were identified.
  - The decision that patients with a good performance status who have recovered from toxicity should receive at least one cycle (and up to two) of consolidation therapy with conventional or intermediate dose cytarabine with or without anthracycline was based on an extrapolation of the evidence from younger patients (age < 55 years) (4) and on the consensus of the Hematology DSG.

- **There is no role for maintenance therapy for patients in first complete remission.**

  Key Evidence
  - Four randomized trials of maintenance therapy showed no significant differences in relapse-free or overall survival compared to the control (5-8).

- **For patients with important comorbidities who are deemed ineligible for induction chemotherapy by their physicians or whose personal preferences are for a palliative approach, treatment with low-dose cytarabine is recommended to optimize disease control while avoiding serious treatment-related toxicities.**

  Key Evidence
  - Burnett et al (9) demonstrated that, in older AML patients deemed unfit for intensive chemotherapy, low-dose cytarabine was associated with higher remission rates and longer survival compared to hydroxyurea, with no difference in toxicities.

- **The routine use of myeloid growth factors (G-CSF or GM-CSF) as an adjunct to intensive chemotherapy in older patients with acute myeloid leukemia is not recommended.**

  Key Evidence
  - An aggregate data meta-analysis pooling results of the published studies of GM-CSF or G-CSF was performed by the Hematology DSG. The meta-analysis did not detect a difference between groups who did or did not receive growth factors with respect to complete response rate, mortality or disease recurrence, overall survival, infection rates, or infectious death. Toxicity data were inconsistently reported and therefore not pooled.

- **There is insufficient evidence to guide a recommendation on the use of specific prognostic factors to guide treatment decisions in older patients.**

  Key Evidence
  - To date there are no prospective trials investigating the use of specific prognostic factors to guide treatment decisions in older patients.

QUALIFYING STATEMENTS

- Treatment decisions in older patients with acute myeloid leukemia are complex and often influenced by comorbid illnesses, consideration of quality of life, and patient preferences. Thus, treatment recommendations described in this evidence-based series may require alteration after discussions with patients and their families.
- The Hematology DSG recognizes that 55 years represents a relatively young age for defining a criterion for an older patient population. This age was chosen based on the parameters of best evidence obtained. As age serves as both a proxy marker of comorbidities and potential differences in disease biology, recommendations have been drafted that account for patient health status and preferences.

Methods

Feedback was obtained through a mailed survey of 82 external review participants in Ontario consisting of medical oncologists and hematologists. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey was mailed out on July 2, 2008. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Hematology DSG reviewed the results of the survey.

Results

Twenty-three responses were received out of the 82 surveys sent (28% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the participants who responded, 12 indicated that the report was relevant to their practice or organizational position, and they completed the survey. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to eight items on the feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear.[A]	10 (90.9%)	1 (9.1%)	0
There is a need for a guideline on this topic.[A]	11 (100%)	0	0
The literature search is relevant and complete.[A]	10 (90.9%)	0	1 (9.1%)
The results of the trials described in the report are interpreted according to my understanding of the data.	10 (90.9%)	0	1 (9.1%)
The draft recommendations in the report are clear.	10 (90.9%)	0	1 (9.1%)
I agree with the draft recommendations as stated.	10 (90.9%)	0	1 (9.1%)
This report should be approved as a practice guideline.	9 (75%)	1 (8.3%)	2 (16.7%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	8 (72.7%)	0	3 (27.3%)

Summary of Written Comments

Eight respondents (66.7%) provided written comments. Five respondents commented that this evidence-based series was an excellent or good-quality document that offers appropriate guidance for physicians. The remaining points contained in the written comments were:

1. What is the basis for recommending "at least one cycle (and up to two) of consolidation with conventional or intermediate dose cytarabine..."? Both Mayer (10) and Stone (11) used four standard courses of cytarabine (100 mg/m^2). No comparison of four cycles to "one or two cycles" has been reported. *Comment from one physician.*
2. The lower limit of the age restriction (55 years) should be loosely applied. It is recognized that setting the limit at 55 years was likely due to the limitations within the published literature. Importantly, most patients aged 55 – 65 years of age are treated. The age cut-off should be higher, i.e. >65 years or >75 years. *Comment from three physicians.*
3. The conclusions of the guideline as well as the included studies are not up to date. One systematic review with meta-analysis that was included (12), reported a significantly

higher complete response rate and five-year overall survival for idarubicin compared to daunorubicin. More details of that review are required in this systematic review and practice guideline. In addition the recommendation that states there is a lack of evidence for consolidation in patients >60 years of age runs counter to data from the Canadian Leukemia Studies Group. A recently completed trial funded by the Canadian Institutes for Health Research (CIHR) and industry enrolled 503 patients to non-cross resistant chemotherapy compared to HDAC in patients 18-80 years of age. Median disease-free survival was higher for IDAC/NOVE compared to HDAC (18 months versus 10.3 months, respectively). In addition, for patients free of disease at six months, the median disease-free survival was 33.4 months after response-adapted therapy compared to after HDAC therapy (p=0.02). This study has been reported in abstract form in Blood and is nearing full publication. Completion of this systematic review and practice guideline should be halted until that publication is available, as these guidelines could undo a lot of progress made in the treatment of AML. *Comment from one physician.*

Modifications/Actions

1. The benefit of intensive post-remission chemotherapy has been established for younger patients; however, the exact benefit of consolidation chemotherapy for older patients is still unclear. There have been no trials comparing consolidation to no further therapy, and others have included quite heterogeneous chemotherapy regimens. As pointed out by the reviewer, the Mayer and Stone studies both compared dose in consolidation, not number of cycles. The only trial that addressed number of cycles was the large randomized trial from the UK (5) (1 cycle vs. 4 cycles) which demonstrated no significant difference in outcomes, but possibly more infectious deaths in those receiving longer consolidation. The Hematology DSG's recommendation that "patients with a good performance status who have recovered from toxicity should receive 1 or 2 cycles of consolidation" was made by consensus.

2. The Hematology DSG recognizes that the trials reviewed for the creation of this guideline included a broad range of patients, from those where currently the use of aggressive attempts at remission might routinely be considered (e.g. those age 56-65) as well as those where only a minority of patients would be treated aggressively (e.g., those age 66 or greater). In the absence of significant weight of evidence to provide recommendations specific to the latter group, the DSG concluded that patient preferences and attention to co-morbidities (physiologic age) remain important considerations in treating elderly patients with AML. The Hematology DSG agreed that the second qualifying statement be replaced by this response.

3. More details from the systematic review (12) were added, specifically that the significant difference in CR rate that this reviewer referred to was for all participants; however, in the subgroup of patients over the age of 60 there was no difference in remission rates between the arms. In fact, in their discussion, the authors point out that the benefit of idarubicin over daunorubicin seemed less definite in older patients. Overall survival was not reported for the elderly subgroup. Regarding the CLSG study, there was not enough detail in the published abstract regarding the elderly subgroup for it to be included in this guideline.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Hematology DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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