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The Use of Imatinib Mesylate (Gleevec™) in Patients with Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia

I. Walker, C.T. Kouroukis, A.E. Haynes, and K. Imrie

Report Date: September 29, 2008

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The 2008 guideline recommendations were put in the

Education and Information section

This means that the recommendation will no longer be maintained but may still be useful for academic or other information purposes.

SUMMARY

QUESTIONS

Does treatment with imatinib mesylate (imatinib) in patients with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) or relapsed/refractory imatinib/dasatinib naïve Ph+ ALL affect overall survival, progression free survival, response, quality of life, and adverse events?

TARGET POPULATION

Adult patients with newly diagnosed or relapsed or refractory imatinib/dasatinib-naive Ph+ ALL.

RECOMMENDATIONS

- **The opinion of the authors is that imatinib is recommended for all patients with imatinib/dasatinib-naive Ph+ ALL, to be administered as part of remission induction therapy.**

  Key Evidence

  ⇒ A single randomized trial that reported much higher complete remission rates for patients receiving induction with imatinib alone compared to induction with chemotherapy (96.3% versus [vs.] 50.0%, respectively; p=0.0001) (1).

⇒ A number of comparative phase II studies reported improvements in complete remission rate, disease-free survival, relapse-free survival or overall survival when imatinib was combined with chemotherapy compared with chemotherapy alone (8,10, 11, 13, 14).

- **The opinion of the authors is that patients who are unsuitable to receive intensive chemotherapy may achieve remission when imatinib is combined with prednisone alone or with non-intensive chemotherapy.**

  Key Evidence

  ⇒ One non-comparative phase II trial reported a complete remission rate of 96.7% for 29 elderly patients that received imatinib and prednisone alone (2).

  ⇒ Another non-comparative phase II trial reported a complete remission rate of 100% for 10 elderly patients that received imatinib, prednisone and vincristine (3).

Qualifying Statements

- There is insufficient evidence to recommend a specific dose and schedule of imatinib. Published studies have used imatinib 400-800 mg/d until the end of the treatment program (1-3).

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For information about the PEBC and the most current version of all reports, please visit the CCO web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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1. Ottmann OG, Wassmann B, Pfeifer H, Giagounidis A, Stelljes M, Dührsen U, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL). Cancer. 2007;109(10):2068-76.
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FULL REPORT

I. QUESTIONS

- Does treatment with imatinib mesylate (imatinib) in patients with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) affect overall survival, progression free survival, response, quality of life, and adverse events? In the context of acute leukemia, the best measure of response is the rate of complete remission.

- Does treatment with imatinib in patients with relapsed or refractory Ph+ ALL affect overall survival, progression free survival, response, quality of life, and adverse events? In the context of acute leukemia, the best measure of response is the rate of complete remission.

II. CHOICE OF TOPIC AND RATIONALE

Acute lymphoblastic leukemia (ALL) is a rare cancer that, in the United States, had an age-adjusted incidence rate of 1.6 per 100,000 men and women per year from 2001-2005 (1). While the survival rate is high for children, most of whom are likely cured, the corresponding results for adults are poor. One of the reasons for the poorer outcome in adults is the higher prevalence of Philadelphia chromosome, a well-established indicator of adverse prognosis.

In a large recently completed United Kingdom/United States (UK/US) trial on adults with newly diagnosed ALL, aged 15-64, the percentage of Philadelphia chromosome-positive cases was 19% (267/1373), and the prevalence increased with age, from 4% in the 15-19 years age group to 26% in those over 50 years of age (2). The trial did not include patients over 64 years of age in whom the prevalence of Philadelphia chromosome is likely to be even higher. In this trial the overall survival at five years in patients having Philadelphia chromosome was significantly worse than that of patients without Philadelphia chromosome (43% vs. 22%, statistics not given) (3).

Imatinib is an inhibitor of the *BCR-ABL* tyrosine kinase (4,5). It has shown efficacy in patients with Ph+ chronic myeloid leukemia (CML). An early trial of imatinib for CML included a small number of patients with Ph+ ALL in the subgroups with blast crisis CML (6). That trial indicated that imatinib is an active agent in Ph+ ALL. Given the rarity of ALL, the even greater rarity of Ph+ ALL, and the fact that tyrosine kinase inhibitor therapy is now included as standard therapy, it is doubtful that a randomized trial of sufficient size will be conducted to determine the effect of imatinib on survival in this patient population.

III. METHODS

This advice report, produced by the Program in Evidence-based Care (PEBC), is a convenient and up-to-date source of the best available evidence on the role of imatinib in the treatment of adult patients with Ph+ ALL, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

A systematic search of the published literature identified all reports relating to the use of imatinib for the treatment of patients with Ph+ ALL. The MEDLINE (1996 to July Week 2, 2008 [July 16]), EMBASE (1996 to 2008, Week 29 [July 16]), and the Cochrane Database of

Systematic Reviews and Cochrane Central Register of Controlled Trials (2008, Issue 3) databases were searched according to the strategies in Appendix A. Abstracts from the American Society of Clinical Oncology (ASCO) (2000-2008) and the American Society of Hematology (ASH) (2000-2007) annual conference proceedings were searched. The National Cancer Institute (NCI) Clinical Trials Register and the United States National Institutes of Health (NIH) Clinical Trials databases were searched to identify ongoing clinical trials, and the National Guidelines Clearinghouse and the CMA Infobase were searched for clinical practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers (IW and AH), and the reference lists from those sources were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in this systematic review if they met the following criteria:

1. Studies were systematic reviews, meta-analyses, or evidence-based practice guidelines that assessed the use of imatinib in patients with Ph+ ALL.
2. Studies were prospective, randomized phase II or III clinical trials assessing the use of imatinib in patients with Ph+ ALL.
3. Studies were non-randomized, prospective phase II clinical trials.
4. Results were reported for any of the following outcomes of interest: overall survival, progression-free survival, response, quality of life, and adverse events.
5. In studies where patients with a disease other than Ph+ ALL were included (e.g., chronic myelogenous leukemia), results must have been reported separately for the group of patients with Ph+ ALL.

Exclusion Criteria

1. Reports published in a language other than English.
2. Letters, editorials, notes, comments, and books.

Synthesizing the Evidence

The authors will conduct a meta-analysis of the results of the identified trials if the design and quality of these trials are appropriate.

IV. RESULTS

Literature Search Results

A total of 139 citations were retrieved from the MEDLINE, EMBASE, and the Cochrane Library databases. Sixteen citations met the inclusion criteria. In addition, 40 abstracts from the annual conference proceedings of ASCO and ASH were identified that met the inclusion criteria. Many of the identified abstracts were of trials that have since been fully published or for which more up-to-date abstracts were available. Only the full publication or most up-to-date abstract has been referenced for each trial. One randomized controlled trial comparing induction therapy with imatinib to age-adapted chemotherapy in patients with newly diagnosed Ph+ ALL was identified (7). In addition, 19 non-randomized clinical trials of imatinib in patients with Ph+ ALL were identified (8-28). No systematic reviews or evidence-based practice guidelines of imatinib in Ph+ ALL were identified.

Trial Quality

One RCT was identified that randomized 55 patients aged >55 years with newly diagnosed Ph+ ALL to remission induction therapy with imatinib (600 mg/day) or to age-adjusted multi-agent chemotherapy (Appendix B) after a short five-day pre-phase period during which all patients received chemotherapy (7). Patients who completed remission

induction therapy, regardless of patient remission status, received up to five cycles of consolidation therapy with imatinib (600 mg/day) and chemotherapy (Appendix B). The primary endpoint of the study was hematologic response rate after remission induction. The authors did not report a sample size requirement; therefore, it is unknown whether that requirement was met. The randomization method, blinding, allocation concealment, and losses to follow-up were not reported. The analysis was intention-to-treat and final. The study received ethics approval.

Nineteen studies were prospective single-arm phase II clinical trials (8-28), of which seven compared the results of enrolled patients to a control group (8-14). Six trials treated patients with Ph+ ALL with imatinib (in induction and/or consolidation/salvage and/or maintenance) and compared the results to a historical control group that did not receive imatinib (8-11,13,14). One trial compared sequential cohorts of patients that received different schedules of imatinib (12). The reported method of analysis in each study was variable. None of the trials reported whether the patients in the treatment group were matched to similar patients in the control group. Three studies reported on similarities and differences for summary statistics of pre-treatment patient characteristics between the treatment and control group (9,11,13). Those included, but are not limited to, factors such as age, gender, hemoglobin, platelets, and central nervous system (CNS) involvement (9,11,13).

The 11 remaining phase II trials were single-arm non-comparative studies (15-28).

Trial Characteristics

Randomized Trials

The randomized trial (7) compared induction imatinib (n=28) to induction chemotherapy without imatinib (n=27) in patients with newly diagnosed Ph+ ALL (Table 1). Both arms received consolidation that included imatinib. The median age was similar in both arms (66 years vs. 68 years, respectively). The full details of the treatment regimen can be found in Appendix B.

Non-randomized comparative phase II trials

Five trials enrolled patients with only newly diagnosed Ph+ ALL (10-14), one trial enrolled newly diagnosed patients as well as those with minimally-treated Ph+ ALL (8), and one trial included patients with newly diagnosed or previously treated Ph+ ALL (9). The treatment regimens used were varied between the trials (Appendix B). Imatinib was added to induction and/or consolidation/salvage and/or maintenance. Most trials either treated patients with stem cell transplantation (SCT) after consolidation or did not report on the use of SCT (Table 1). The largest trial enrolled 153 patients and compared the results with 267 historical patients (9). The remaining trials enrolled 20 to 54 patients. The treatment details for the historical control group in the trial reported by de Labarthe et al (10) were reported by Dombret et al (29).

Non-comparative phase II trials

Twelve non-comparative phase II trials were identified (15-28). The trials enrolled patients with either newly diagnosed or relapsed/refractory Ph+ ALL, or both (Appendix C1). The full regimen details for these trials can be found in Appendix B. The majority of trials treated patients with imatinib added to induction therapy (16-28)). Imatinib was also administered either prior to or following SCT (15,18,19,23,25,27,28). The trials ranged in size from 10 patients to 68 patients, with the median age ranging from 41.5 years to 69 years in seven trials (Appendix C1).

Table 1. Patient and trial characteristics of comparative trials examining imatinib in Ph+ ALL.

Author, year (ref)	Patient characteristics	Intervention[a]	N	Age, mdn (yr)
Randomized trials				
Ottmann, 2007 (7)	Newly diagnosed Ph+ ALL or Ph+ CML in first lymphoid or bilineage BP, age > 55 years, not a candidate for allogeneic SCT, WHO PS ≤2, no prior tx except prephase chemo	induction: imatinib → consolidation: imatinib + chemo	28	66
		induction: chemo → consolidation: imatinib + chemo	27	68
Non-randomized comparative phase II trials				
Thomas, 2008 (8) abs	Newly diagnosed or minimally-treated Ph+ ALL	Imatinib + hyper-CVAD	54	51
		Hyper-CVAD	48	NR
Fielding, 2007 (9) abs	Ph+ ALL	Induction chemo + imatinib → consolidation imatinib → allogeneic SCT → imatinib	153[b]	42
		Induction → allogeneic SCT	267	40
de Labarthe, 2007 (10)	Newly diagnosed Ph+ ALL, age 15-59 years	Prephase chemo → variable induction + imatinib → consolidation + imatinib	45	45
		No imatinib – details NR	198	NR
Delannoy, 2006 (11)	Newly diagnosed Ph+ ALL, age ≥55 years	Induction chemo → consolidation/salvage + imatinib → 10 blocks of maintenance (for patients with CR)—2 with imatinib	30	65.8
		Induction → consolidation/salvage → maintenance	21	61.3
Wassmann, 2006 (12)	Newly diagnosed Ph+ ALL or CML lymphoid blast crisis, age >18 years, ECOG PS 0-2. Patients enrolled in the alternating imatinib schedule had achieved CR for 28d.	Alternating imatinib: prephase chemo → induction → imatinib → consolidation chemo → imatinib → SCT	47	46
		Concurrent imatinib: prephase chemo → induction chemo + imatinib →consolidation + imatinib → SCT	45	41
Lee, 2005 (13)	Newly diagnosed Ph+ ALL, age <60 years, ECOG PS 0-2,	Induction Hyper-CVAD → imatinib → consolidation/salvage chemo → imatinib → SCT (patients in CR) or salvage chemo (patients not in CR)	29	36
		Induction (ida/vinc/pred/asparginase) → consolidation/salvage chemo → SCT	33	35
Lee, 2005 (14)	Newly diagnosed Ph+ ALL, age ≥15 years, Karnofsky PS ≥70	Induction chemo + imatinib → consolidation + imatinib → maintenance imatinib	20	37
		Induction chemo → consolidation	18	44

Notes: abs=abstract; ALL=acute lymphoblastic leukemia; BP=blast phase; chemo=chemotherapy; CML=chronic myeloid leukemia; CR=complete remission; CVAD=cyclophosphamide, vincristine, doxorubicin, dexamtheasone; d=day(s); ECOG=Eastern Cooperative Oncology Group; ida=idarubicin; N=number of patients; Ph+=Philadelphia chromosome-positive; pred=prednisone; PS=performance status; ref=reference; SCT=stem cell transplantation; tx=treatment; vinc=vincristine; WHO=World Health Organization; yr=year(s).

[a]Full regimen details including dose and schedule information can be found in Appendix B.

[b]Eighty-nine patients received imatinib following induction; after an amendment in 2005, 64 patients received imatinib with the second phase of induction in addition.

Results

Survival and response

Randomized trials

The randomized trial (7) reported no significant differences in overall survival (OS) or disease-free survival (DFS) for patients that received imatinib induction compared to chemotherapy induction after a median follow-up of 11.2 months (Table 2). The complete remission (CR) rate after induction therapy was significantly higher for imatinib induction compared to chemotherapy induction (96.3% vs. 50.0%; p=0.0001). The CR rate after consolidation therapy was 100% vs. 85.2%, respectively (p=not reported).

Non-randomized comparative phase II trials

The results of the non-randomized comparative phase II trials can be found in Table 2. Three trials reported comparisons between summary statistics for certain pre-treatment patient characteristics but did not report whether treatment patients were matched to a control (9,11,13). Fielding et al reported no significant differences in OS or CR after induction (9). Lee et al (13) reported a significant difference in OS for imatinib compared to no imatinib (median 29.4 months vs. 12.8 months; p=0.019). Delannoy et al (11) reported significant differences in relapse-free survival (RFS) for imatinib vs. no imatinib (median 20.1 months vs. 4.2 months; p=0.0003). Complete remission rate was significantly higher for imatinib after induction (70% vs. 28.5%, respectively; p=0.003) and after consolidation/salvage (90% vs. 48%; p=0.001).

The remaining trials did not report whether pre-treatment differences existed between the treatment and historical control groups, nor did they report on how the groups were compared (8,10,14). Two trials (8,10) reported significantly higher OS and DFS for imatinib compared to no imatinib (Table 2). One of those trials also reported a significant difference in CR after induction for patients that received imatinib (10).

Another trial compared an alternating schedule of imatinib to a concurrent schedule (12). No significant differences in OS or RFS were identified (Table 2).

Non-comparative phase II trials

The results for the non-comparative phase II trials of imatinib can be found in Appendix C2. Complete remission after induction was reported in eight trials and ranged from 30% to 100% of patients (Appendix C2). Overall survival was reported in five trials (16-23) and ranged from 13.3 months (follow-up not reported) to 29.9 months (follow-up median 18 months). Median disease-free survival was reported in two trials and was eight months (follow-up median five months) and 9.9 months (follow-up not reported) (17,28). One trial reported a complete remission rate of 96.7% in 29 patients that received imatinib in combination with prednisone, without chemotherapy or with palliative chemotherapy (16).

Adverse events

The incidence of adverse events for each of the comparative trials can be found in Table 3. In the randomized trial (7), the rates of grade 3/4 non-hematological adverse events were significantly higher among patients that received induction chemotherapy compared to induction with imatinib (86% vs. 39%; p=0.005). Grade 3/4 nausea/vomiting (7.1% vs. 3.7%) and grade 3/4 diarrhea (3.6% vs. 0) were more common in the imatinib arm; however, the authors did not report whether those differences were significant (7).

None of the non-randomized comparative phase II trials reported the rates of adverse events for the control groups, and four trials did not report any adverse event data, for either arm (8,9,12,14). Delannoy et al (11) reported that 30% of 30 patients experienced a grade 3/4 non-hematological adverse event. Two studies reported that 10% of patients experienced grade 3/4 nausea/vomiting (10,13); however, in one study no patients experienced grade 3/4

nausea/vomiting (11). Lee et al (13) also reported that 50% of 20 patients experienced febrile neutropenia and that all patients experienced grade 3/4 neutropenia.

The non-comparative phase II trials of imatinib in patients with Ph+ ALL can be found in Appendix C3. Most trials reported very little data for adverse events. Grade 3/4 nausea/vomiting was the most commonly reported adverse event, occurring in 3.3% of 30 patients to 17% of 24 patients in three trials (16-19). One of those trials also reported that grade 3/4 diarrhea occurred in 4% of 24 patients (18,19). Grade 3/4 non-hematological adverse events were reported in two trials and occurred in 43.3% of 30 patients and in 5.6% of 54 patients (16,23). One trial reported that 50% of 22 patients experienced a grade 3/4 adverse event (15). Grade 3/4 neutropenia occurred in 50% of 68 patients in one trial (20-22). In a different trial, 26% of 24 patients experienced neutropenic fever (18,19).

Table 2. Efficacy outcomes of comparative trials examining imatinib in Ph+ ALL.

Author, year (ref)	Intervention	N	OS	DFS/PFS/ RFS	CR after induction (%)	CR after induction with PB recovery (%)	CR after consolidation /salvage (%)	Follow-up mdn (mos)
Randomized Trials								
Ottmann, 2007 (7)	induction: imatinib → consolidation: imatinib + chemo	28	Mdn (mos) 23.5	Mdn DFS (mos) 13.7	96.3[a]	85.2[a]	100	11.2
	induction: chemo → consolidation: imatinib + chemo	27	12.3 p=ns	14.5 p=ns	50.0[a] p=0.0001	23.1[a]	85.2	11.2
Non-randomized comparative phase II trials								
Thomas, 2008 (8) abs	Imatinib + hyper-CVAD	54	3-yr (%) 55	DFS 3-yr (%) 62	77.8	1.9	NR	48
	Hyper-CVAD	48	15 p<0.001	14 p<0.001	NR	NR	NR	NR
Fielding, 2007 (9) abs	Induction chemo + imatinib → consolidation imatinib → allogeneic SCT → imatinib	153[b]	3-yr (%) 23	NR	91/81[c]	NR	NR	NR
	Induction → allogeneic SCT	267	26	NR	83	NR	NR	NR
de Labarthe, 2007 (10)	Prephase chemo → variable induction + imatinib → consolidation + imatinib	45	18-mos (%) 65	DFS 18-mos (mos) 51	96	NR	96	NR
	No imatinib – details NR	198	39 p=0.05	31 p=0.02	71 p<0.001	NR	NR	NR
Delannoy, 2006 (11)	Induction chemo → consolidation/salvage + imatinib → 10 blocks of maintenance (for patients with CR)—2 with imatinib	30	Mdn (mos) 23.2	Mdn RFS (mos) 20.1	70	NR	90	24
	Induction → consolidation/salvage → maintenance	21	11.2	4.2 p=0.0003	28.5 p=0.003	NR	48 p=0.001	NR
Wassmann, 2006 (12)	Alternating imatinib: prephase chemo → induction → imatinib → consolidation chemo → imatinib → SCT	47	Mdn (mos) 16.3	RFS 2-yr (%) 52	94	NR	NR	NR
	Concurrent imatinib: prephase chemo → induction chemo + imatinib →consolidation + imatinib → SCT	45	19.6 p=0.97	61 p=0.83	96	NR	NR	NR
Lee, 2005 (13)	Induction Hyper-CVAD → imatinib → consolidation/salvage chemo → imatinib → SCT (patients in CR) or salvage chemo (patients not in CR)	29	3-yr (%) 78.1	DFS 3-yr (%) 78.1	79.3	NR	Salvage 50 (3/6)	NR
	Induction (ida/vinc/pred/asparginase) → consolidation/salvage chemo → SCT	33	11.6	11.6	81.8 p=0.803	NR	16.7 (1/6) p=0.545	NR
Lee, 2005 (14)	Induction chemo + imatinib → consolidation + imatinib → maintenance imatinib	20	Mdn (mos) 29.4	Mdn RFS (mos) 27.0	95	NR	NR	26
	Induction chemo → consolidation	18	12.8 p=0.019	9.3 p=0.009	83	NR	NR	NR

Notes: abs=abstract; chemo=chemotherapy; CR=complete remission rate; CVAD=cyclophosphamide, vincristine, doxorubicin, dexamtheasone; DFS=disease-free survival; ida=idarubicin; mdn=median; mos=months; N=number of patients; NR=not reported; ns=not significant; OS=overall survival; PB=peripheral blood; PFS=progression-free survival; pred=prednisone; ref=reference; RFS=relapse-free survival; SCT=stem cell transplantation; vinc=vincristine; yr=year(s).

[a]For CR after induction, only 27 patients were evaluable in the induction imatinib arm and 26 in the induction chemotherapy arm.

[b]Of 153 patients that received imatinib, 89 patients received imatinib during consolidation only, while 64 patients also received imatinib during induction therapy due to a protocol amendment if 2005 that added imatinib to induction therapy.

[c]Complete response after induction for: induction imatinib patients (n=64)/chemotherapy induction only patients (n=89).

Table 3. Grade 3 or 4 adverse events related to treatment with imatinib in trials of patients with Ph+ ALL.

Author, year (ref)	Intervention	N	All G3/4 AE's (%)	Non-heme G3/4 AE's (%)	G3/4 nausea/ vomiting (%)	G3/4 diarrhea (%)	Neutropenic fever (%)	G3/4 Neutropenia
Randomized Trials								
Ottmann, 2007 (7)	induction: imatinib → consolidation: imatinib + chemo	28	NR	39	7.1	3.6	NR	
	induction: chemo → consolidation: imatinib + chemo	27	NR	86 p=0.005	3.7	0	NR	
Non-randomized phase II trials								
Comparative trials								
Thomas, 2008 (8) abs	Imatinib + hyper-CVAD	54	NR	NR	NR	NR	NR	NR
	Hyper-CVAD	48	NR	NR	NR	NR	NR	NR
Fielding, 2007 (9) abs	Induction chemo + imatinib → consolidation imatinib → allogeneic SCT → imatinib	153[b]	NR	NR	NR	NR	NR	NR
	Induction → allogeneic SCT	267	NR	NR	NR	NR	NR	NR
de Labarthe, 2007 (10)	Prephase chemo → variable induction + imatinib → consolidation + imatinib	45	NR	NR	10/36[a]	NR/14[a]	NR	NR
	No imatinib – details NR	198						
Delannoy, 2006 (11)	Induction chemo → consolidation/salvage + imatinib → 10 blocks of maintenance (for patients with CR)—2 with imatinib	30	NR	30	0	0	NR	NR
	Induction → consolidation/salvage → maintenance	21	NR	NR	NR	NR	NR	NR
Wassmann, 2006 (12)	Alternating imatinib: prephase chemo → induction → imatinib → consolidation chemo → imatinib → SCT	47	NR	NR	NR	NR	NR	NR
	Concurrent imatinib: prephase chemo → induction chemo + imatinib →consolidation + imatinib → SCT	45	NR	NR	NR	NR	NR	NR
Lee, 2005 (13)	Induction Hyper-CVAD → imatinib → consolidation/salvage chemo → imatinib → SCT (patients in CR) or salvage chemo (patients not in CR)	29	NR	NR	NR	NR	NR	NR
	Induction (ida/vinc/pred/asparginase) → consolidation/salvage chemo → SCT	33	NR	NR	NR	NR	NR	NR
Lee, 2005 (14)	Induction chemo + imatinib → consolidation + imatinib → maintenance imatinib	20	NR	NR	10	0	50	100
	Induction chemo → consolidation	18	NR	NR	NR	NR	NR	NR

Notes: abs=abstract; AE=adverse event(s); chemo=chemotherapy; CR=complete remission; CVAD=cyclophosphamide, vincristine, doxorubicin, dexamtheasone; G3/4=grade 3 or 4; ida=idarubicin; N=number of patients; non-heme=non-hematological; NR=not reported; PFS=progression-free survival; pred=prednisone; ref=reference; RFS=relapse-free survival; SCT=stem cell transplantation; vinc=vincristine.

[a]Adverse events reported for induction/consolidation.

V. DISCUSSION

Only one randomized trial evaluating the use of imatinib in patients with Ph+ ALL has been conducted and reported to date. In this trial, there was a markedly improved remission rate in those receiving imatinib, 96.3% compared with 50.0% in those not receiving imatinib. Overall survival was not different between both arms. Given the small number of patients enrolled in the trial and the inclusion of imatinib in the administration of consolidation to patients in both arms following the remission induction phase, a survival difference would not be expected. Three of the seven non-randomized trials report improved complete response rates and three report improved survival. In patients with acute leukemia, achievement of a complete remission is felt to be a very important outcome.

It is important to note that Ph+ ALL is rare; therefore accruing enough patients to attain sufficient statistical power to evaluate an endpoint such as OS could take up to a decade. A search of the U.S National Institutes of Health (NIH) clinical trials database revealed two ongoing randomized trials of imatinib in Ph+ ALL. The first is enrolling young adults with ALL (age 18-59 years) and separating patients into one of three subgroups based on disease: group A: T-ALL or B-ALL that is Ph-; group B: B-ALL that is Ph- and CD20+; group C Ph+ ALL. Ph+ ALL patients are to be randomized to receive either an imatinib-based induction or a chemotherapy + imatinib induction. Although the target enrolment is 1080 patients, the record does not indicate how many patients with Ph+ ALL are to be enrolled. The primary endpoint for the patients with Ph+ ALL is minimal residual disease after induction and/or consolidation. The second trial is randomizing elderly patients (age > 55 years) to an imatinib-based induction or to a standard chemotherapy induction. The target enrolment was not reported; however, the primary outcome is the complete remission rate after induction therapy. Neither trial has overall survival as a primary endpoint, and neither trial is likely to have sufficient statistical power to compare OS between the treatment and control arms. It is unlikely that definitive trials examining OS will be conducted because of the rarity of the disease and because the high early responses already observed have resulted in widespread use of imatinib or other tyrosine kinase inhibitors in all patients. Given these two facts, the trial reported by Ottmann et al (7) constitutes the highest quality evidence that currently exists for Ph+ ALL.

The randomized trial by Ottmann demonstrated that induction with imatinib significantly improves the CR rate compared to induction with chemotherapy. Complete remission following induction was the trial's primary outcome. The authors reported that no significant differences existed for OS and DFS for imatinib compared to chemotherapy; however, the median follow-up was only 11.2 months, patients in both arms received consolidation that included imatinib, and the trial was, most likely underpowered to detect differences in survival endpoints. The phase II trials had similar CR rates with imatinib in patients with newly diagnosed or relapsed/refractory Ph+ ALL.

The toxicity of imatinib was significantly better with respect to the rate of grade 3/4 non-hematological adverse events for induction with imatinib compared to induction chemotherapy. The rates of grade 3/4 nausea/vomiting appeared to be raised with the use imatinib; however, no significant differences were reported.

The opinion of the authors is that imatinib is recommended for all patients with Ph+ ALL, and imatinib should be initiated at the onset of ALL therapy. It can be used in combination with chemotherapy, either intensive or non-intensive; alternatively, in patients who are unsuitable for chemotherapy, it may be combined with prednisone alone.

VI. 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 investigating the use of imatinib in patients with Ph+ ALL that met our eligibility criteria. Appendix D provides details of the identified ongoing trials.

VII. RECOMMENDATIONS AND EVIDENCE

Target Population

Adult patients with newly diagnosed or relapsed or refractory imatinib/dasatinib-naive Ph+ ALL.

Recommendations

- **The opinion of the authors is that imatinib is recommended for all patients with imatinib/dasatinib-naive Ph+ ALL, to be administered as part of remission induction therapy.**

  Key Evidence

  ⇒ A single randomized trial that reported much higher complete remission rates for patients receiving induction with imatinib alone compared to induction with chemotherapy (96.3% versus [vs.] 50.0%, respectively; p=0.0001) (1).

  ⇒ A number of comparative phase II studies reported improvements in complete remission rate, disease-free survival, relapse-free survival or overall survival when imatinib was combined with chemotherapy compared with chemotherapy alone (8,10, 11, 13, 14).

- **The opinion of the authors is that patients who are unsuitable to receive intensive chemotherapy may achieve remission when imatinib is combined with prednisone alone or with non-intensive chemotherapy.**

  Key Evidence

  ⇒ One non-comparative phase II trial reported a complete remission rate of 96.7% for 29 elderly patients that received imatinib and prednisone alone (2).

  ⇒ Another non-comparative phase II trial reported a complete remission rate of 100% for 10 elderly patients that received imatinib, prednisone and vincristine (3).

Qualifying Statements

- There is insufficient evidence to recommend a specific dose and schedule of imatinib. Published studies have used imatinib 400-800 mg/d until the end of the treatment program (1-3).

VIII. CONFLICTS OF INTEREST

The authors of this report were asked to disclose conflicts of interest. No potential conflicts were declared.

IX. ACKNOWLEDGEMENTS

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Appendix A. Literature search strategies.

MEDLINE (OVID)

1. acute lymphoblastic leuk?emia:.mp.
2. exp leukemia, lymphoid/
3. 1 or 2
4. (philadelphia adj2 positive).mp.
5. (Ph adj2 positive).mp.
6. Ph+.mp.
7. Philadelphia chromosome/
8. or/4-7
9. 3 and 8
10. imatinib.mp.
11. gleevec.mp.
12. glivec.mp.
13. STI571.mp.
14. or/10-13
15. 9 and 14
16. meta-analysis as topic/
17. meta analysis.pt.
18. meta analy$.tw.
19. metaanaly$.tw.
20. (systematic adj (review$1 or overview$1)).tw.
21. or/16-20
22. cochrane.ab.
23. embase.ab.
24. (cinahl or cinhal).ab.
25. science citation index.ab.
26. bids.ab.
27. cancerlit.ab.
28. or/22-27
29. reference list$.ab.
30. bibliograph$.ab.
31. hand-search$.ab.
32. relevant journals.ab.
33. manual search$.ab.
34. or/29-33
35. selection criteria.ab.
36. data extraction.ab.
37. 35 or 36
38. review.pt.
39. review literature as topic/
40. 38 or 39
41. 37 and 40
42. comment .pt.
43. letter.pt.
44. editorial.pt.
45. or/42-44
46. 21 or 28 or 34 or 41
47. 46 not 45

48. randomized controlled trials as topic/
49. randomized controlled trial.pt.
50. random allocation/
51. double blind method/
52. single blind method/
53. exp Clinical Trials as Topic/
54. exp clinical trial/
55. (clinic$ adj trial$1).tw.
56. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
57. placebos/
58. placebo$.tw.
59. (allocated adj2 random$).tw.
60. random allocation.tw.
61. randomly allocated.tw.
62. or/48-61
63. case report.tw.
64. letter.pt.
65. historical article.pt.
66. or/63-65
67. 62 not 66
68. 47 or 67
69. practice guideline/
70. practice guideline$.mp.
71. 69 or 70
72. 68 or 71
73. 15 and 72
74. limit 73 to (English language and humans)

EMBASE (OVID)

1. acute lymphoblastic leukemia/
2. acute lymphoblastic leuk?emia$.mp.
3. 1 or 2
4. Philadelphia 1 Chromosome/
5. (philadelphia adj2 positive).mp.
6. (Ph adj2 positive).mp.
7. Ph+.mp.
8. or/4-7
9. 3 and 8
10. imatinib.mp.
11. gleevec.mp.
12. glivec.mp.
13. STI571.mp.
14. imatinib/
15. or/10-14
16. 9 and 15
17. exp meta-analysis/
18. ((meta adj analy$) or metaanaly$).tw.
19. (systematic ad (review$1 or overview$1)).tw.
20. or/17-19

21. cancerlit.ab.
22. cochrane.ab.
23. embase.ab.
24. (cinahl or cinhal).ab.
25. science citation index.ab.
26. bids.ab.
27. or/21-26
28. reference list$.ab.
29. bibliograph$.ab.
30. hand-search$.ab.
31. manual search$.ab.
32. relevant journals.ab.
33. or/28-32
34. data extraction.ab.
35. selection criteria.ab.
36. 34 or 35
37. review.pt.
38. 36 and 37
39. letter.pt.
40. editorial.pt.
41. 39 or 40
42. 20 or 27 or 33 or 38
43. 42 not 41
44. clinical trial/
45. randomized controlled trial/
46. randomization/
47. single blind procedure/
48. double blind procedure/
49. crossover procedure/
50. placebo/
51. randomi?ed control$ trial$.tw.
52. RCT.tw.
53. random allocation.tw.
54. randomly allocated.tw.
55. allocated randomly.tw.
56. (allocated adj2 random$).tw.
57. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
58. placebo$.tw.
59. prospective study/
60. or/44-59
61. case study/
62. case report.tw.
63. abstract report/
64. letter/
65. or/61-64
66. 60 not 65
67. 43 or 66
68. exp practice guidline/
69. practice guideline/
70. practice guideline$.tw.

71. 68 or 69
72. 67 or 70
73. 16 and 71
74. limit 73 to (human and English language)

Cochrane Central Register of Controlled Trials (CCTR) and Cochrane Database of Systematic Reviews (CDSR)

1. acute lymphoblastic leuk?emia$.mp.
2. (Philadelphia adj2 positive).mp.
3. (Ph adj2 positive).mp.
4. Ph+.mp.
5. or/2-4
6. 1 and 5
7. imatinib.mp.
8. gleevec.mp.
9. glivec.mp.
10. STI571.mp.
11. or/7-10
12. 6 and 11

Annual Conference Proceedings of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH)

Search terms used: imatinib, Gleevec, Glivec, Philadelphia-chromosome, Ph+, acute lymphoblastic leukemia.

APPENDIX B. Dose and schedule information for trials of imatinib in Ph+ ALL.

Author, year (ref)	Treatment Arms	Treatment details
Randomized trials		
Ottmann, 2007 (7)	Induction + imatinib → consolidation + imatinib	Prephase: **dex** 10 mg/m^2 orally d1-5 + **cyclo** 200 mg/m^2 i.v. d3,4,5 + **MTX** 12 mg i.th. d1 → remission induction: **imatinib** 600 mg/d d1-28 → consolidation: **imatinib** 600 mg/d + cycles I,III,V: **MTX** 500 mg/m^2 24-hr i.v. d1,15 + **6-MP** 25 mg/m^2 orally d1-20; cycles II,IV: **Ara-C** 75 mg/m^2 1-hr i.v. d1-5 + **teniposide** 60 mg/m^2 1-hr i.v. d1-5.
	Induction → consolidation + imatinib	Prephase: **dex** 10 mg/m^2 orally d1-5 + **cyclo** 200 mg/m^2 i.v. d3,4,5 + **MTX** 12 mg i.th. d1 → induction: **dex** 10 mg/m^2 orally d7,8;14-17 + **vinc** 1 mg i.v. d7,14 + **ida** 8 mg/m^2 0.5-hr i.v. d7,8,14,15 + **cyclo** 500 mg/m^2 1-hr i.v. d21,35 + **Ara-C** 60 mg/m^2 i.v. d22-25;29-32 + **MTX/Ara-C/dex** 12 mg/40 mg/4 mg i.th. d13,21,28,35 + **G-CSF** 5 µg/kg s.c. d7 until ANC > 1x10^9/L → consolidation: **imatinib** 600 mg/d + cycles I,III,V: **MTX** 500 mg/m^2 24-hr i.v. d1,15 + **6-MP** 25 mg/m^2 orally d1-20; cycles II,IV: **Ara-C** 75 mg/m^2 1-hr i.v. d1-5 + **teniposide** 60 mg/m^2 1-hr i.v. d1-5.
Non-randomized phase II trials		
Comparative trials		
Thomas, 2008 abs (8)	Imatinib + Hyper-CVAD	**Imatinib** 600 mg d1-14 → **imatinib** 600 mg/d courses 2-8 → **imatinib** 800 mg/d for 2yr maintenance → **imatinib** indefinitely. **Allogeneic SCT** in first CR where feasible.
	Hyper-CVAD	NR
Fielding, 2007 abs (9)	Induction + imatinib → consolidation imatinib → allogeneic SCT → imatinib	Induction: 2 phases of **chemotherapy** (details NR) + **imatinib** 600 mg/d phase 2 (added in 2005) → consolidation: **imatinib** 600 mg/d → intensification: high-dose **MTX** + **allogeneic SCT** → **imatinib** 600 mg/d for 2yr or until relapse.
	Induction → allogeneic SCT	Induction: 2 phases of **chemotherapy** (details NR) → intensification: high-dose **MTX** + **allogeneic SCT**.
de Labarthe, 2007 (10)	Prephase → induction (+ imatinib in poor early responders who then received SCT and no consolidation) → consolidation + imatinib (good early responders)	Prephase: pred 60 mg/m^2/d orally d-7to-1 + MTX 15 mg i.th. d-7to-4 → induction 1: daun 50 mg/m^2/d i.v. d1-3 + cyclo 750 mg/m^2/d i.v. d1 + vinc 2 mg i.v. d1,8 + pred 60 mg/m^2/d orally d1-14 + asparaginase 6000 IU/m^2/d i.v. d8,10,12 + MTX 15 mg i.th d1,8 + Ara-C 40 mg i.th. d1,8 + dex 40 mg i.th. d1,8 → **For good early responders:** induction 2: daun 30 mg/m^2/d i.v. d15,16 + cyclo 750 mg/m^2/d d15 + vinc 2 mg i.v. d15,22 + asparaginase 6000 IU/m^2/d i.v. d20,22,24,26,28 + G-CSF 150 µg/m^2/d s.c. or i.v. from d17 → consolidation: mitox 10 mg/m^2/d i.v. d1-3 + Ara-C 2000 mg/m^2/12hr i.v. d1-4 + imatinib 600 mg/d orally d1-SCT + MTX 15 mg i.th. d8,15 + Ara-C 40 mg i.th. d8,15 + dex 40 mg i.th. d8,15 + G-CSF 5 µg/kg/d s.c. or i.v. from d9 → SCT for patients in CR. **For poor early responders**, following induction 1: vinc 2 mg i.v.d1,8,15,22 + dex 40 mg orally or i.v. d1-2,8-9,15-16,22-23 + imatinib 800 mg/d orally d1-SCT + MTX 15 mg i.th. d1,8,15,22 + Ara-C 40 mg i.th. d1,8,15,22 + dex 40 mg i.th. d1,8,15,22 → SCT for patients in CR.
	Induction → consolidation/salvage → SCT[a]	Induction: pred 60 mg/m^2 orally or i.v. d1-7,15-21 + vinc 2 mg i.v. d1,8,15,22 + cyclo 750 mg/m^2 i.v. d1,8 + anthra[b] + MTX 15 mg i.th. d1,8,15,22 + Ara-C 40 mg i.th. d1,8,15,22 + methylpred 40 mg i.th. d1,8,15,22 → consolidation/salvage: Ara-C 1000 mg/m^2/12h 3-hr i.v. d1-4 + mitox 10 mg/m^2 i.v. d3-5 + MTX 15 mg i.th. d1 + Ara-C 40 mg i.th. d1 + methylpred 40 mg i.th. d1 → autologous SCT
Delannoy, 2006 (11)	Prephase → induction → consolidation with imatinib → maintenance with alt imatinib	Prephase (d-7-0): **methylpred** 40 mg/m^2/d + **MTX** 10 mg i.th. → induction (d1-35): **vinc** 1 mg/m^2 d1,8,15,22 + **cyclo** 400 mg/m^2 d1,8,15,22 + **daun** 40 mg/m^2 d1,8,15,22 + **methylpred** 60 mg/m^2 alt d1-22 + **MTX** 10 mg i.th. x2 → consolidation/salvage (d36-95): **imatinib** 600 mg/d + **methylpred** 96 mg d49-52,79-82 + **MTX** 10 mg x2 → Maintenance (d96-730): block 1 (d96-155) **6-MP** 60 mg/m^2 d96-126 + **cranial RT** (18 Gray in 10 doses) from d96 on + **daun** 40 mg/m^2 d127 + **Ara-C** 60 mg/m^2 s.c. d127-131 + **asparaginase** 500 U/kg i.v. or s.c. d127-131; block 2 (d156-215) **imatinib** 600 mg/d +

Author, year (ref)	Treatment Arms	Treatment details
		methylpred 96 mg d169-172,197-200; block 3 (d216-275) **Ara-C** 1 g/m^2 2-hr i.v. twice daily x5d from d216 + **mitox** 10 mg/m^2 i.v. d216,217 + at recovery **6-MP** 60 mg/m^2/d; block 4 (d276-335) **imatinib** 600 mg/d + **methylpred** 96 mg d289-292,317-320; block 5 (336-recovery) **vinc** 0.4 mg/d c.i.v. d336-339 + **dox** 9 mg/m^2 c.i.v. d336-339 + **methylpred** 96 mg d336-339; block 6 (recovery-d395) **6-MP** 60mg/m^2/d + **MTX** 20 mg/m^2 q1wk orally; block 7 (396-recovery) **etop** 200 mg/m^2 d396 + **cyclo** 1 g/m^2 d396; block 8 (recovery-d455) **6-MP** 60 mg/m^2/d + **MTX** 20 mg/m^2 q1wk orally; block 9 (456-recovery) **cyclo** 650 mg/m^2 d456 + **Ara-C** 75 mg/m^2 s.c. d456-459 + **thioguanine** 60 mg/m^2 d457-469; block 10 (recovery-730) **6-MP** 60 mg/m^2/d + **MTX** 20 mg/m^2 q1wk orally.
	Induction → consolidation → maintenance	Induction (d1-35): **vinc** 1mg/m^2 d1,8,15,22 or **vind** (details NR) + **cyclo** 400 mg/m^2 d1,8,15,22 + **daun** 40 mg/m^2 d1,8,15,22 + **methylpred** 60 mg/m^2 alt d1-22 + **MTX** 10 mg i.th. 2 times → consolidation: **Ara-C** 1 g/m^2 2-hr i.v. twice daily x5d + **mitox** 10 mg/m^2 i.v. x2d then **IFN-α** for 3 mos then **vinc** 0.4 mg/d c.i.v. x4d + **dox** 9 mg/m^2 c.i.v. x4d + **dex** 40 mg/d x4d → maintenance: **6-MP** + **MTX** for 18 mos (details NR).
Wassmann, 2006 (12)	Prephase → induction → alt imatinib and consolidation → SCT	Prephase: dex 10 mg/m^2 orally d1-5 + cyclo 200 mg/m^2 i.v. d3-5 + MTX 15 mg i.th. d1 → induction 1: dex 10 mg/m^2 orally d6-7,13-16 + vinc 2 mg i.v. d6,13,20 + daun 45 mg/m^2 i.v. d6,7,13,14 + asparaginase 1000 U/m^2 2-hr i.v. d20 + G-CSF 5 µg/kg s.c. d6+ → induction 2: cyclo 1000 mg/m^2 i.v. d26,46 + Ara-C 75 mg/m^2 i.v. d28-31,35-38,42-45 + 6-MP 60 mg/m^2 orally d26-46 + MTX 15 mg i.th. d28,35,42 + G-CSF 5 µg/kg s.c. until ANC > 1x10^9/L + CNS irradiation 24 Gy over 12d → imatinib 400-600 mg/d → consolidation: dex 10 mg/m^2 orally d1-5 + vind 3 mg/m^2 i.v. d1 + MTX 1.0-1.5 mg/m^2 24-hr i.v. d1 + etop 250 mg/m^2 1-hr i.v. d4,5 + Ara-C 1-2 g/m^2 3-hr i.v. d5 + G-CSF 5 µg/kg s.c. d7+ + MTX 15 mg i.th. d12 + Ara-C 40 mg i.th. + dex 4 mg i.th. → imatinib 400-600 mg/d → SCT
	Prephase → induction + imatinib → consolidation + imatinib → SCT	Prephase: dex 10 mg/m^2 orally d1-5 + cyclo 200 mg/m^2 i.v. d3-5 + MTX 15 mg i.th. d1 → induction 1: dex 10 mg/m^2 orally d6-7,13-16 + vinc 2 mg i.v. d6,13,20 + daun 45 mg/m^2 i.v. d6,7,13,14 + asparaginase 1000 U/m^2 2-hr i.v. d20 + G-CSF 5 µg/kg s.c. d6+ + imatinib 600 mg/d → induction 2: cyclo 1000 mg/m^2 i.v. d26,46 + Ara-C 75 mg/m^2 i.v. d28-31,35-38,42-45 + 6-MP 60 mg/m^2 orally d26-46 + MTX 15 mg i.th. d28,35,42 + G-CSF 5 µg/kg s.c. until ANC > 1x10^9/L + CNS irradiation 24 Gy over 12d + imatinib 600 mg/d → consolidation: dex 10 mg/m^2 orally d1-5 + vind 3 mg/m^2 i.v. d1 + MTX 1.0-1.5 mg/m^2 24-hr i.v. d1 + etop 250 mg/m^2 1-hr i.v. d4,5 + Ara-C 1-2 g/m^2 3-hr i.v. d5 + G-CSF 5 µg/kg s.c. d7+ + MTX 15 mg i.th. d12 + Ara-C 40 mg i.th. + dex 4 mg i.th. → imatinib 400-600 mg/d + imatinib 600 mg/d → SCT
Lee, 2005 (13)	Induction → imatinib → consolidation/salvage → imatinib → SCT	Induction: hyper cyclo 300 mg/m^2/12h d1-3 + vinc 1.4 mg/m^2 d4,11 + ida 12 mg/m^2 d4,11 + dex 40 mg d1-4,11-14; after recovery of WBC and platelets: **For patients in CR** → imatinib 400 or 600 mg/d x4wk → consolidation: Ara-C 2 g/m^2/12h d1-5 + mitox 12 mg/m^2 d1,2 → imatinib 400 or 600 mg/d until SCT. **For patients not in CR** → imatinib 600 mg/d x4wk → salvage: Ara-C 2 g/m^2/12h d1-4 + mitox 12 mg/m^2 d1-4 + etop 100 mg/m^2 d5-7. MTX + Ara-C + methylpred administered i.th. during induction and consolidation (6x total).
	Induction → consolidation/salvage → SCT	Induction: ida + vinc + pred + asparaginase → consolidation/salvage: except imatinib, patients received same regimens as imatinib group → SCT. MTX + Ara-C + methylpred administered i.th. during induction and consolidation (6x total).
Lee, 2005 (14)	Induction + imatinib → consolidation + imatinib → SCT	Induction: daun 50 mg/m^2 i.v. d1-3 + vinc 2 mg i.v. d1,8,15,22 + pred 60 mg/m^2 d1-28 + asparaginase i.m. 4000 U/m^2 d17-28 → consolidation A (courses 1,3,5,7): daun 50 mg/m^2 i.v. d1,2 + vinc 2 mg i.v. d1,8 + pred 60 mg/m^2 orally d1-14 + asparaginase 12000 U/m^2 i.m. d2,4,7,9,11; consolidation B (courses 2,4,6,8): Ara-C 300 mg/m^2 i.v. d1,4,8,11 + etop 75 mg/m^2 d1,4,8,11 → SCT First 12 patients: induction: imatinib mg/d x14d → consolidation: imatinib

Author, year (ref)	Treatment Arms	Treatment details
		400 mg/d d1-14 x8 courses Subsequent patients: induction: imatinib 600 mg/d → consolidation: imatinib 400 mg/d
	Induction → consolidation → SCT	Induction: daun 50 mg/m^2 i.v. d1-3 + vinc 2 mg i.v. d1,8,15,22 + pred 60 mg/m^2 d1-28 + asparaginase i.m. 4000 U/m^2 d17-28 → consolidation A (courses 1,3,5,7): daun 50 mg/m^2 i.v. d1,2 + vinc 2 mg i.v. d1,8 + pred 60 mg/m^2 orally d1-14 + asparaginase 12000 U/m^2 i.m. d2,4,7,9,11; consolidation B (courses 2,4,6,8): Ara-C 300 mg/m^2 i.v. d1,4,8,11 + etop 75 mg/m^2 d1,4,8,11 → SCT
Non-comparative trials		
Carpenter, 2007 (15)	SCT → imatinib	SCT → imatinib 400 mg/d d1-365
Vignetti, 2007 (16)	Prephase → induction imatinib	Prephase: pred 10-40 mg/m^2/d d1-7 → induction: imatinib 800 mg/d + pred 40 mg/m^2/d d1-45
Rea, 2006 (17)	Induction + imatinib	Imatinib 800 mg/d d1-56 + vinc 2 mg i.v. d1,8,15,22 + dex 40 mg/d orally or i.v. d1-2,8-9,15-16 + MTX 15 mg i.th. d1,8,15,22 + Ara-C 40 mg i.th. d1,8,15,22 + dex 40 mg i.th. d1,8,15,22
Yanada, 2007 (18) abs Towatari, 2004 (19)	Induction + imatinib → consolidation + imatinib → maintenance + imatinib	Induction: cyclo 1200 mg/m^2 3-hr i.v. d1 + daun 60 mg/m^2 1-hr i.v. d1-3 + vinc 1.3 mg/m^2 i.v. d1,8,15,22 + pred 60 mg/m^2 orally d1-21 + imatinib 600 mg/d orally d8-63 + MTX 15 mg i.th. d29 + Ara-C 40 mg i.th. d29 + dex 4 mg i.th. d29 → consolidation, odd courses: MTX 1 g/m^2 24-hr i.v. d1 + Ara-C 2 g/m^2/12-hr 3-hr i.v. d2-3 + MTX 15 mg i.th. d1 + Ara-C 40 mg i.th. d1 + dex 4 mg i.th. d1; even courses: imatinib 600 mg/d orally d1-28 + MTX 15 mg i.th. d1 + Ara-C 40 mg i.th. d1 + dex 4 mg i.th. d1 → maintenance: vinc 1.3 mg/m^2 i.v. d1 + pred 60 mg/m^2 orally d1-5 + imatinib 600 mg/d orally d1-28
Wassmann, 2004 (20) Wassmann, 2003 (21) Ottmann, 2002 (22)	Imatinib	Imatinib 400 or 600 mg/d (800 mg/d for patients that relapsed)
Rousselot, 2007 (23) abs	Induction + imatinib → consolidation + imatinib → maintenance Pegasys/ imatinib or SCT	Induction: vinc 2 mg/d i.v. x2d + dex 40 mg/d orally x2d q1wk x4wk + imatinib 800 mg/d → consolidation: vinc 2 mg/d i.v. x2d + dex 40 mg/d orally x2d q1mo x4mo + imatinib 600 mg/d + 6-MP → Pegasys 45 µg s.c. q1wk + imatinib 400 mg/d for 2yr *OR* SCT
Mukhopadhyay, 2007 (24) abs	Induction + imatinib	Imatinib 400 mg/d + pred 40 mg/m^2 for 6wk then tapering dose for 2wk + vinc 2 mg/m^2 q1wk x6wk
Wetzler, 2007 (25) abs	Induction imatinib→ SCT → maintenance imatinib	Induction: imatinib 800 mg/d x4wk → high-dose MTX i.v. and i.th. q1wk x3wk → imatinib 800 mg/d x4wk → allogeneic or autologous SCT → maintenance imatinib
Lickliter, 2004 (26) abs	Prephase imatinib → induction + imatinib	Prephase: imatinib 600 mg/d x1wk → relapsed ALL: standard-dose ida + Ara-C + imatinib 600 mg/d → after recovery, imatinib 600 mg/d; newly diagnosed ALL: induction: pred 60 mg/m^2 orally or i.v. d1-7,15-21 + vinc 2 mg i.v. d1,8,15,22 + cyclo 750 mg/m^2 i.v. d1,8 + anthra[b] + MTX 15 mg i.th. d1,8,15,22 + Ara-C 40 mg i.th. d1,8,15,22 + methylpred 40 mg i.th. d1,8,15,22 → consolidation/salvage: Ara-C 1000 mg/m^2/12h 3-hr i.v. d1-4 + mitox 10 mg/m^2 i.v. d3-5 + MTX 15 mg i.th. d1 + Ara-C 40 mg i.th. d1 + methylpred 40 mg i.th. d1 → autologous SCT
Norasetthada, 2004 (27) abs	Imatinib → SCT following non-myeloablative conditioning → imatinib	Imatinib 600 mg/d orally → allogeneic SCT (after non-myeloablative conditioning) → imatinib 600 mg/d orally x14d
Ribera, 2004 (28) abs	Induction + imatinib → consolidation + imatinib → allogeneic SCT	Induction: imatinib 400 mg/d orally + vinc 1.5 mg/m^2/wk + daun 60 mg/m^2/wk + pred 60 mg/m^2/d x4wk → consolidation 1: imatinib 400 mg/d orally + MTX 1.5 g/m^2 + teniposide + Ara-C → allogeneic SCT or consolidation 2[c]: imatinib 400 mg/d orally for up to 1-yr + vinc + daun +

Author, year (ref)	Treatment Arms	Treatment details
	dex + cyclo	

Notes: abs=abstract; alt=alternating; anthra=anthracycline; Ara-C=cytarabine; c.i.v.=continuous intravenous infusion; CNS=central nervous system; CR=complete remission; CVAD=cyclophosphamide, vincristine, doxorubicin, dexamtheasone; cyclo=cyclophosphamide; d=day(s); daun=daunorubicin; dex=dexamethasone; dox=doxorubicin; etop=etoposide; G-CSF=granulocyte-colony stimulating factor; hr=hour(s); ida=idarubicin; IFN-α=interferon-α; i.m.=intramuscular; i.th.=intrathecally; i.v.=intravenously; methylpred=methylprednisolone; mitox=mitoxantrone; mos=months; MTX=methotrexate; NR=not reported; pred=prednisone; RT=radiation therapy; s.c.=subcutaneously; SCT=stem cell transplantation; vinc=vincristine; vind=vindesine; yr=year(s); 6-MP=6-mercaptopurine; →=followed by; .

[a]Details of the treatment regimen for the historical control group were obtained from Dombret et al (29).

[b]Patients were randomized to receive either daunorubicin 30 mg/m^2 i.v. d1-3,15-16 or idarubicin 9 mg/m^2 d1-3,8.

[c]Second consolidation in patients without an HLA-identical family or marrow unrelated donor.

Appendix C1. Patient and trial characteristics of non-comparative phase II trials examining imatinib in Ph+ ALL.

Author, year (ref)	Patient characteristics	Intervention[a]	N[b]	Age, mdn (yr)
Carpenter, 2007 (15)	Ph+ ALL or CML beyond first chronic phase who received allogeneic SCT and eligible for myeloablative conditioning.	SCT → imatinib	15	NR
Vignetti, 2007 (16)	Ph+ ALL age > 60 years.	Prephase → induction imatinib	30	69
Rea, 2006 (17)	Ph+ ALL or LBC CML, ECOG PS 0-2, no CNS involvement	Induction + imatinib	18	NR
Yanada, 2007 (18) abs Towatari, 2004 (19)	Newly diagnosed Ph+ ALL age 15-64 years, ECOG PS 0-3.	Induction + imatinib → consolidation + imatinib → maintenance + imatinib	24	41.5
Wassmann, 2004 (20) Wassmann, 2003 (21) Ottmann, 2002 (22)	Relapsed/refractory Ph+ ALL age ≥ 18 years, ECOG PS 0-2.	Imatinib	68	48
Rousselot, 2007 (23) abs	Resistant/refractory Ph+ ALL or lymphoid blast crisis CML or newly diagnosed Ph+ ALL age >55 years.	Induction + imatinib → consolidation + imatinib → maintenance Pegasys/ imatinib or SCT	54[c]	62
Mukhopadhyay, 2007 (24) abs	Ph+ ALL, age > 50 years	Induction + imatinib	10	64
Wetzler, 2007 (25) abs	Ph+ ALL age 15-59 years with CR/PR after one cycle of a 4-5 drug induction regimen	Induction imatinib→ SCT → maintenance imatinib	35	NR
Lickliter, 2004 (26) abs	Ph+ ALL	Prephase imatinib → induction + imatinib	17	NR
Norasetthada, 2004 (27) abs	Ph+ ALL	Imatinib → SCT following non-myeloablative conditioning → imatinib	11[d]	51
Ribera, 2004 (28) abs	Newly diagnosed Ph+ ALL	Induction + imatinib → consolidation + imatinib → allogeneic SCT	19	43[e]

Notes: abs=abstract; ALL=acute lymphoblastic leukemia; CML=chronic myeloid leukemia; CNS=central nervous system; CR=complete response; ECOG=Eastern Cooperative Oncology Group; LBC=lymphoid blast crisis; mdn=median; N=number of patients; Ph+=Philadelphia chromosome-positive; PR=partial response; PS=performance status; ref=reference; SCT=stem cell transplantation; yr=year(s).

[a]Full regimen details including dose and schedule information can be found in Appendix B.

[b]Number of patients with Ph+ ALL.

[c]Twenty-two patients had resistant or refractory Ph+ ALL, three patients had relapsed Ph+ ALL, 25 patients were elderly and had newly diagnosed Ph+ ALL, and four patients had lymphoid blast crisis CML.

[d]The 11 patients were split into two cohorts: six patients received imatinib, while five patients did not.

[e]Mean age.

Appendix C2. Efficacy outcomes reported in non-comparative phase II trials examining imatinib in Ph+ ALL.

Author, year (ref)	Intervention	N	OS	DFS/PFS/ RFS	CR after induction (%)	CR after induction with PB recovery (%)	CR after consolidation /salvage (%)	Follow-up mdn (mos)
Carpenter, 2007 (15)	SCT → imatinib	15	NR	NR	NR	NR	NR	17
Vignetti, 2007 (16)	Prephase → induction imatinib	29	Mdn 20 mos	DFS 1-yr: 48%	96.7	NR	NA	NR
Rea, 2006 (17)	Induction + imatinib	18	Mdn 13.3 mos	Mdn DFS 9.9 mos	94.4	NR	NA	NR
Yanada, 2007 (18) abs Towatari, 2004 (19)	Induction + imatinib → consolidation + imatinib → maintenance + imatinib	24	1-yr 89%	1-yr EFS 68%	95.8	NR	NR	12
Wassmann, 2004 (20) Wassmann, 2003 (21) Ottmann, 2002 (22)	Imatinib	68	18-mos 22.6%	6-mos PFS 22.8%	30	NR	NA	NR
Rousselot, 2007 (23) abs	Induction + imatinib → consolidation + imatinib → maintenance Pegasys/ imatinib or SCT	54	Mdn SCT: 29.9 mos Maint: 27.9 mos	NR	85	NR	NR	18
Mukhopadhyay, 2007 (24) abs	Induction + imatinib	10	NR	NR	100	NR	NR	8
Wetzler, 2007 (25) abs	Induction imatinib→ SCT → maintenance imatinib	35	NR	NR	88.6	NR	NR	NR
Lickliter, 2004 (26) abs	Prephase imatinib → induction + imatinib	14	NR	NR	64.3	NR	NR	NR
Norasetthada, 2004 (27) abs	Imatinib → SCT following non-myeloablative conditioning → imatinib	6[a]	NR	NR	NA	NA	NA	NR
Ribera, 2004 (28) abs	Induction + imatinib → consolidation + imatinib → allogeneic SCT	19	NR	Mdn DFS 8 mos	NR	NR	84.2	5

Notes: abs=abstract; CR=complete remission rate; DFS=disease-free survival; EFS=event-free survival; maint=maintenance; mdn=median; mos=months; N=number of evaluable patients; NA=not applicable; NR=not reported; OS=overall survival; PB=peripheral blood; PFS=progression-free survival; ref=reference; RFS=relapse-free survival; SCT=stem cell transplantation; yr=year(s).

[a]All six patients had previously received induction therapy. Patients received imatinib upon enrolment and all six relapsed prior to SCT.

Appendix C3. Grade 3 or 4 adverse events related to treatment with imatinib in non-comparative phase II trials.

Author, year (ref)	Intervention	N	All G3/4 AE's (%)	Non-heme G3/4 AE's (%)	G3/4 nausea/ vomiting (%)	G3/4 diarrhea (%)	Neutropenic fever (%)	G3/4 Neutropenia
Carpenter, 2007 (15)	SCT → imatinib	22[a]	50[b]	NR	NR	NR	NR	NR
Vignetti, 2007 (16)	Prephase → induction imatinib	30	NR	43.3	3.3	NR	NR	NR
Rea, 2006 (17)	Induction + imatinib	31[a]	NR	NR	9.7	NR	NR	NR
Yanada, 2007 (18) abs Towatari, 2004 (19)	Induction + imatinib → consolidation + imatinib → maintenance + imatinib	24	NR	NR	17	4	26	NR
Wassmann, 2004 (20) Wassmann, 2003 (21) Ottmann, 2002 (22)	Imatinib	68	NR	NR	NR	NR	NR	50
Rousselot, 2007 (23) abs	Induction + imatinib → consolidation + imatinib → maintenance Pegasys/ imatinib or SCT	54	NR	5.6	NR	NR	NR	NR
Mukhopadhyay, 2007 (24) abs	Induction + imatinib	10	NR	NR	NR	NR	NR	NR
Wetzler, 2007 (25) abs	Induction imatinib→ SCT → maintenance imatinib	35	NR	NR	NR	NR	NR	NR
Lickliter, 2004 (26) abs	Prephase imatinib → induction + imatinib	14	NR	NR	NR	NR	NR	NR
Norasetthada, 2004 (27) abs	Imatinib → SCT following non-myeloablative conditioning → imatinib	6[c]	NR	NR	NR	NR	NR	NR
Ribera, 2004 (28) abs	Induction + imatinib → consolidation + imatinib → allogeneic SCT	19	NR	NR	NR	NR	NR	NR

Notes: abs=abstract; AE=adverse event(s); G3/4=grade 3 or 4; N=number of patients; non-heme=non-hematological; NR=not reported; PFS=progression-free survival; ref=reference; RFS=relapse-free survival; SCT=stem cell transplantation.

[a]Toxicity data were reported for all patients: data for Ph+ ALL patients were not reported separately.

[b]Grade 2-5 adverse events.

[c]All six patients had previously received induction therapy. Patients received imatinib upon enrolment and all six relapsed prior to SCT.

[a]Adverse events reported for induction/consolidation.

APPENDIX D. ONGOING TRIALS.

Study comparing imatinib with chemotherapy as induction in elderly patients (age > 55 years) with Philadelphia positive acute lymphoblastic leukemia (ALL)

Protocol ID:	NCT00199186,CSTI571ADE10, GMALL-STI571-ELDERLY-01/02
Last date modified:	October 18, 2007
Trial type:	Randomized, open-label, active control
Accrual:	NR
Primary outcome:	Complete remission rate after induction therapy
Sponsorship:	Johann Wolfgang Goethe University Hospitals
Status:	Accruing

Young adult (age 18-59 years) with acute lymphoblastic leukemia (ALL): randomized trial between an imatinib-based induction and a chemotherapy + imatinib induction. Trial is split into three subgroups based on disease: GRALL 2005 (T ALL or B ALL Ph-); GRAALL 2005 R (ALL Ph- CD20+); GRAAPH 2005 (ALL Ph+).

Protocol ID:	NCT00327678, GRAAPH 2005: ALL Ph
Last date modified:	May 6, 2008
Accrual:	1080 (Ph+ ALL group: NR)
Trial type:	Randomized, open-label, active control
Primary outcome:	Event-free survival, percentage of patients with minimal residual disease < 10-4 after induction and/or consolidation
Sponsorship:	Group for Research in Adult Acute Lymphoblastic Leukemia, Projet Hospitalier de Recherche Clinique no. AO<O4144-P040429 Assistance Publique – Hôpitaux de Paris
Status:	Accruing

Notes: NR=not reported.