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**Recommendation Report SCT-4 ARCHIVED**

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

# Stem Cell Transplantation in Lymphoma

*Members of the Stem Cell Transplantation Expert Panel*

**Recommendation Report SCT-4 was ARCHIVED in 2021 by the Stem Cell Transplantation Expert Panel. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.**
**See Section 3: Document Assessment and Review for details.**

**Recommendation Report SCT-4 is comprised of 3 sections. You can access the full report here:**
**https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/971**



December 13, 2012

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**Recommendation Report History**

| GUIDELINE VERSION | SYSTEMATIC REVIEW | | PUBLICATIONS | NOTES and KEY CHANGES |
|---|---|---|---|---|
| | Search Dates | Data | | |
| Original December 13, 2012 | 2006 to Feb 2011 | Full Report | Web publication | This document updated a 2009 recommendation report: Stem Cell Transplantation in Adults. *K. Imrie, R.B. Rumble, M. Crump, the Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care* [Report Date: January 30, 2009]. |
| Reviewed February 25, 2021 | 2011 to May 2020 | New data found in Section 3: Document Assessment and Review | Updated web publication | 2012 recommendations are ARCHIVED |

Ontario Health
Cancer Care Ontario

**Recommendation Report SCT-4: Section 1**

# Stem Cell Transplantation in Lymphoma: Recommendations

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

**Report Date: December 13, 2012**



## CLINICAL QUESTION

What is the role of stem cell transplantation in the treatment of the various lymphomas?

## TARGET POPULATION

All adult patients with lymphoma who are being considered for treatment that includes either bone marrow or stem cell transplantation.

## QUALIFYING STATEMENT

The patient selection process and the ultimate decision to perform a stem cell transplant should take into account not only disease-related characteristics, but also co-morbidities and patient preferences.

## RECOMMENDATIONS AND KEY EVIDENCE

### Hodgkin Lymphoma (HL)

| **Recommendation 1** |
|---|
| Stem cell transplantation is not recommended as part of routine primary therapy for HL. Standard treatment for HL remains chemotherapy with or without radiation. |
| **Evidence**<br>Of three papers obtained [one randomized trial [1], one prospective cohort study [2], and one retrospective cohort study [3,4]], none contained any evidence that transplantation as part of |

| |
|---|
| routine upfront therapy provides any benefits. The Expert Panel continues to endorse chemotherapy with or without radiation as standard treatment for HL. |
| **Recommendation 2** |
| Autologous stem cell transplantation is the recommended treatment option for chemo-sensitive patients with HL who are refractory to or who have relapsed after primary chemotherapy. Patients with stable disease following salvage chemotherapy could also remain eligible for autologous stem cell transplantation. Patients with progressive disease despite salvage chemotherapy should not be offered autologous stem cell transplantation outside the context of a clinical trial. |
| **Evidence**<br>This Recommendation was brought forward from the 2009 Recommendation Report [5].[1] As none of the more-recent evidence included in this report refutes this earlier recommendation, the Expert Panel continues to endorse it. |
| **Recommendation 3** |
| Allogeneic stem cell transplantation is an option for chemo-sensitive patients with refractory or relapsed HL if they have a syngeneic (identical twin) donor, or following autologous stem cell transplantation failure, or alternatively in patients in whom sufficient numbers of autologous stem cells cannot be collected. |
| **Evidence**<br>This Recommendation was brought forward from the 2009 Recommendation Report [5]. As none of the more-recent evidence included in this report refutes this earlier recommendation, the Expert Panel continues to endorse it. One retrospective cohort study [4] detected an overall survival difference in favour of reduced-intensity conditioning compared with myeloablative conditioning followed by allogeneic stem cell transplantation. |

## Non-Hodgkin Lymphomas (NHL)

| |
|---|
| ***Aggressive Histology NHL (AH-NHL) - Including Diffuse Large B-Cell Lymphoma, Transformed Lymphoma, and Aggressive Histology T-Cell Lymphomas*** |
| **Recommendation 4** |
| Autologous stem cell transplantation is the recommended option for chemo-sensitive patients with AH-NHL refractory to or relapsed after primary therapy. |
| **Evidence**<br>One clinical practice guideline [6] recommended autologous stem cell rescue following high-dose therapy as second-line therapy for diffuse large B-cell lymphoma. As none of the more-recent evidence included in this report refutes this earlier recommendation, the Expert Panel continues to endorse it. |
| **Recommendation 5** |
| Allogeneic stem cell transplantation is an option for chemo-sensitive patients with refractory or relapsed AH-NHL if they have a syngeneic (identical twin) donor, or following autologous stem cell transplantation failure, or alternatively in patients in whom sufficient numbers of autologous stem cells cannot be collected. |

**Evidence**

This Recommendation was brought forward from the 2009 Recommendation Report [5]. As none of the more-recent evidence included in this report refutes this earlier recommendation, the Expert Panel continues to endorse it.

One clinical practice guideline [7] recommended that patients with diffuse large B cell lymphoma and good performance status that respond to rescue CT should be enrolled in approved clinical studies testing new treatments, allogeneic stem cell transplantation, or supportive therapies.

**Recommendation 6 – *Revised 2020***

Stem cell transplantation could be considered for selected patients with AH-NHL as part of primary therapy.

**Evidence – *Added to the 2020 Review***

This recommendation was modified from the 2012 Recommendation Report that stated that stem cell transplantation is not recommended for patients with AH-NHL as part of primary therapy [8]. This change was made based on Expert Panel consensus and in consideration of two retrospective studies [9,10] suggesting that transplantation as part of primary therapy might provide some benefits in patients with AH T-Cell lymphomas (e.g., angioimmunoblastic T-cell lymphoma).

**QUALIFYING STATEMENT - *Added to the 2020 Review (See Section 3 for details)***

- A PEBC Guideline assessing the management of patients with primary central nervous system diffuse large B cell lymphoma, a rare type of aggressive B cell lymphoma, supports consolidation therapy with autologous stem cell transplantation as part of first line therapy. The guideline can be found at https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/49406.
- Although beyond the scope of this recommendation report, the Expert Panel recognizes that the recently approved chimeric antigen receptor-T (CAR-T) cell therapy is becoming the preferred option over allogeneic stem cell transplantation for patients with diffuse large B cell lymphoma (and its variants) or transformed lymphoma who have relapsed following autologous stem cell transplantation or who have been treated with at least two lines of therapy.

- ***Follicular Lymphoma (FL)***

**Recommendation 7**

Autologous or allogeneic transplantation are options for chemo-sensitive patients with poor prognosis FL refractory to or relapsed after primary therapy.

**Evidence:**

This recommendation is supported by evidence obtained from a systematic review [11], and a clinical practice guideline [6]. The systematic review [11] recommended autologous SCT as salvage treatment based on pre-rituximab data, as there was a demonstrated benefit in both OS and PFS. The clinical practice guideline [6] stated that either autologous stem cell transplantation or allogeneic stem cell transplantation were acceptable options for second-line or subsequent treatment.

- ***Burkitt's Lymphoma***

| Recommendation 8 |
|---|
| Autologous and allogeneic transplantation are options for chemo-sensitive patients with Burkitt's lymphoma refractory to or relapsed after primary treatment. |
| ***Evidence***<br>This Recommendation was brought forward from the 2009 Recommendation Report [5]. As none of the more-recent evidence included in this report refutes this earlier recommendation, the Expert Panel continues to endorse it. |

- ***Mantle Cell Lymphoma (MCL)***

| Recommendation 9 |
|---|
| Autologous stem cell transplantation is recommended for patients with MCL in first remission. |
| ***Evidence***<br>This Recommendation was modified slightly from the 2009 Recommendation Report [5] that stated that autologous stem cell transplantation was an option for eligible patients only. This change was made based on Expert Panel consensus and in consideration of a paper on the topic published by Dreyling et al [12] (see Discussion in Section 2). |
| **QUALIFYING STATEMENT - *Added to the 2020 Review (See Section 3 for details)***<br>A PEBC Recommendation Report assessing the management of patients newly diagnosed with MCL also supports consolidation with autologous stem cell transplantation as part of first line therapy. The report can be found at https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/66326 |
| **Recommendation 10** |
| Select patients with MCL in first or second remission may be considered for allogeneic transplant. Autologous transplantation is also an option for chemo-sensitive patients with MCL in second remission. |
| ***Evidence***<br>This Recommendation was brought forward from the 2009 Recommendation Report [5] and modified slightly to include allogeneic transplantation for select patients in first remission based on consensus from the Expert Panel. |
| **QUALIFYING STATEMENT - *Added to the 2020 Review (See Section 3 for details)***<br>Although beyond the scope of this recommendation report, there is emerging evidence showing that CAR-T cell therapy may be of value in relapsed MCL, and may evolve to be the preferred option over allogeneic transplantation in selected patients. |

[1]Stem Cell Transplantation in Adults. *K. Imrie, R.B. Rumble, M. Crump, the Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care* [Report Date: January 30, 2009].

## FUTURE RESEARCH

Many new chemotherapeutic compounds are being tested in lymphoma as part of upfront treatment, at the time of relapse and in a maintenance schedule. Depending on the results of such trials, the numbers of patients who might require a transplant could decrease. In the situation of allogeneic transplantation, technologies allowing less morbidity or mortality or an increase in available donors could increase the number of lymphoma patients potentially eligible for allogeneic transplantation.

**IMPLICATIONS FOR POLICY**

At this time, we expect no significant change or perhaps a slight increase in the numbers of lymphoma patients who might require stem cell transplantation. Improvement in upfront therapy or treatment at the time of relapse may decrease the numbers, although no significant changes are expected in the foreseeable future.

**RELATED PROGRAM IN EVIDENCE-BASED CARE REPORTS**

Stem Cell Transplantation in Adults. K. Imrie, R.B. Rumble, M. Crump, the Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care [Report Date: January 30, 2009]. Available at: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=35448

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*Updating*

All PEBC documents are maintained and updated
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**Recommendation Report SCT-4: Section 2**

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

# Stem Cell Transplantation in Lymphoma: Summary of Methods and Evidence

*C.T. Kouroukis, R.B. Rumble, J. Kuruvilla, M. Crump, J. Herst, and C. Hamm*

**The 2012 recommendations have been ARCHIVED. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.**

**Report Date: December 13, 2012**



## QUESTION

What is the role of stem cell transplantation in the treatment of the various lymphomas?

## INTRODUCTION

The lymphomas comprise various malignancies that originate from lymphocytes in different developmental stages and that use distinct oncogenic pathways, but that may appear identical under microscopic examination [13]. In Canada, the non-Hodgkin's lymphomas have the fourth highest cancer incidence reported in males (4200 estimated new cases; 2011), and the fifth in females (3400 estimated new cases), and are the fifth most-common cause of cancer death for both sexes combined (3000 estimated deaths; 2011), representing a significant burden [14]. While Hodgkin's lymphoma is generally considered curable [15], the disease still affects many Canadians, often young individuals, with an estimated incidence of 920 new cases for 2011 [14]. As lymphoma patients represent a very heterogeneous group, even within each subtype [15], and treatment benefits and toxicity effects change as chemotherapy, radiation, and SCT therapies evolve, a systematic review of the available evidence is warranted.

The goal of this Recommendation Report is to review the most-current evidence comparing treatment modalities that include a stem cell transplantation component, and to make a series of clinical recommendations to inform clinicians, patients and other stakeholders of the treatment options available.

## METHODS

This advice report, produced by the Program in Evidence-Based Care (PEBC) of CCO, is a convenient and up-to-date source of the best-available evidence on stem cell transplantation in lymphoma, 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. Members of

the CCO Stem Cell Transplant Steering Committee provided feedback and helped to draft this report, which was intended to update the findings of a previous CCO report completed in 2009 [16].

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**

The MEDLINE (OVID) database [2006 through February (week three) 2011] was systematically searched for evidence on March 1, 2011 using the strategy that appears in Appendix A. A total of 634 hits were obtained, and after excluding irrelevant papers according to a title and abstract review, 30 were ordered for full-text review. Of these 30 ordered for full-text review, 14 met the inclusion criteria and were retained.

**Study Selection Criteria**

***Inclusion Criteria***

Articles were selected based on the following criteria:

1. Systematic reviews with or without meta-analysis or Clinical Practice Guidelines if evidence was obtained with systematic review.
2. Fully published Randomized Controlled Trials (RCTs) on patients with lymphoma that received SCT and reported on survival and/or Quality of Life (QoL).
3. Fully published non-randomized studies on patients with lymphoma that received SCT and had an appropriate contemporaneous control group that reported on survival or QoL.
4. Reports published in English only.

**Synthesizing the Evidence**

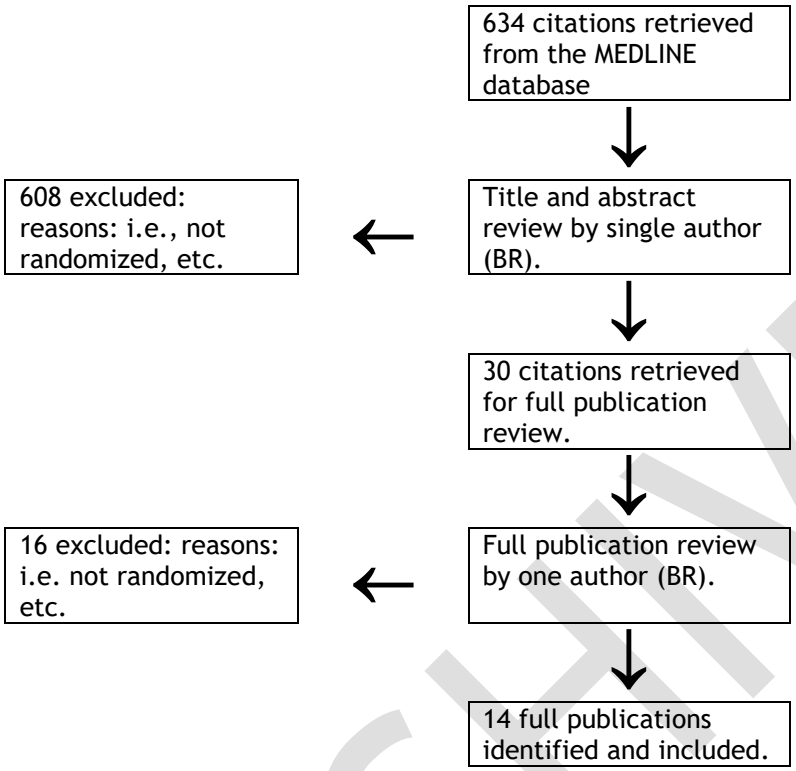
No pooling was planned for this report but would be considered if data allow.

**Assessment of Study Quality**

The quality of the included evidence was assessed as follows: For systematic reviews that would be used as the evidence base for our recommendations, the AMSTAR tool would be used to assess quality. For Clinical Practice Guidelines, the AGREE 2 instrument would be used, but only if adaptation of the recommendations was being considered. Any meta-analysis would be assessed for quality using similar criteria as used for RCTs, where appropriate. RCTs would be assessed for quality by examining the following seven criteria: the method of randomization, reporting of blinding, the power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, but non-randomized, evidence would be assessed according to full reporting of the patient selection criteria, the interventions each patient received and of all relevant outcomes.

**RESULTS: Literature search results and quality appraisal**

**Figure 1. Selection of studies investigating stem cell transplantation in lymphoma from the MEDLINE search results**




**Quality of included studies**

***Hodgkin's lymphoma***

Four papers were obtained on Hodgkin's lymphoma [1-4] comprising a randomized trial [1], one prospective cohort study [2], and two retrospective cohort studies [3,4].

The randomized trial reported by Arakelyan et al [1] allocated patients to either chemotherapy followed by radiation or chemotherapy followed by autologous stem cell transplantation. Randomization was performed at each centre using blocks of six. Blinding, sample size calculations, and power calculations were not reported on. Statistical analysis for qualitative data was done using chi-square or a two-tailed Fisher's exact test. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test with a set level of significance of 0.05 (two-sided test). The primary outcome was freedom from treatment failure, and the secondary outcome was five-year overall survival.

The prospective cohort study reported by Majhail et al [2] fully described the patient populations, and reported differences in age (younger in the UCB group) and in the duration of first complete remission (shorter in the UCB group). The interventions used were fully detailed. The outcomes of neutrophil engraftment, GVHD, two-year PFS rates, and TRM were fully reported.

The retrospective cohort study reported by Morabito et al [3] fully described the included patient population with no differences being reported. The interventions used were fully detailed. The outcomes of complete response rates and overall survival were well

reported. The investigators made an attempt to reduce biases due to the retrospective nature of the study through a multivariate analysis for survival using age, B-symptoms, performance status, and treatment received as variables.

The retrospective cohort study reported by Sureda et al [4] fully described the included patients population, and reported differences in time to allografting (earlier in RIC group), more BMT in MAC patients, more PBSCT in RIC patients, heavier pretreatment in RIC group, longer time interval between diagnosis and alloSCT in RIC group, and previous treatment failure following prior ASCT in RIC group. The outcomes and the methods of analysis used were fully reported, but no steps were taken to reduce biases due to the retrospective nature of the study.

***Non-Hodgkin's lymphoma***

*1. Aggressive non-Hodgkin lymphoma and diffuse large B-cell lymphoma*

For aggressive non-Hodgkin lymphoma, one meta-analysis [17] and one RCT [18] were obtained. In the meta-analysis, reported by Greb et al [17], eligible studies were obtained by systematically searching the Cochrane Controlled Trials Registry, MEDLINE, EMBASE, as well as other Internet databases of ongoing trials, unpublished literature, and relevant conference proceedings from the year 1990 through to the end of January 2005. No language-based restrictions were used in this search. Included evidence was RCTs comparing first-line high-dose chemotherapy (HDCT) followed by ASCT with conventional CT in patients with biopsy-proven aggressive NHL. Included studies needed to have at least 20 patients per arm, and the majority of patients in each arm had to have a diagnosis of aggressive NHL. Two reviewers performed data extraction independently, with disagreements being resolved via discussion with a third party. Studies that met the inclusion criteria were assessed for quality based on method of randomization, blinding, whether or not it was an ITT analysis, and reporting of dropouts and withdrawals. For all planned analyses, both fixed- and random-effects models were used, with the random-effects analysis being used to test the robustness of the fixed-effects analysis results. Results for time-to-event outcomes (OS, EFS) were expressed as Hazard Rates (HR) based on Individual Patient Data (IPD). Where IPD were not available, data were estimated from the survival curves using the methods of Parmar et al. For binary outcomes, the Relative Risk (RR) was calculated along with 95% CIs. The Mantel-Maenszel method was used for pooling. For all tests, a two-sided level of significance of $\alpha$=0.05 was used. Heterogeneity was explored via subgroup analysis using study quality, study size, proportion of patients with large diffuse B-cell lymphoma, proportion of patients with bone marrow involvement, HDCT regimen used, proportion of patients that actually received HDCT, source of data, treatment regimen before HDCT, status at time of randomization, and age-adjusted IPI score as possible sources. Possible associations between time-to-induction therapy and survival were tested in a linear meta-regression. For endpoints that included more than four trials, funnel plots were generated, and a linear-regression test was performed to test for potential biases. Numbers needed to treat (NTT) were calculated for all outcomes to assist interpretation. In summary, this was a well-performed meta-analysis that took all reasonable steps to ensure all relevant data were obtained, and that considered all relevant outcomes in its analyses.

The RCT reported by Baldissera et al [18] allocated patients to either 12 weeks of chemotherapy or six weeks of the same regimen followed by autologous SCT. Randomization was performed centrally via fax, with patients allocated into blocks of six. Blinding was not reported on. The sample size of 166 patients was calculated using a desired power of 80% to detect a survival difference of 20% in favour of the SCT group. It must be noted that the trial was stopped early due to poor accrual, and the primary outcome of survival was underpowered to detect a difference. The study had a reported median follow-up of 23

months. Statistical analysis of the baseline characteristics was compared using the $X^2$ or Fisher's test (dichotomous variables) and the Wilcoxon test (continuous variables). For time-to-event variables, Kaplan-Meier curves were done and compared using the log-rank test. The influence of variables (gender, ECOG status, histology, presence of bulky disease, number of extranodal sites, LDH level) on the time-to-even outcomes were tested with a Cox regression analysis and expressed as Hazard Ratios. No withdrawals or losses to follow-up were reported. No external sources of funding were named.

For Diffuse large B-cell lymphoma, two CPGs [6,7] were obtained along with one retrospective cohort study [19]. As neither of the CPGs that were obtained [reported by Barosi et al [7] and Zelenetz et al [6]] were suitable for adapting, no formal assessment of quality was performed, but recommendations appear in the Results section.

The retrospective cohort study reported by Lazarus et al [19] fully described the included patient population and reported differences in disease stage at diagnosis (lower in ASCT), International Prognostic Index (lower in ASCT), likelihood of B-symptoms (lower in ASCT), likelihood of extranodal disease (lower in ASCT), likelihood of marrow involvement (lower in ASCT), likelihood of chemo-sensitive disease (higher in ASCT), likelihood of being in complete response (higher in ASCT), likelihood of having prior radiation (lower in ASCT), and finally, ASCT patients had a greater likelihood of being transplanted later in the disease course. The interventions each patient received were as reported to the Center for International Blood & Marrow Transplant Research database. The main outcomes of interest were identified in the methods, and TRM, disease progression, PFS, and OS were all well reported. The additional outcomes of aGVHD, cGVHD, and cause of death were also reported on.

*2. T-cell lymphoma*

As the CPG reported by Zelenetz et al [6] was not suitable for adapting, no formal assessment of quality was performed, but recommendations appear in the Results section.

The retrospective cohort study reported by Lee et al [20] fully described the included patient population and reported differences in age younger than 60 years (more younger patients in the ASCT group) and proportion of patients with localized disease (fewer in the ASCT group). The interventions each patient received were obtained as reported from the records of three previous studies in Korea, and were all well described. The outcomes of disease-specific survival and RFS were described in the methods section and were well reported.

*3. Follicular lymphoma*

As the systematic review reported by Oliansky et al [11] was not suitable for replacing the evidence base upon which to form recommendations, no formal assessment of quality was performed, but findings appear in the Results section.

As the CPG reported by Zelenetz et al [6] was not suitable for adapting, no formal assessment of quality was performed, but recommendations appear in the Results section.

The RCT reported by Gyan et al [21] allocated patients with previously untreated follicular lymphoma to either conventional doxorubicin-based chemotherapy or to high-dose chemotherapy followed by SCT. Randomization was performed centrally and stratified by centre. Blinding was not reported on. The study was powered at 80% to detect a 25% difference in event-free survival, based on a projected event-free survival rate of 50% in the conventional CT treatment group. Time-to-event curves were calculated according to the Kaplan-Meier method and compared using the log-rank test on an intent-to-principle. Multivariate analyses of survival outcomes were done using the Cox proportional hazards model investigating the following variables as possible predictors: age at inclusion, sex, ECOG

performance status, LDH levels, disease stage, haemoglobin levels, splenomegaly, histology, and treatment group. This study includes results based on nine years of follow-up. There were no withdrawals or losses to follow-up reported. The Ministry of Health (France) and the Schering-Plough Corporation both provided funding.

## RESULTS: Clinical evidence

### *Hodgkin lymphoma*

For Hodgkin lymphoma, four papers were retained comprising a randomized trial [1], one prospective cohort study [2], and two retrospective cohort studies [3,4] including a total of 398 patients. These studies tested different treatment approaches. The studies by Majhail et al [2] and Sureda et al [4] reported on patients with relapsed/refractory disease who underwent allogeneic transplantation, and the studies by Arakelyan et al [1] and Morabito et al [3] reported on patients who underwent autologous transplantation for either as part of primary therapy (Arakelyan et al) or for primary refractory disease (Morabito et al). None of the obtained papers reported significant differences for either progression-free survival (PFS) or treatment-related mortality (TRM). Outcomes are detailed in Table 1.

Regarding allogeneic stem cell transplants, the study by Sureda et al [4] reported on outcomes of reduced-intensity conditioning versus regular myeloablative conditioning. This was the only study to show an overall survival benefit with statistically significant benefits detected in survival at five years in favour of treatment with RIC (RIC, 28% vs. MAC, 22%; p=0.003). In this study, significant benefits were also seen for GVHD in favour of treatment with RIC detected at both 100 days (RIC, 44% vs. MAC, 38%; p=0.05) and one year (RIC, 38% vs. MAC, 33%; p=0.05).

The study by Majhail et al [2] reported on outcomes of either allogeneic transplant recipients of unrelated umbilical cord blood versus matched related donors. Statistically significant benefits were detected in median days to neutrophil engraftment in favour of treatment with UBC (UBC, 10 vs. MSD, 7; p=0.02).

The study by Arakelyan et al [1] randomized patients with previously untreated Hodgkin's lymphoma to early intensive chemotherapy versus standard chemotherapy (with ABVD) followed by high-dose chemotherapy and autologous stem cell transplantation. There were no differences in overall survival or progression-free survival.

Finally the study by Morabito et al [3] looked at outcomes of primary refractory Hodgkin's lymphoma in those patients treated with high-dose chemotherapy and autologous stem cell transplantation versus those treated with combination chemotherapy alone. Although there was a difference in survival favouring the autologous stem cell transplant group, the number of patients was small and the study non-randomized and prone to selection bias.

**Table 1. Hodgkin's lymphoma**

| Author, year | Comparison | Overall Survival (OS) | Progression-free Survival (PFS) | Neutrophil engraftment | Graft-versus-Host Disease (GVHD) | Treatment-related Mortality (TRM) |
|---|---|---|---|---|---|---|
| *Randomized trial* | | | | | | |
| Arakelyan et al, 2008 [1]<br><br>1997-2004<br>GOE-LAMS H97-HR | VABEM-RT<br>n=82 | 5 year:<br>86.8%<br>(95%CI, 79-94) | 5 year:<br>78.9<br>(95%CI, 70-87.8) | NR | NR | NR |
| | ABVD-BEAM + ASCT<br>n=76 | 85.9%<br>(95%CI, 77.7-94.1)<br>p=ns | 74.9<br>(95%CI, 65-84.7)<br>p=ns | NR | NR | NR |
| *Prospective cohort studies* | | | | | | |
| Majhail et al, 2006 [2]<br><br>2000-2005 | RIC → UCB<br>n=9 | 2 year:<br>51%<br>(95%CI, 16-86) | 2 year:<br>25%<br>(95%CI, 0-55) | 10%<br>(95%CI, 6-28) | Grade 3-4:<br>33% | 100d/180d:<br>11%/22% |
| | RIC → MSD<br>n=12 | 48%<br>(95%CI, 19-77)<br>p=ns | 20%<br>(95%CI, 0-44)<br>p=ns | 7%<br>(95%VI, 5-12)<br>**p=0.02** | 33%<br><br>p=ns | 17%/25%<br><br>p=ns/p=ns |
| *Retrospective cohort studies* | | | | | | |
| Morabito et al, 2006 [3]<br><br>1988-2002 | CC<br>n=24 | 4 year:<br>33% | NR | NR | NR | NR |
| | HDC<br>n=27 | 81%<br>**p=0.02** | NR | NR | NR | NR |
| Sureda et al, 2008 [4]<br><br>1997-2001 | RIC<br>n=89 | 5 year:<br>28%<br>(95%CI, 18-38) | 5 year:<br>18%<br>(95%CI, 10-26) | NR | 100d: 44%<br>(95%CI, 35-57)<br>1yr: 38%<br>(95%CI, 28-52) | NR |
| | MAC<br>n=79 | 22%<br>(95%CI, 13-36)<br>**p=0.003** | 20%<br>(95%CI, 11-28)<br>p=0.07 | NR | 100d: 38%<br>(95%CI, 28-52) **p=0.05**<br>1yr: 33%<br>(95%CI, 22-48) **p=0.05** | NR |

Note: VABEM-RT, vindesine, 1 mg/m$^2$ d1-5 as a continuous IV, doxorubicin 33 mg/m$^2$ IV d1-3, BCNU, 140 mg/m$^2$ IV d3, etoposide, 200 mg/m$^2$ IV d3-5, and methylprednisolone, 120 mg/m$^2$ IV d1-5), adjuvant RT (20GY at 10Gy/week) that included all initially involved lymph node sites (16Gy added for lymph node masses that initially measured 5 cm); ABVD, ASCT d0, doxorubicin, 25 mg/m$^2$ IV d1 and d15, bleomycin, 10 mg/m$^2$ IV d1 and d15, vinblastine, 6 mg/m$^2$ IV d1 and d15, dacarbazine, 375 mg/m$^2$ IV d1 and d15, and methylprednisolone, 120 mg/m$^2$ IV d1 and d15; UCB, reduced-intensity conditioning (RIC) followed by allo-SCT using umbilical cord blood (at least 4 of 6 HLA-A, HLA-B, or DRB1 antigens that were matched to the recipient and — if 2 donor units were infused — to each other as well); MSD, RIC followed by allo-SCT using a matched sibling donor (MSD); CC,

conventional chemotherapy (vinblastine, bleomycin, methotrexate plus involved-field RT); HDC, high-dose chemotherapy for intermediate-risk patients (four courses ABVD or EVE (etoposide, vincristine, epidoxorubicin) or EVA (etoposide, vincristine, adriamycin) plus IF-RT or for high-risk patients (six courses of ABVD, MOPPEBVCAD (mechlorethamine, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, bleomycin), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), or 12 weeks of Stanford V regimen (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone) plus RT to residual masses or to sites of previously bulky disease); RIC, carmustine 300 mg/m$^2$ IV, etoposide 600 to 800 mg/m$^2$ IV, cytarabine 800 to 1,600 mg/m2 IV, melphalan 100 to 140mg/m$^2$ IV (BEAM regimen), and fludarabine plus intermediate doses of one or two alkylating agents or low-dose TBI (2 to 4 Gy). Intermediate doses of alkylating agents consisted of busulfan 8 to 10 mg/kg orally, melphalan 80 to 140 mg/m$^2$ IV, cyclophosphamide 60 to 120 mg/kg IV, or thiotepa (5 to 10 mg/kg IV); MAC, combinations of cyclophosphamide with high-dose total-body irradiation (TBI; ≥8 Gy) or high-dose busulfan (16 mg/kg total dose by mouth or equivalent dose IV]), with or without other cytotoxic agents.

### *Non-Hodgkin's lymphoma*

*1. Aggressive non-Hodgkin's lymphoma*

For aggressive non-Hodgkin's lymphoma, three papers were retained: a meta-analysis reported by Greb et al [17], a CPG reported by Zelenetz et al [6] and an RCT reported by Baldissera et al [18]. These publications included patients with a variety of histologies, including diffuse large B-cell, anaplastic and T-cell lymphomas.

The meta-analysis reported by Greb et al [17] pooled results for studies comparing HDCT with conventional chemotherapy in the first-line treatment of aggressive non-Hodgkin's lymphoma of various histologies. Outcomes pooled were CR, OS, EFS, adverse effects, and the influence of the age-adjusted International Prognostic Index (aaIPI) risk factors. Fifteen trials that included a total of 2728 patients were obtained. For CR, 14 studies (2126 patients) were analyzed. Pooling detected a difference in favour of treatment with HDCT (RR=1.11; 95%CI, 1.04-1.18; p<0.05). No statistical heterogeneity was detected (p=0.09), and sub-group analysis did not detect any differences. For OS, 14 studies (2444 patients) were analyzed. Pooling did not detect a difference in OS (HR=1.05; 95%CI, 0.92-1.19; p=ns). No statistical heterogeneity was detected (p=0.14). Subgroup analysis did detect a difference between studies that reported results according to the intent-to-treat (ITT) principle compared with per-protocol (PP) analysis (p=0.03) where a survival benefit was detected in studies using the ITT method of reporting. An additional analysis that excluded studies without ITT data available did increase the overall survival HR, but it remained non-significant. For EFS, 12 trials (1795 patients) were analyzed. Pooling did not detect a difference between the groups (HR=0.92; 95%CI, 0.80-1.05; p=ns). For adverse effects, 14 trials (2555 patients) were analyzed. Pooling did not detect a difference (RR=1.29; 95%CI, 0.93-1.79; p=ns). For aaIPI, 12 trials (2235 patients) were analyzed. Pooling detected a difference in good-risk patients where treatment with HDCT negatively affected OS (HR=1.46; 95%CI, 1.02-2.09; p<0.05). No difference was detected for poor-risk patients treated with HDCT. A difference was detected between good-risk and poor-risk patients being treated with HDCT in favour of good risk (p=0.03).

In the CPG reported by Zelenetz et al [6] for the National Comprehensive Cancer Network (NCCN), recommendations were provided for first-line therapy, first-line consolidation therapy, second-line therapy for patients who are eligible for high-dose treatment with autologous stem cell rescue, and second-line therapy for patients who are not eligible for high-dose treatment. Transplant related indications are as follows:

- High-dose therapy with autologous stem cell rescue as part of first-line consolidation treatment.
- Autologous stem cell rescue following high-dose therapy as second-line therapy
- Regarding T-cell lymphoma, transplant-related indications are as follows:
- As part of first-line consolidation treatment, all patients (except aaIPI low risk) should be consolidated with HDT and autologous SCT rescue (except for ALK-1 + ALCL, which is

associated with a good prognosis and does not require consolidation transplant if in remission).
- As part of second-line therapy following salvage chemotherapy.

For the RCT reported by Baldissera et al [18], no statistically significant differences were reported, possibly due to the early stoppage due to lack of accrual. Results appear in Table 2.

**Table 2. Aggressive non-Hodgkin's lymphoma**

| Author, year | Comparison | Overall Survival (OS) | Progression-free Survival (PFS) | Neutrophil Engraftment | Graft-versus-Host Disease (GVHD) | Treatment-related Mortality (TRM) |
|---|---|---|---|---|---|---|
| *Randomized controlled trial* | | | | | | |
| Baldassera et al, 2006 [18]<br><br>1998-2003 | VACOP-B<br>12 week<br>n=27 | 47% | 47% | NR | NR | NR |
| | VACOP-B followed by HDS + ASCT<br>6 week<br>n=29 | 40%<br><br>p=ns | 30%<br><br>p=ns | NR | NR | NR |

Note: VACOP-B, etoposide 50 mg/m$^2$ IV d1 and 100 mg p.o. d2 and d3 weeks 3,7,11, doxorubicin 50 mg/m$^2$ weeks 1,3,5,7,9,11, cyclophosphamide 350 mg/m$^2$ IV weeks 1,5,9, vincristine 1.2 mg/m$^2$ weeks 2,4,8,10,12, bleomycin 10 U/m$^2$ weeks 2,4,6,8,10,12, prednisone 45 mg/m$^2$ p.o. daily for 1 week and every other day from weeks 2 to 12; HDS, cyclophosphamide 4 g/m$^2$ followed by etoposide 2 g/m$^2$; ASCT, autologous stem cell transplantation.

For diffuse large B-cell lymphoma (DLBCL) specifically, two papers were retained, a CPG reported by Barosi et al [7], and another, a retrospective cohort study reported by Lazarus et al [19].

In the CPG reported by Barosi et al [7], a systematic review of the literature was performed by the Italian Society of Hematology (SIE), the Italian Society of Experimental Hematology (SIES), and the Italian Group for Bone Marrow Transplantation (GITMO). Evidence obtained was graded according to the methods developed by the Scottish Intercollegiate Guideline Network (SIGN). Based on the evidence obtained, recommendations were provided for patients in first-line treatment for stage I-II disease, first-line treatment for stage III-IV disease, restaging and monitoring, and second-line treatment. Transplant recommendations were provided for advanced-stage patients as part of initial therapy and at the time of relapse as follows:

- Patients with advanced-stage disease (stages III and IV), an intermediate-to-high IPI score who are <65 years of age may receive front-line HDT followed by autologous SCT within an approved study protocol. These patients should also receive non-abbreviated debulking treatment.
- Allogeneic SCT is not recommended for any patient.
- Patients who do not experience a CR following first-line treatment <65 years of age should receive a non–cross-resistant regimen (e.g., ICE, DHAP, MIME, HDS) with or without rituximab.

- Patients with a good performance status (PS) who respond to rescue CT should be enrolled in approved clinical studies testing new treatments, allogeneic SCT, or supportive therapies.
- Patients at first relapse should receive non–cross-resistant CT with or without rituximab followed by HDT/SCT in eligible patients (<65 years of age, chemo-sensitive disease, good PS, no comorbidities, good availability of autologous stem cells).

That CPG also recommends the use of PBSCT over BM. Double autologous SCT is not recommended.

In the retrospective cohort study reported by Lazarus et al [19], patients had received either autologous SCT or allogeneic SCT. Statistically significant differences were detected for overall survival at one year in favour of autologous SCT (66% vs. 33%; p<0.05) and in TRM at one year, also in favour of autologous SCT (12% vs. 41%; p<0.001). For both of these comparisons, differences were not detected at five years. Results for that study appear in Table 3.

**Table 3. Diffuse large B-cell lymphoma**

| Author, year | Comparison | Overall Survival (OS) | | Progression-free Survival (PFS) | | Neutrophil Engraftment | | Graft-versus-Host Disease (GVHD) | | Treatment-related Mortality (TRM) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Retrospective cohort studies* | | | | | | | | | | | |
| | | 1yr | 5yr | 1yr | 5yr | 1yr | 5yr | Acute[1] | Chronic 5 year | 1yr | 5yr |
| Lazarus et al, 2010 [19]<br><br>1995-2003 | ASCT n=837 | 66% | 49% | NR | NR | NR | NR | N/A | N/A | 12% | 45% |
| | AlloSCT n=79 | 33%<br>**p<0.05** | 22%<br>p=ns | NR<br>p=ns | NR<br>p=ns | NR | NR | | | 41%<br>**p<0.001** | 18%<br>p=ns |

Note: ASCT, autologous stem cell transplantation; AlloSCT, allogeneic stem cell transplantation; NR, not reported; N/A, not applicable.
[1] Within 100 days, Grades 2-4.

*2. T-cell lymphoma*

Transplantation in T-cell lymphoma was reported in a retrospective cohort study reported by Lee et al [20]. Patients that had received either high-dose chemotherapy (HDC) with autologous SCT or conventional CT with radiation therapy (RT) were compared. No significant differences were detected for any of the outcomes of interest. Results for that study appear in Table 4.

**Table 4. T-cell lymphoma**

| Author, year | Comparison | Overall Survival (OS) | Progression-free Survival (PFS) | Neutrophil Engraftment | Graft-versus-Host Disease (GVHD) | Treatment-related Mortality (TRM) |
|---|---|---|---|---|---|---|
| *Retrospective cohort studies* | | | | | | |
| Lee et al, 2008 [20] | ASCT + HDC n=47 | 56.2% | NR | NR | NR | NR |
| | ConCT + RT | 47.6% | NR | NR | NR | NR |

| | | | | | | |
|---|---|---|---|---|---|---|
| | n=34 | p=0.13 | | | | |

Note: HDC, high-dose chemotherapy: various regimens used including CBV (etoposide, carmustine, cy), BEAM (carmustine, etoposide, cytarabine, melphalan), MCEC (ranimustine, cy, etoposide, carboplatin), BEAC (carmustine, etoposide, cytarabine, cy), Cy/TBI (cy and total body irradiation), VCT (etoposide, cy, and TBI); ConCT, conventional chemotherapy: anthracycline-containing regimens ± RT (n = 25) or non–anthracycline-containing regimens ± RT or involved-field RT or surgery plus RT. Anthracycline-based regimens used included CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), dose-escalated CHOP (deCHOP), velCHOP (velcade plusCHOP), CEOP (Cy, epirubicin, vincristine, prednisolone), CEOP/ProMACE (CEOP followed by Cy, doxorubicin, etoposide, prednisone), MACOPB (methotrexate, doxorubicin, Cy, vincristine, prednisone, bleomycin), CHOEP (Cy, doxorubicin, vincristine, etoposide, prednisolone), ProMace, ProMace/Cytabom (ProMace plus cytabarabine, bleomycin, vincristine, methotrexate, leucovorin), COPBLAM (Cy, vincristine, prednisone, bleomycin, doxorubicin, procarbazine), EPOCH (etoposide, doxorubicin, vincristine, Cy, prednisolone), cisplatin/Cy/adriamycin/vindesine/prednisolone, and epi-COP (epirubicin, Cy, vincristine, prednisolone). The non-anthracycline-containing regimens used were IMEP (ifosfamide, methotrexate, etoposide),ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine), DHAP (dexamethasone, cytarabine, cisplatin), DeVIC (carboplatin, etoposide, ifosfamide, dextamethasone), IMVP-16 (ifosfamide, methotrexate , etoposide), and VIPD (etoposide, ifosfamide, cisplatin, dexamethasone). For suitable patients, IFRT was offered for localized disease following CT.

*3. Follicular lymphoma*

For follicular lymphoma, three papers were retained: a systematic review reported by Oliansky et al [11], a CPG reported by Zelenetz et al [6], and an RCT reported by Gyan et al [21].

In the systematic review reported by Oliansky et al [11], the PubMed and MEDLINE databases, along with web sites developed by the National Library of Biotechnology Information were searched for evidence for the years 1990 through June 10, 2008. Evidence was obtained and graded according to the methods of Harbour & Miller. Evidence was gathered on autologous SCT compared with non-transplant treatment (10 studies), autologous SCT compared with allogeneic SCT (five studies), autologous SCT alone (five studies), and allogeneic SCT alone (one study). The following recommendations were made in consideration of both the available evidence and expert opinion:

- Autologous SCT is not recommended as first-line treatment for most patients, as there was no demonstrated OS benefit.
- Autologous SCT is recommended as salvage treatment based on pre-rituximab data, as there was a demonstrated benefit in both OS and PFS.
- Autologous SCT is recommended for transformed follicular lymphoma patients.
- Prior to allogeneic SCT, either RIC or MAC are acceptable options.
- HLA-matched related and HLA-matched unrelated are equally effective for RIC allogeneic SCT.

In the CPG reported by Zelenetz et al [6] for the National Comprehensive Cancer Network (NCCN), recommendations were provided for first-line treatment, first-line for the elderly or the infirm, first-line with extended dosing, second-line and subsequent treatment, and second-line extended dosing. Regarding transplantation, it was only recommended as part of second-line and subsequent therapy with autologous SCT rescue and with allogeneic SCT rescue in highly selected patients, but the selection criteria for these patients was unspecified.

In the trial reported by Gyan et al [21], patients were allocated to either HDC with autologous SCT or conventional CT with immunotherapy as part of upfront therapy. Statistically significant differences were detected in favour of HDC with autologous SCT in nine-year PFS (64% vs. 39%; p=0.004) but not in overall survival. Results appear in Table 5.

**Table 5. Follicular lymphoma**

| Author, year | Comparison | Overall Survival (OS) 9-year | Progression-free Survival (PFS) 9-year | Neutrophil Engraftment | Graft-versus-Host Disease (GVHD) | Treatment-related Mortality (TRM) |
|---|---|---|---|---|---|---|
| *Randomized controlled trial* | | | | | | |
| Gyan et al, 2009 [21]<br><br>GOE-LAMS 064<br><br>1994-2001 | ASCT + HDC<br>n=86 | 76%<br>(95%CI, 67-85) | 64%<br>(95%CI, 54-75) | NR | NR | NR |
| | ConCT + immunotherapy<br>n=80 | 80%<br>(95%CI, 72-89)<br>p=ns | 39%<br>(95%CI, 28-50)<br>**p=0.004** | NR | NR | NR |

Note: ASCT, autologous stem cell transplantation; HDT, High-dose chemotherapy: VCAP (vindesine, cyclophosphamide, doxorubicin, prednisone). Patients with a complete response, a very good partial response, or a partial response after the second or third VCAP cycle went on to stem cell harvesting and one course of IMVP1617 prior to transplantation. Patients not experiencing CR, VGPR, or PR following VCAP received salvage therapy with 2-3 courses of dexamethasone, cytarabine, and cisplatin (DHAP). If at least a PR was obtained after DHAP, stem cells were harvested. Stem cell purging was offered to all patients if the grafts collected contained at least 108 mononuclear cells/kg. Immunologic purging was performed either with immunomagnetic-bead negative selection or with positive selection of $CD34^+$ cells according to the individual centre procedures. If the graft did not contain at least 104 colony-forming units–granulocyte/macrophage/kg for bone marrow samples or $2 \times 10^4$ CFU-GM/kg for peripheral blood stem cells, patients were not transplanted and alternative treatment was offered. The conditioning regimen started 4 to 6 weeks after the IMVP16 or the last DHAP cycle in responding patients and consisted of total-body irradiation, administered in fractionated doses (200 cGy) twice daily on 3 consecutive days, followed by cyclophosphamide (60 mg/kg on 2 consecutive days) in all patients. Stem cells were reinfused within 48 hours of completing the conditioning regimen; ConCT, conventional chemotherapy: 6 CHVP (cyclophosphamide, doxorubicin, vepeside, prednisone) administered monthly, followed by a maintenance phase that consisted of one cycle every 2 months for 1 year (responders and stable disease only). Concomitant subcutaneous interferon alpha-2b was administered at $5 \times 10^6$ units subcutaneously 3 times per week for 18 months.

## DISCUSSION

### *Hodgkin's Lymphoma*

Regarding transplantation for HL, the committee agreed that there is no role for any type of transplant as part of the upfront treatment for HL. In the setting of primary refractory disease or relapsed disease, after salvage chemotherapy, autologous transplantation was considered a standard treatment. The degree of chemo-responsiveness after salvage chemotherapy was discussed. The committee felt that a strict PR or CR to salvage was not necessary to continue treatment with high-dose chemotherapy and transplant.

Allogeneic transplantation for HL was discussed. The evidence is variable, and there are concerns regarding significant toxicities; however, there may be a proportion of patients that may derive some benefit. If considered, an allogeneic transplant would need to be considered on a case-by-case basis after failure of autologous transplantation in terms of risks and benefits. Early referral to a transplant centre for consultation is important in the management of such patients.

### *Aggressive Histology Lymphoma*

Regarding aggressive histology non-Hodgkin's lymphoma, the recommendations have slightly changed from 2009. Patients with aggressive histology lymphoma who do not appear to have achieved a CR should be further evaluated with biopsy or PET scan of residual masses or both prior to initiation of second-line therapy. Patients with primary CNS lymphoma should be considered for consolidation with high dose chemotherapy and an autologous stem cell

transplant following response to first line combination chemotherapy. In patients with aggressive histology T cell lymphoma or transformed lymphoma, stem cell transplantation as part of upfront therapy could be considered.

*Burkitt's Lymphoma*

There were no new citations found for Burkitt's lymphoma. The committee reviewed the available literature and is aware of a narrative review regarding stem cell transplantation in Burkitt's lymphoma [22], and an abstract report summarizing the CIBMTR experience [23]. The recommendation remains the same as in the 2009 guideline.

*Follicular Lymphoma*

Regarding follicular lymphoma, the Committee endorsed the consideration of transplant after failure of first-line therapy, rather than after second-line therapy as in the 2009 recommendations.

*Mantle Cell Lymphoma*

The recommendation for autologous stem cell transplant for MCL at the time of first remission was strengthened from being an option to being recommended. This was based on two abstracts reports with longer follow-up than the original trial publication [12]. Both abstracts suggest an overall survival benefit for MCL patients who received high-dose chemotherapy and autologous stem cell transplant following induction with CHOP-R type chemotherapy. It was also believed that in select patients with MCL with high-risk features, allogeneic transplantation in first remission might be considered on a case-by-case basis.

**CONCLUSIONS**

Stem cell transplantation, both autologous and allogeneic, continues to play an important role in the treatment of the various lymphomas. Autologous transplantation remains a standard therapy for relapsed or refractory aggressive-histology lymphoma and Hodgkin's lymphoma and as part of upfront therapy in mantle cell lymphoma and primary CNS lymphoma. Allogeneic stem cell transplantation also remains an option for patients with both relapsed and/or refractory lymphomas and Hodgkin's as outlined in the text. Research is ongoing, and new treatment options may expand the number of patients to whom treatment with SCT is offered, and minimize toxicities associated with allogeneic transplantation.

**ONGOING TRIALS** (www.clinicaltrials.gov) (updated August 30, 2011)

| Protocol ID | Title, details |
|---|---|
| **Hodgkin's lymphoma** | |
| NCT00784537 | High-dose Chemotherapy and Stem Cell Transplantation, in Patients PET-2 Positive, After 2 Courses of ABVD and Comparison of RT Versus no RT in PET-2 Negative Patients (HD0801)<br>Study ID: IIL-HD0801, EudracT Number 2008−002684−14<br>Status: recruiting<br>Updated: June 23, 2011 |
| NCT01100502 | A Phase 3 Study of Brentuximab Vedotin (SGN-35) in Patients at High Risk of Residual Hodgkin Lymphoma Following Stem Cell Transplant (The AETHERA Trial) |

| | |
|---|---|
| | Study ID: SGN35-005<br>Status: recruiting<br>Updated: July 28, 2011 |
| NCT00920153 | Three Different Therapy Regimens in Treating Patients With Previously Untreated Hodgkin Lymphoma<br>Study ID: CDR0000633503, GOELAMS-LH2007, GOELAMS-ID-RCB#2007-A01079-44, INCA-RECF0754, AMGEN-GOELAMS-LH2007<br>Status: recruiting<br>Updated: February 23, 2011 |
| NCT00981760 | Intentional Rejection of the Donor Graft Using Recipient Leukocyte Infusion(s) Following Nonmyeloablative Allogeneic Stem Cell Transplantation<br>Study ID: 07-068<br>Status: recruiting<br>Updated: May 3, 2010 |
| NCT00469729 | Efficacy and Safety Study of StemEx®, to Treat Subjects With High Risk Hematologic Malignancies, Following Myeloablative Therapy (ExCell)<br>Study ID: GC P#02.01.001<br>Status: recruiting<br>Updated: June 19, 2011 |
| NCT00928018 | Tacrolimus/Sirolimus/Methotrexate Versus Tacrolimus/Methotrexate or Cyclosporine/Mycophenolate Mofetil for GVHD Prophylaxis After Reduced Intensity Allogeneic Stem Cell Transplantation for Patients With Lymphoma<br>Study ID: 09-073<br>Status: recruiting<br>Updated: June 22, 2011 |
| **Aggressive-Histology NHL Including Diffuse Large B-Cell Lymphoma and Aggressive T-Cell Lymphomas (AH-NHL)** | |
| NCT00078949 | Comparison of Two Salvage Chemotherapy Regimens Before Autologous Stem Cell Transplantation With or Without Maintenance Rituximab in Treating Patients With Relapsed or Refractory Aggressive Non-Hodgkin's Lymphoma<br>Study ID: LY12, CAN-NCIC-LY12, CDR0000353203<br>Status: recruiting<br>Updated: August 15, 2011 |
| **Follicular lymphoma, Burkitt's lymphoma, Mantle Cell lymphoma** | |
| None listed | |



**CONFLICT OF INTEREST**

The authors reported on potential conflicts of interest relating to the topic, and none were declared.

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## APPENDIX A. Literature search strategy

Database: Ovid MEDLINE(R) without Revisions <1996 to February Week 3 2011>
Search Strategy:

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1 exp lymphoma/ (53645)
2 lymphoma.mp. (75502)
3 1 or 2 (79518)
4 exp bone marrow transplantation/ (17414)
5 exp stem cell transplantation/ (35651)
6 exp peripheral blood stem cell transplantation/ (2209)
7 4 or 5 or 6 (50122)
8 3 and 7 (5993)
9 letter.pt. (395350)
10 comment.pt. (337438)
11 editorial.pt. (189314)
12 9 or 10 or 11 (650106)
13 exp Randomized Controlled Trial/ (203448)
14 randomized controlled trial.mp. (207059)
15 exp Clinical Trial/ (419981)
16 Comparative Study/ (781963)
17 13 or 14 or 15 or 16 (1102334)
18 pooling.mp. (4008)
19 pooled analysis.mp. (1822)
20 exp Meta-Analysis/ (24488)
21 meta-analyses.mp. (6654)
22 systematic review.mp. (20174)
23 health technology assessment.mp. (915)
24 exp Evidence-based Medicine/ (40396)
25 clinical practice guideline.mp. or exp Practice Guideline/ (13293)
26 or/17-25 (1191103)
27 17 or 26 (1191103)
28 27 not 12 (1159734)
29 8 and 28 (1390)
30 limit 29 to (English language and humans and yr="2006 -Current") (429)

## APPENDIX B. DEVELOPMENT & REVIEW

This Recommendation Report was created to update the 2009 Stem Cell Transplantation in Adults report. Using the Recommendations in that report as a starting point, evidence published from the original report's literature search dates to current was performed to gather the most evidence.

### 2009 RECOMMENDATIONS[1]

**Hodgkin's Lymphoma (HL)**

- Autologous stem cell transplantation is the recommended treatment option for eligible chemo-sensitive patients with HL who are refractory to or who have relapsed after primary chemotherapy.
- Allogeneic stem cell transplantation is an option for chemo-sensitive patients with refractory or relapsed HL who are not candidates for autologous stem cell transplantation or who have a syngeneic (identical twin) donor.
- Stem cell transplantation is not recommended as part of primary therapy for HL.

**The Non-Hodgkin's Lymphomas**

1. ***Aggressive-Histology NHL Including Diffuse Large B-Cell Lymphoma and Aggressive T-Cell Lymphomas (AH-NHL)***
   - Autologous stem cell transplantation is the recommended option for eligible chemo-sensitive patients with AH-NHL refractory to or relapsed after primary therapy.
   - Allogeneic stem cell transplantation is an option for eligible chemo-sensitive patients with refractory or relapsed AH-NHL who are not candidates for autologous stem cell transplantation or who have a syngeneic (identical twin) donor.
   - Stem cell transplantation is not recommended for patients with AH-NHL as part of primary therapy.

2. ***Follicular Lymphoma (FL)***
   - Autologous or allogeneic transplantation are options for selected patients with poor prognosis FL that progresses after second-line therapy.

3. ***Burkitt's Lymphoma***
   - Autologous and allogeneic transplantation are options for selected patients with Burkitt's lymphoma beyond first remission.
   - Stem cell transplantation is not recommended for patients with Burkitt's lymphoma in first complete remission.

4. ***Mantle Cell Lymphoma (MCL)***
   - Autologous stem cell transplantation is an option for eligible patients with MCL in first remission.
   - Autologous or allogeneic transplantation are options for selected patients with MCL in second remission.

[1]Stem Cell Transplantation in Adults. *K. Imrie, R.B. Rumble, M. Crump, the Advisory Panel on Bone Marrow and Stem Cell Transplantation, and the Hematology Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care* [Report Date: January 30, 2009].

Ontario Health
Cancer Care Ontario

**Recommendation Report SCT-4: Section 3**

# Stem Cell Transplantation in Lymphoma

**Document Review Summary**

*A. Balitsky, N. Varela, T. Kouroukis, and members of the Stem Cell Transplantation Expert Panel*

February 25, 2021

***The 2012 recommendations are***

***ARCHIVED***

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

## OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2012.

In March 2018, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (NV) conducted an updated search of the literature. Two clinical experts (AB, TK) reviewed and interpreted the new eligible evidence and proposed the existing recommendations should be archived. The Stem Cell Transplant Expert Panel (see Appendix 1 for Expert Panel membership) archived the recommendations found in Section 1 (Recommendation Report) on February 25, 2021.

## DOCUMENT ASSESSMENT AND REVIEW RESULTS

### Questions Considered

1. What is the role of stem cell transplantation (SCT) in the treatment of the various lymphomas?

**Literature Search and New Evidence**

The updated search (February 2011 to May 2020) yielded 17 comparative studies (14 retrospective and three randomized controlled trials) that evaluated the role of autologous SCT in the treatment of various lymphomas. An additional search in clinicaltrials.gov yielded no ongoing trials. No evidence from comparative studies was found addressing the role of SCT in patients with Burkitt's lymphoma or mantle cell lymphoma (MCL). One study was found addressing the role of SCT in patients with primary central nervous system lymphoma for which evidence was not reported in the 2012 recommendation report. Brief results of the identified publications are shown in the Document Review Tool; the search strategy is in Appendix 2.

**Impact on the Recommendation Report and Its Recommendations**

Since novel therapies including chimeric antigen receptor (CAR) T-cell therapy are transforming the standard of care of different lymphoma subtypes, the clinical experts recommended this guidance recommendation report should be archived. Specific guidance documents for the management of Mantle Cell Lymphoma (MCL) and Primary Central Nervous System Lymphoma (PCNSL) have been developed by OH (CCO)-PEBC and more guidance documents focused on novel therapies will be developed; a guideline around the management of relapsed/refractory diffuse large B-cell lymphoma (DLBCL) that incorporates stem cell transplant, CAR T-cell therapy, and other novel combinations are planned.

Considering that an archived document may be used for academic or historical information purposes, the clinical experts suggested a modification to Recommendation 6 and additional qualifying statements for Recommendations 9 and 10.

Recommendation 6

The clinical experts proposed that this recommendation addressing the use of SCT in patients with aggressive histology non-Hodgkin lymphoma (AH-NHL) should change from not recommending SCT to considering SCT. This is based on two comparative retrospective studies suggesting that upfront SCT might benefit selected patients with AH T-Cell lymphomas [9,10], as well as acknowledging its emergence into current practice.

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| *Original recommendation (2012):* Stem cell transplantation **is not recommended** for patients with AH-NHL as part of primary therapy. |
| *Suggested revised recommendation:* Stem cell transplantation **could be considered** for selected patients with AH-NHL as part of primary therapy. |

Furthermore, two qualifying statements were added to this recommendation. The first to direct readers to a relevant PEBC Guideline addressing the management of primary central nervous system diffuse large B cell lymphoma, a rare type of aggressive B cell lymphoma (SCT-8 https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/49406). The second to recognize recently approved chimeric antigen receptor-T (CAR-T) cell therapy as a potentially preferred option over allogeneic SCT for patients with diffuse large B cell lymphoma who have relapsed following autologous SCT or who have been treated with at least two lines of therapy.

Recommendation 9

*Autologous stem cell transplantation is recommended for patients with MCL in first remission*

A qualifying statement was added to this recommendation to direct readers to a PEBC Recommendation Report (SCT-9) assessing the management of patients with newly diagnosed MCL that supports consolidation with autologous SCT as part of first line therapy.

Recommendation 10

*Select patients with MCL in first or second remission may be considered for allogeneic transplant. Autologous transplantation is also an option for chemo-sensitive patients with MCL in second remission*

A qualifying statement was added to this recommendation to recognize the new CAR-T cell therapy that may evolve to be a preferred option over SCT for the treatment of selected patients with relapsed MCL.

After review of the evidence and proposals by the clinical experts, the Stem Cell Transplant Expert Panel ARCHIVED the 2012 recommendations on the role of stem cell transplantation in the treatment of lymphoma.

Ontario Health
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# Document Review Tool

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| **Number and Title of Document under Review** | Stem Cell Transplantation in Lymphoma |
| **Current Report Date** | December 13, 2012 |
| **Date Assessed (by DSG or Clinical Program Chairs)** | March 9, 2018 |
| **Health Research Methodologist** | Norma Varela |
| **Clinical Experts** | Amaris Balitsky, Tom Kouroukis |
| **Approval Date and Review Outcome (once completed)** | February 25, 2021 |

Original Question(s):

What is the role of stem cell transplantation in the treatment of the various lymphomas?

Target Population:

All adult patients with lymphoma who are being considered for treatment that includes either bone marrow or stem cell transplantation.

Study Selection Criteria:

Articles were selected based on the following criteria:

1. Systematic reviews with or without meta-analysis or clinical practice guidelines if evidence was obtained with systematic review.
2. Fully published randomized controlled trials (RCT) on patients with lymphoma that received SCT and reported on survival and/or quality of life (QoL).
3. Fully published non-randomized studies on patients with lymphoma that received SCT and had an appropriate contemporaneous control group that reported on survival or QoL.
4. Reports published in English only.

Search Details:

- February 2011 to May 2020. Cochrane Database of Systematic Reviews (intended to identify the most current systematic review/meta-analysis, if existing), MEDLINE (OVID), EMBASE (OVID), and https://clinicaltrials.gov/

Summary of new evidence:

From 3163 hits, from MEDLINE and EMBASE, 16 publications that met the inclusion criteria were retained and summarized below.

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| Clinical Expert Interest Declaration: Amaris Balitsky, Tom Kouroukis, and Norma Varela had no conflicts to declare. | |
| 1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed) | NO* |
| 2. Does the newly identified evidence support the existing recommendations? | YES |
| 3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary) | YES |
| **Review Outcome as recommended by the Clinical Expert** | ARCHIVED<br><br>*Based on clinical practice and in consideration of retrospective comparative evidence, the recommendation surrounding aggressive histology non-Hodgkin's lymphoma (Recommendation 6) should be modified from "*not recommended*" to "*could be considered*," as there are certain histologies which may benefit, such as angioimmunoblastic T-cell lymphoma. |
| ***If the outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?*** | |
| **DSG/GDG Commentary** | |

Evidence Table 1: Lymphoma Types Addressed in 2012 Guideline

| Observational Studies with Contemporaneous Control Group | | | | |
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| **Author [study years)** | **Patients characteristics (N, setting, median age, median follow-up)** | **Arm 1: SCT N, Treatment** | **Arm 2: Non-SCT N, Treatment** | **Brief Results OS, QoL** |
| **Hodgkin Lymphoma** | | | | |
| Gao et al. 2019 [24]<br><br>[2010 – 2013] | N=89 RET<br><br>Upfront<br>Newly diagnosed, stage III-IV; IPS ≥ 3; Deauville > 3° at interim PET/CT. Includes young population<br><br>Age 33 (4-70) yrs.<br>• ASCT: 33 (8-62)<br>• CT: 35 (4-70)<br><br>Follow-up: 54 (12-84) mo. | N=45<br><br>MOED + BEAC + ASCT | N= 44<br><br>2 cycles DHAP | **ASCT vs. CT**<br>3-year PFS: 89% vs. 71%; *p*=0.017<br>HR: 6.3 (1.9 to 20.1); *p*=0.002<br><br>3-year OS: 91% vs. 73%; *p*=0.025<br>HR: 6.4 (1.9 to 21.5); *p*=0.003<br><br>**TOXICITIES**<br>Myelosuppression 100% vs. 63.6%; *p*<0.001<br><br>**Conclusion**: ASCT as a first-line consolidation treatment could improve outcome of patients with advanced-stage high risk HL whose interim PET/CT was positive.<br>**Note:** While treatment is being given, an interim PET scan that is positive may result in intensification of treatment, whereas treatment may be decreased if PET is negative. |
| **Hodgkin and Non-Hodgkin Lymphomas** | | | | |
| Ghosh et al. 2016 [25]<br><br>[2008-2013] | N= 987 RET<br><br>Upfront<br>Patients with HL and NHL undergoing their first RIC or non-MA conditioning allo-SCT.<br><br>Age<br>• Haplo-SCT: 55 (18-75)<br>• MSD: 54 (18-77)<br><br>Follow-up: 3 yrs. | Haplo-SCT: 180<br>• Follicular: 28<br>• DLBCL: 65<br>• MCL: 21<br>• Mature T, NK-cell: 22<br>• Hodgkin: 44<br>GVHD prophylaxis with cyclophosphamide with or without calcineurin inhibitor and mycophenolate<br><br>MSD: 807<br>• Follicular: 204 | | **Haplo-SCT vs. MSD**<br>3-year PFS: 48% vs. 48%; *p*=0.96<br>3-year OS: 61% vs. 62%; *p*=0.82<br><br>Multivariable analysis: No significant difference<br><br>**TOXICITIES**<br>• Acute GVHD 100d: 27% vs. 25%, *p*=0.84<br>• Chronic GVHD 1yr: 12% vs. 45%, *p*<0.001<br><br>**Conclusion**: Compared with RIC MSD-SCT, Haplo-SCT with cyclophosphamide significantly reduces the risk of chronic GVHS without compromising relapse and survival. |

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| | | • DLBCL: 189<br>• MCL: 113<br>• Mature T, NK-cell: 123<br>• Hodgkin: 178<br>GVHD prophylaxis with calcineurin inhibitor-based. | | |
| **Non-Hodgkin Lymphomas** | | | | |
| **Aggressive Lymphomas** | | | | |
| • ***B-Cell*** *(DLBCL NOS, PMBL, DLBCL/BL, FLG3, BL, Other);* ***T-Cell*** *(PTCL NOS, ALCL, AITL)* | | | | |
| Stiff et al. 2013 [26]<br><br>[1999-2007] | N=253 RCT (SWOG-9704)<br><br><u>Upfront</u><br>Patients with high-intermediate-risk or high-risk disease who had response to five cycles of CHOP induction CT.<br><br>Age 51 (18-66) yrs.<br><br>Follow-up: 6.3 yrs. | N=125<br>• B Cell: 110<br>• T Cell: 15<br><br>CHOP/CHOP-R (1 cycle) + TBI or BCNU + VP16 + CP | N=128<br>• B Cell: 114<br>• T Cell: 14<br><br>CHOP/CHOP-R (3 cycles)<br><br>29/62 (47%) relapsed and underwent salvage CT and transplantation.<br>A total of 18/62 (29%) of patients who had a relapse survived without disease. | **ASCT vs. CT**<br><u>2-years PFS</u>: 69% vs. 55%, HR 0.58; *p*=0.005<br>• <u>B-Cell Lymphoma</u>: HR 0.54; *p*= 0.004<br>• <u>High-Intermediate-Risk (n=165)</u>: 66% vs. 63%; *p*= 0.32<br>• <u>High-Risk (n=88)</u>: 75% vs. 41%; *p*= 0.001<br><br><u>2-years OS</u>: 74% vs. 71%, HR 0.79; *p*= 0.30<br>• <u>B-Cell Lymphoma</u>: HR 0.74; *p*= 0.21<br>• <u>High-Intermediate-Risk</u>: 70% vs. 75%; *p*= 0.48<br>• <u>High-Risk</u>: 82% vs. 64%; *p*= 0.01<br>No differential treatment effect was noted between patients with B-Cell and T-Cell lymphoma (*p*=0.46 for PFS; *p*=0.56 for OS).<br><br>**TOXICITIES:** Greater grade 3-4 toxic effects among patients who underwent SCT (no p values reported)<br><br>**Conclusion**: Early transplantation appears to be beneficial for the small group of patients presenting with high-risk disease.<br>Improvement in progression-free survival was observed for the combined high-risk and high-intermediate-risk groups but no improvement in overall survival, probably because 29% of patients in the control group who had a relapse or progression after standard therapy had long-term progression-free survival after salvage therapy that often included transplantation. |
| • ***Nodal Peripheral T-Cell Lymphoma*** *(PTCL NOS, AITL, ALCL, ALK-negative)* | | | | |
| Park et al. 2019 [10] | N=119 RET | N=36 | N=83 | **ASCT vs. Non-ASCT** |

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| [2010-2014] | Upfront<br>New diagnosis histologically confirmed PTCL.<br>The majority received anth-bCT as the first-line treatment.<br>Approximately half of the diagnosis in both groups was PTCL NOS.<br><br>Age<br>• ASCT: 57.5 (23-75) yrs.<br>• Non-ASCT: 64.5 (24-89) yrs.<br><br>Follow-up: 2.8 yrs. | • ALK-neg: 4<br>• AITL: 17<br>• PTCL NOS: 15<br><br>BEAM + ASCT<br><br>**Note ASCT vs. Non-ASCT**<br>higher proportion of AITL: 47% vs. 22%, *p*=0.01<br>higher proportion of advanced-stage III-IV: 92% vs. 64%, *p*<0.01, mainly in the PTCL NOS group: 93% vs. 61.5%, *p*=0.02 | • ALK-neg: 26<br>• AITL: 18<br>• PTCL NOS: 39<br><br>**Note Non-ASCT vs. ASCT**<br>higher proportion of ALCL 31% vs. 11%, *p*=0.02 | 2-years PFS: 57.6 vs. 47.5 mo. *p*=0.23<br>• ALK-neg: Median not reached in either group *p*= 0.27; 100% vs. 83.8%<br>• AITL: NR vs. 18.6 mo. *p*=0.10*; 68.8% vs. 41.2%<br>• PTCL NOS: No significantly different *p*=0.46<br><br>2-years OS: NR vs. 57.6 mo. *p*=0.06; 87.8% vs. 70.2%<br>• ALK-neg: Median not reached in either group *p*= 0.39<br>• AITL: NR vs. 24.3 mo. *p*<0.01*; 93.3% vs. 52.9%<br>• PTCL NOS: No significantly different *p*=0.78<br><br>Multivariable Analysis<br>The following factors were associated with improved OS<br>• ASCT: HR, 0.37; 95% CI 0.15 to 0.89; *p*=0.03*<br>• Advanced stage III/IV: HR, 2.65; 95% CI 1.08 to 6.55; *p*=0.03*<br><br>**Conclusion**: ASCT was independently associated with improved survival.<br>• ASCT was associated with superior survival for patients with advanced-stage disease.<br>• *ASCT significantly improved OS and PFS for patients with AITL but not for patients with other PTCL subtypes.<br>• ASCT may provide a benefit in special clinical scenarios, but the broader applicability of this strategy should be determined in prospective RCTS. |
| Fossard et al. 2018 [27]<br><br>[2000-2015] | N=269 RET<br><br>Upfront<br>In complete or partial remission at the end of induction treatment.<br><br>Age<br>• ASCT: 52 (19-66) yrs.<br>• Non-ASCT: 53 (19-65) yrs.<br><br>Follow-up: 4.8 yrs. | N=134<br><br>(112 underwent ASCT)<br>• ALK-Pos ALCL: 31<br>• AITL: 57<br>• PTCL NOS: 46 | N=135<br><br>(133 didn't undergo ASCT)<br>• ALK-Pos ALCL: 37<br>• AITL: 66<br>• PTCL NOS: 32 | **ASCT vs. Non-ASCT Multivariable Analysis according to Intention-to-Treat**<br>5-years OS: 59.2% vs. 60.4%<br>HR: 1.08; 95% CI 0.68 to 1.69; *p*=0.74<br><br>5-year PFS: 46.3% vs. 40.5%<br>HR: 1.02; 95% CI 0.69 to 1.50; *p*=0.89<br>The authors reported that subgroup analyses did not reveal any further difference for patients according to risk category but data not shown.<br><br>**Conclusion**: Data do not support the use of ASCT for upfront consolidation for patients with PTCL-NOS or ALK-ALCL with partial or complete response after induction. |

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| Al-Mansour et al. 2019 [28]<br><br>[1999-2007] | N=28 RET<br>Subgroup analysis of the SWOG S9704 RCT.<br>• PTCL NOS: 11<br>• ALCL: 10<br>• AITL: 7<br><br><u>Upfront</u><br>Untreated and those who received only one prior cycle of CT<br><br>Age 50 (20-65) yrs.<br><br>Follow-up: 7.8 (2.9-12.4) yrs. | N=15<br><br>CHOP/CHOP-R X1 + TBI or BCNU (300 $m^2$) + VP16 + CP | N=13<br><br>CHOP/CHOP-R X3 | **ASCT vs. Non-ASCT – Intent-to-Treat**<br><u>5-year OS</u><br>40% vs. 45%; *p*= 0.98<br><br><u>5-year PFS</u><br>40% vs. 38%; *p*=0.56<br><br>No difference was observed based on IPI, or histologic subtype.<br><br>**Conclusion**: T-cell NHL auto-transplanted in first remission did not appear to benefit from consolidative ASCT.<br>30% of the patients dropped pre-randomization mostly to progression and therefore, suggests that improved induction regimens should be developed |
| Mehta et al. 2013 [9]<br><br>[2001-2011] | N=65 RET<br><br><u>Upfront</u><br><br>Age 58 (22-75) yrs.<br><br>Follow-up: 4 yrs. | Allo-SCT: 5<br>HD-ASCT: 34 | Non-SCT : 26 | **HD-ASCT vs. Non-ASCT – Intent-to-Treat**<br><u>4-year PFS</u>: 73.2 vs. 6.4 mo. *p*<0.001<br><u>4-year OS</u>: 103.5 vs. 8.3 mo. *p*<0.001<br><br>**Allo-SCT vs. Non-ASCT – Intent-to-Treat**<br><u>4-year PFS</u>: 30.6 vs. 6.4 mo. *p*=0.193<br><u>4-year OS</u>: NR vs. 8.3 mo. *p*=0.042<br><br>**Conclusion**: Upfront HD-ASCT carries higher rate of OS and PFS in PTCL, which has traditionally been difficult to treat. |
| • ***Transformed Follicular Lymphoma*** | | | | |
| Villa et al. 2013 [29]<br><br>[1994-2010] | N= 172 RET<br><br><u>Upfront and Relapsed</u><br>Biopsy-proven follicular non-Hodgkin lymphoma and subsequently biopsy-proven aggressive histology B-cell lymphoma transformation. Approximately half of the patients underwent transplantation in first CR or PR and approximately one third in second CR or PR. | <u>Allo-SCT</u>: 22<br>MSD: 14<br>MUD: 7<br>MRD: 1<br>Received a median of two systemic therapy regimens for follicular lymphoma. Two patients had undergone prior auto-SCT for relapsed follicular lymphoma. | <u>RTX-containing CT</u>: 53<br>Received a median of one regimen for follicular lymphoma. | **Allo-SCT vs. ASCT**<br><u>5-year OS</u>: 45% vs. 57%; *p*=0.12<br><u>5-year PFS</u>: 45% vs. 55%; *p*=0.52<br><br><u>Multivariable Analysis</u><br><u>OS</u>:<br>Auto-SCT vs. CT: HR 0.13, 95% CI 0.05 to 0.34; *p*<0.001<br>Allo-SCT vs. CT: HR 0.44, 95% CI 0.16 to 1.24; *p*=0.12<br>Allo-SCT vs. Auto-SCT: HR 1.50, 95% CI 0.65 to 3.47; *p*=0.35<br><br><u>PFS</u> |

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| | Age<br>• Allo-SCT: 48 (31-56) yrs.<br>• ASCT: 55 (32-65) yrs.<br>• RTX-CT: 57 (30-65) yrs.<br><br>Follow-up: 7.5 yrs. | ASCT: 97<br>Received a median of one regimen for follicular lymphoma.<br><br>Conditioning regimens<br>TBI: 55% of allo-SCT and 4% of auto-SCT.<br>Myeloablative: >95% of allo-SCT | | ASCT vs. CT: HR 0.09, 95% CI 0.04 to 0.22; $p<0.001$<br>Allo-SCT vs. CT: HR 0.19, 95% CI 0.07 to 0.53; $p=0.001$<br>Allo-SCT vs. ASCT: HR 0.89, 95% CI 0.41 to 1.97; $p=0.78$<br><br>**TOXICITIES**<br>• GVHD (50% acute, 42% chronic): Allo-SCT<br>• 5-year SCT-related-mortality: 23% allo-SCT, 5% auto-SCT<br><br>**Conclusion:** Eligible patients with transformed follicular lymphoma may benefit from ASCT when compared to rituximab-containing regimens.<br>Allo-SCT may be considered in certain circumstances, particularly if an autologous stem cell graft cannot be collected or if better strategies emerge to minimize TRM.<br>Relapse and TRM remain significant problems in patients with transformation who undergo SCT, even in the rituximab era. |
| • ***Large B-Cell Lymphoma*** | | | | |
| Cai et al. 2014 [30] | N= 45 RET<br><br>Relapsed or Refractory<br><br>Age<br>• SCT: 60 (49-69)<br>• Non-SCT: 69.5 (24-85)<br>• Statistical significant differences for international prognostic index score $p=0.008$<br><br>Follow-up: 24 mo. | LR + SCT: 9 (4 auto; 5 allo)<br>• DLBCL: 4<br>• FLG3: 1<br>• TL: 4<br><br>Conditioning regimen<br>Allo-SCT: 2 MA, 3 RIC.<br>Three patients received stem cells from a MUD and two from a MSD<br><br>Auto-SCT: BEAM | LR: 36<br>• DLBCL: 28<br>• FLG3: 3<br>• TL: 5 | **SCT vs. non-SCT**<br>Median PFS: NR vs. 2 mo.; $p=0.000$<br>Median OS: NR vs. 8 mo.; $p=0.003$<br><br>**TOXICITIES**<br>Two of the 9 patients with LBCL who underwent SCT died; one who had DLBCL died of GVHD and one who had FLG3 died of liver failure following auto-SCT.<br><br>**Conclusion:** Patients with LBCL who underwent SCT had significantly longer PFS and OS than the non-SCT group. The novel combination of LR offers a bridge to SCT in patients with relapsed/refractory aggressive B-cell NHL. |
| **Diffuse Large B-Cell Lymphoma (DLBCL)** | | | | |
| Van Den Neste et al. 2016 [31]<br><br>[2003-2008] | N=203 RCT<br><br>Third-Line<br>Failed to proceed to *per-protocol* BEAM+ASCT after three cycles of R-ICE or DHAP (CORAL study | ASCT: 56<br>Allo-SCT: 8<br><br>Third-line treatment: | Non-SCT: 139 | **SCT vs. Non-SCT – Intent-to-Treat Analysis**<br>166/203 patients were assessable (37 auto-SCT, 7 allo-SCT)<br><br>Median OS: 11.1 (8.3-19.5) vs. 3.3 (2.7-4.2) mo;<br>2-year OS: 33.9% vs. 9.3%; $p<0.0001$ |

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| | [32]), and were candidates for third-line regimen (PR or CR)<br><br>Age 55 (19-65) yrs.<br><br>Follow-up: 30.1 mos. | • ICE-like: 31<br>• DHAP-like: 30<br>• Gemcitabine-containing: 23<br>• Dexa-BEAM: 15<br>• CHOP-like: 14<br>• Miscellaneous: 53<br>Immunochemotherapy was used in 33% of the patients. | | **ASCT vs. Allo-SCT**:<br>Median OS: 11.5 vs. 7.9 mo.; *p*=0.3650<br><br>The transplanted patients had significantly lower IPI at failure and were better responders after third-line salvage regimen 68.8% compared to 31.2% in non-transplanted patients (*p*<0.001)<br><br>**Conclusion:** Third-line salvage chemotherapy can lead to response followed by transplantation and long-term survival in DLBCL patients. However, improvement of salvage efficacy is an urgent need with new drugs. |
| **Follicular Lymphoma** | | | | |
| Smith et al. 2018 [33]<br><br>[2002-2014] | N=440 RET<br><br>Relapse or Progression<br>Early treatment failure within 2-yrs of frontline RTX-containing CT<br><br>Age<br>• ASCT: 56 (23-79) yrs.<br>• MSD: 52 (29-68)<br>• MUD: 53 (21-74)<br><br>Follow-up: 69-73 mo.<br>• Auto-SCT: 73 (3-142) mo.<br>• MSD: 69 (3-152) mo.<br>• MUD: 73 (12-121) mo. | **ASCT**: 240<br>More likely to have grade 3 histology<br><br>Conditioning regimens: TBI-based, BEAM, CBV, Bu/MEL, Bu/Cy, or Other<br><br>**Allo-SCT**: 200<br>• MSD: 105<br>• MUD: 95<br>Allo-SCT patients were younger, more heavily pre-treated, and more likely to have advanced-stage disease at diagnosis, extranodal or bone marrow involvement and to be chemorefractory before transplantation.<br><br>Conditioning Regimens: Myeloablative, Non- | | **Auto-SCT vs. MSD vs. MUD**<br>5-years adjusted OS<br>70% vs. 73% vs. 49%; *p*=0.0008<br>5-years adjusted PFS<br>38% vs. 52% vs. 43%; *p*=0.10<br>5-years adjusted NRM<br>5% vs. 17% vs. 33%; *p*<0.0001<br><br>Multivariable analysis<br>First-24 months after SCT<br>• MUD was associated with significant increased risk of mortality in comparison with auto-SCT (RR 3.47; *p*<0.0001)<br>After-24 months after SCT<br>• MSD was associated with significant reduced risk of mortality in comparison with auto-SCT (RR 0.29, *p*=0.004)<br>• Allo-SCT (MSD and MUD) had superior PFS in comparison with Auto-SCT (RR, 0.67 and 0.40 respectively; *p*=0.001).<br><br>**TOXICITIES – GVHD MSD vs. MUD**<br>Acute grade 2-4 at d100: 35% vs. 35%, *p*=0.94<br>Acute grade 3-4 at d100: 13% vs. 16%, *p*=0.62<br>Chronic at 2 years: 54% vs. 58%, *p*=0.54<br><br>**Conclusion:** Patients with high risk follicular lymphoma undergoing Auto-SCT have low NRM and promising 5-year OS rate. |

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| | | myeloablative/RIC, unknown | | Stem cell transplantation (either MSD Allo-SCT or Auto-SCT) is an appropriate and effective option for transplant eligible follicular lymphoma patients with early treatment failure (relapse or progression within 2 years of frontline RTX-containing regimen)<br>Although MUD allo-SCT has excellent disease control, high non-related mortality was associated with inferior OS. |
| Klyuchnikov et al. 2016 [34]<br><br>[2000-2012] | N=197 RET<br><br>Relapsed or Refractory<br>Grade 3, undergoing a first-SCT<br><br>Age<br>• Allo: 53 (36-64)<br>• Auto: 57 (27-76)<br><br>Follow-up:<br>• Allo: 57 (5-132) mo.<br>• Auto: 59 (3-145) mo. | **RIC + Auto-SCT**: 136<br>BEAM and CBV. Eight received TBI<br><br>**RIC + Allo-SCT**: 61<br>Fludarabine in combination with alkylating agent. Thirteen received TBI<br><br>Allo-SCT patients were younger, more heavy pre-treated, and had longer interval between diagnosis and SCT. | | **Auto-SCT vs. Allo-SCT**<br>5-year PFS: 36% vs. 51%; *p*=0.07<br>5-year OS: 59% vs. 54%; *p*=0.7<br><br>Multivariable Analysis – OS after auto-SCT<br>Within 24 months: RR 0.43, 95% CI 0.4 to 0.78; *p*=0.005<br>Beyond 24 months: RR 3.6, 95% CI 1.05 to 12.2; *p*=0.04<br><br>**TOXICITIES**<br>• Neutrophil and platelet engraftment:<br>• Acute GVHD 100d: 25%<br>GVHD was the most frequent cause of death in the Allo-SCT, as opposed to relapse in the ASCT.<br><br>**Conclusion:** In grade 3 Follicular lymphoma patients treated with contemporary rituximab-based chemotherapies, RIC allo-SCT when compared to ASCT is associated with potentially improved survival outcomes in a subset of long-term survivors.<br>In the first 24-months post SCT, ASCT was associated with improved OS, but in long-time survivors (beyond 24 months) it was associated with inferior OS. |
| Tomblyn et al. 2011 [35]<br><br>[2004-2006] | N=30 RCT<br><br>Relapsed<br><br>Age<br>• Allo-SCT: 48 (40-64)<br>• ASCT: 50 (36-66)<br><br>Follow-up: 36 (1-51) mo. | Allo-SCT: 8 (MSD)<br><br>ASCT: 22 | | **ASCT vs. Allo-SCT**<br>3-year PFS: 63% vs. 86%<br>3-year OS: 73% vs. 100%<br><br>**TOXICITIES Grade 3-5** (elevated liver enzymes and bilirubin, vascular leak, hemorrhage, pulmonary symptoms including pneumonitis, mucositis, and delayed neutropenia): 15 (75%) vs. 4 (57%).<br>TRM 15% at 1 year and 21.8% at 3 years vs. no deaths after Allo-SCT<br>GVHD after Allo-SCT Three patients had grade I acute GVHD, and the maximum severity of chronic GVHD was mild in 2 patients and moderate in 2 patients. |

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| | | | | **Conclusion**: The authors concluded that both ASCT and allo-SCT result in promising 3-year OS and PFS in patients with relapsed FL. However, p-values were no reported. |
| le Gouill et al. 2011 [36] | N=153 RET<br><br>Relapse<br>Patientss in progression after first-line therapy with or without addition of rituximab to CT and interferon (patients from the FL2000 trial).<br><br>Follow-up: 31 mo. | ASCT: 42 | Non-SCT: 111 | **ASCT vs. Non-SCT**<br>3-year OS: 92% vs. 63%, *p*=0.0003<br><br>Multivariable Analysis: ASCT and period of progression/relapse affected overall survival<br><br>**Conclusion**: Regardless of front-line rituximab exposure, this study supports incorporating ASCT in the therapeutic approach at first relapse for follicular lymphoma patients. |
| Andresen et al. 2012 [37] | N=124 RET<br><br>Upfront | ASCT: 63 | R-CHOP: 61 | There was tendency for better QoL in the ASCT arm, maybe due to a higher proportion of patients in CR or a longer follow-up period (8.5 years in the ASCT arm vs. 4.5 years in the conventional CT arm)<br>Significant differences in favor of the ASCT arm only in the functional subcategory social functioning (*p*=0.04) and the symptomatic subcategory pain (*p*=0.01), with no significant differences in all other categories. |
| **Mantle Cell Lymphoma** | | | | |
| Cai et al. 2014 [30] | N=52 RET<br><br>Relapsed or refractory<br><br>Age<br>• SCT: 59 (46-71)<br>• Non-SCT: 71 (50-85)<br>• Statistical significant differences for age *p*=0.001 and international prognostic index score *p*=0.006<br><br>Follow-up: 24 mo. | LR + RIC + Allo-SCT: 13<br><br>Three patients received stem cells from a MSD and ten from a MUD | LR: 39 | **Allo-SCT vs. non-SCT**<br>Median PFS: 19 vs. 2 mo.; *p*=0.304<br>Median OS: 24 vs. 28 mo.; *p*=0.87<br><br>**TOXICITIES**<br>Nine of the 13 patients with MCL who underwent SCT died, eight (89%) of them from complications related to allo-SCT (GVHD, pneumonia and sepsis).<br><br>**Conclusion:** Patients with MCL who underwent SCT did not have longer PFS, or OS than those who did not undergo SCT, although the patients in the non-SCT group were older and had a higher MIPI than the SCT group. |

**Abbreviations: AITL** (angioimmunoblastic T-cell lymphoma); **ALCL** (anaplastic large-cell lymphoma); **ALK-negative** (anaplastic lymphoma kinase-negative anaplastic large cell lymphoma); **allo-SCT** (allogeneic stem cell transplantation); **anth-bCT** (anthracycline-containing chemotherapy); **ASCT** (autologous stem cell transplantation); **BCNU** (carmustine 150 mg/m$^2$ x 3d); **BEAC** (carmustine 300 mg/m$^2$ IV d1, etoposide 200 mg/m$^2$ IV per day d2-5, cytarabine 300 mg/m$^2$ per day d2-5, and cyclophosphamide 30 mg/kg per day IV d3-5.

Stem cell reinfusion was performed on day 0, and G-CSF 300 µg was subcutaneously administered once a day from day +1 until engraftment); **BEAM** (carmustine, etoposide, cytarabine, melphalan); **BL** (Burkitt lymphoma); **Bu/Cy** (busulfan and cyclophosphamide); **Bu/Mel** (busulfan and melphalan); **CBV** (cyclophosphamide, carmustine, etoposide); **CHOP** (cyclophosphamide, adriamycin, vincristine, prednisone); **CHOP-Like** (cyclophosphamide, doxorubicin, vincristine, prednisone); **CHOP-R/R-CHOP** (cyclophosphamide, adriamycin, vincristine, prednisone plus rituximab); **CP** (cyclophosphamide 100 mg/kg); **CT** (chemotherapy); **DHAP** (cisplatinum 100 mg/$m^2$ IV d1, cytarabine 2 g/$m^2$ IV q12 h d2, dexamethasone 40 mg IV d 1-4); **DLBCL** (diffuse large B-cell lymphoma); **DLBCL/BL** (unclassifiable, with features intermediate between diffuse large B-cell lymphoma and burkitt's lymphoma); **DLBCL NOS** (diffuse large B-cell lymphoma not otherwise specified); **FLG3** (follicular lymphoma, grade 3); **GVHD** (graft-versus-host disease); **Haplo-SCT** (haploidentical hematopoietic cell transplantation); **HL** (Hodgkin lymphoma); **HR** (hazard ratio); **IPI** (international prognostic index); **IPS** (international prognostic score); **LR** (lenalidomide and rituximab); **MCL** (mantle cell lymphoma); **Miscellaneous** (acute lymphoblastic leukemia (ALL)-type protocols, and others treatments including Lenalidomide, vincristine, bleomycin, fludarabine, bendamustine, in monotherapy or in various combinations. Gentamicin was mostly combined with vinorelbine, oxaliplatin, dacarbazine or cyclophosphamide); **MOED** (mitoxantrone 6 mg/$m^2$ IV d1-3, vincristine 1.4 mg/$m^2$ (maximum, 2 mg) IV d1, etoposide 100 mg/$m^2$ IV d1-3, and dexamethasone 20 mg on days 1-5, plus granulocyte colony-stimulating factor); **MRD** (mismatched related donor); **MSD** (matched sibling donor); **MUD** (matched unrelated donor); **NHL** (non-Hodgkin lymphoma); **NK-cell** (natural killer cell); **non-MA** (non-myeloablative); **PET/CT** (positron emission tomography/computer tomography); **PMBL** (primary mediastinal large B-cell lymphoma); **PTCL NOS** (peripheral T-cell lymphoma not otherwise specified); **R/RTX** (rituximab); **RCT** (randomized controlled trial); **RET** (retrospective); **RIC** (reduced intensity conditioning); **R-ICE** (rituximab-ifosfamide, etoposide and carboplatin); **TBI** (total body irradiation 12 Gy/8 Fx); **TL (**transformed lymphoma; **TRM** (transplantation-related mortality); **VP16** (etoposide 60 mg/Kg).

## Evidence Table 2: Lymphoma Types Not Addressed in 2012 Guideline

| **Observational Studies with Contemporaneous Control Group** | | | | |
|---|---|---|---|---|
| **Author [study years)** | **Patients characteristics (N, setting, median age, median follow-up)** | **Arm 1: SCT N, Treatment** | **Arm 2: Non-SCT N, Treatment** | **Brief Results OS, QoL** |
| **Non-Hodgkin Lymphoma** | | | | |
| **Primary Central Nervous System Lymphoma (PCNSL)** | | | | |
| Choi et al. 2013 [38]<br><br>[2007-2012] | N=45 RET<br><br>Relapsed or refractory<br>Patients who relapsed after high dose MTX-based CT, or were refractory to HD-MTX.<br>Salvage CT: ICE/D or HD-MTX<br><br>Age 57 (19-72) yrs.<br><br>Follow-up: 53.4 mo. | HD-CT + ASCT: 18<br>• Relapse 13<br>• Refractory 5 | HD-CT: 27<br>• Relapse 22<br>• Refractory 5<br><br>HD-CT containing thiotepa and busulfan | **ASCT vs. CT**<br>PFS: 19.5 vs. 6.7 mo. *p*=0.023, HR 0.17; *p*= 0.002<br>OS: HR 0.22; *p*= 0.022<br><br>Multivariable analysis: Refractoriness to initial treatment and no ASCT were significantly associated with poor survival outcome.<br><br>**Conclusion**: HD-CT with thiotepa and busulfan followed by ASCT showed a disease-free and overall survival benefit, together with a favourable toxicity profile in refractory or relapsed PCNSL. |

**Abbreviations: CT** (chemotherapy); **HD-MTX** (high-dose methotrexate); **ICE/D** (ifosfamide, carboplatin, etoposide, and dexamethasone); **RET** (retrospective).

**Appendix 1. Members of the Expert Panel**

| Name | Site | Conflict of Interest Declaration |
|---|---|---|
| Isabelle Bence-Bruckler | Ottawa | Advisory Board Attendance for Gilead, Novartis, Seagen; our center has received lymphoma database support from Roche, Abbvie, Seagen, Gilead, and Teva; Co-investigator on the ZUMA trial |
| Michael Crump | Princess Margaret Hospital, Toronto | None declared |
| Michael Kennah | Ottawa | Consultancy/Advisory board for Gilead, Novartis, and Celgene |
| Vishal Kukreti | Princess Margaret Hospital, Toronto | Honoraria for Celgene, Takeda, and Amgen |

**Appendix 2. Search Strategy**
Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R); OVID EMBASE.

Dates Searched: February 1, 2011 to May 11, 2020.

| | |
|---|---|
| 1 | exp lymphoma/ |
| 2 | lymphoma.mp. |
| 3 | 1 or 2 |
| 4 | exp bone marrow transplantation/ |
| 5 | exp stem cell transplantation/ |
| 6 | exp peripheral blood stem cell transplantation/ |
| 7 | 4 or 5 or 6 |
| 8 | 3 and 7 |
| 9 | letter.pt. |
| 10 | comment.pt. |
| 11 | editorial.pt. |
| 12 | 9 or 10 or 11 |
| 13 | exp Randomized Controlled Trial/ |
| 14 | randomized controlled trial.mp. |
| 15 | exp Clinical Trial/ |
| 16 | Comparative Study/ |
| 17 | 13 or 14 or 15 or 16 |
| 18 | pooling.mp. |
| 19 | pooled analysis.mp. |
| 20 | exp Meta-Analysis/ |
| 21 | meta-analyses.mp. |
| 22 | systematic review.mp. |
| 23 | health technology assessment.mp. |
| 24 | exp Evidence-based Medicine/ |
| 25 | clinical practice guideline.mp. or exp Practice Guideline/ |
| 26 | or/17-25 |
| 27 | 17 or 26 |
| 28 | 27 not 12 |
| 29 | 8 and 28 |
| 30 | limit 29 to (english language and humans) |

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## DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE – A**RCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document, however, may still be useful for education or other information purposes. The document is designated archived on the CCO website and each page is watermarked with the words "ARCHIVED."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.