Recommendation Report SCT-4

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

Stem Cell Transplantation in Lymphoma

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

Report Date: December 13, 2012

The full Recommendation Report SCT-4 is comprised of 2 sections and is available on the CCO website (http://www.cancercare.on.ca) PEBC Collaborative Projects page at:

http://www.cancercare.on.ca/toolbox/qualityguidelines/other-reports/collaborative-pr-ebss/

Section 1: Recommendations
Section 2: Summary of Methods and Evidence

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Recommendation Report SCT-4: Section 1

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

Stem Cell Transplantation in Lymphoma: Recommendations

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

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

<table>
<thead>
<tr>
<th>Hodgkin’s Lymphoma (HL)</th>
</tr>
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<tbody>
<tr>
<td>• Stem cell transplantation is not recommended as part of routine primary therapy for HL. Standard treatment for HL remains chemotherapy with or without radiation.</td>
</tr>
</tbody>
</table>

Evidence:
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.

| Autologous stem cell transplantation (ASCT) 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:
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.
Allogeneic stem cell transplantation is an option for chemo-sensitive patients with refractory or relapsed HL if they have a syngeneic (identical twin) donor, 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 retrospective cohort study (4) detected an overall survival difference, and this was in favour of reduced-intensity conditioning compared with myeloablative conditioning followed by allogeneic SCT.

### Non-Hodgkin’s Lymphomas (NHL)

**Aggressive Histology NHL Including Diffuse Large B-Cell Lymphoma, Transformed Lymphoma and Aggressive Histology T-Cell Lymphomas (AH-NHL)**

- Autologous stem cell transplantation is the recommended option for chemo-sensitive patients with AH-NHL refractory to or relapsed after primary therapy.

**Evidence, Diffuse Large B-Cell Lymphoma:**
One CPG (6) recommended autologous stem cell rescue following high-dose therapy as second-line therapy.

- Allogeneic stem cell transplantation is an option for chemo-sensitive patients with refractory or relapsed NHL if they have a syngeneic (identical twin) donor, following autologous stem cell transplantation failure, or alternatively in patients in whom sufficient numbers of autologous stem cells cannot be collected.

**Evidence, Transformed Lymphoma, Aggressive Histology T-Cell Lymphomas (AH-NHL):**
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.

**Evidence, Diffuse Large B-Cell Lymphoma:**
One CPG (7) recommended patients with a good performance status (PS) that respond to rescue CT should be enrolled in approved clinical studies testing new treatments, allogeneic SCT, or supportive therapies.

**Evidence, Transformed Lymphoma, Aggressive Histology T-Cell Lymphomas (AH-NHL):**
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.

- Stem cell transplantation is not recommended for patients with AH-NHL as part of primary therapy.

**Evidence:**
None of the evidence obtained supported the use of SCT in primary treatment of AH-NHL, and the Expert Panel endorses this position.

### Follicular Lymphoma (FL)

- 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 (8), and a CPG (6). The systematic review (SR) (8) recommended autologous SCT as salvage treatment based on pre-rituximab data, as there was a demonstrated benefit in both OS and PFS. The CPG (6) stated that either autologous SCT or allogeneic SCT were acceptable options for second-line or subsequent treatment.
**Burkitt’s Lymphoma**

- Autologous and allogeneic transplantation are options for chemo-sensitive patients with Burkitt’s lymphoma refractory to or relapsed after primary treatment.

**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.

**Mantle Cell Lymphoma (MCL)**

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

**Evidence:**
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 (9) (see Discussion section).

- 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:**
This Recommendation was brought forward from the 2009 Recommendation Report (5) and modified slightly to include allogeneic transplant for select patients in first remission based on consensus from the Expert Panel.

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**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].

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REFERENCES


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

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 (1). 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 (2). While Hodgkin’s lymphoma is generally considered curable (3), the disease still affects many Canadians, often young individuals, with an estimated incidence of 920 new cases for 2011 (2). As lymphoma patients represent a very heterogeneous group, even within each subtype (3), 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 (4).

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

634 citations retrieved from the MEDLINE database

608 excluded: reasons: i.e., not randomized, etc.

Title and abstract review by single author (BR).

30 citations retrieved for full publication review.

16 excluded: reasons: i.e. not randomized, etc.

Full publication review by one author (BR).

14 full publications identified and included.

Quality of included studies

Hodgkin’s lymphoma

Four papers were obtained on Hodgkin’s lymphoma (5-8) comprising a randomized trial (5), one prospective cohort study (6), and two retrospective cohort studies (7,8).

The randomized trial reported by Arakelyan et al (5) 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 (6) 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 (7) 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 (8) 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.

Aggressive non-Hodgkin lymphoma and diffuse large B-cell lymphoma

For aggressive non-Hodgkin lymphoma, one meta-analysis (9) and one RCT (10) were obtained. In the meta-analysis, reported by Greb et al (9), 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 (10) 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 \( \chi^2 \) 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-event 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 (11,12) were obtained along with one retrospective cohort study (13). As neither of the CPGs that were obtained [reported by Barosi et al (11) and Zelenetz et al (12)] 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 (13) 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.

**T-cell lymphoma**

As the CPG reported by Zelenetz et al (12) 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 (14) 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.

**Follicular lymphoma**

As the systematic review reported by Oliansky et al (15) 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 (12) 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 (16) 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 (5), one prospective cohort study (6), and two retrospective cohort studies (7,8) including a total of 398 patients. These studies tested different treatment approaches. The studies by Majhail et al (6) and Sureda et al (8) reported on patients who underwent allogeneic transplantation, and the studies by Arakelyan et al (5) and Morabito et al (7) 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 (8) 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 (6) 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 (5) 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 (7) 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Comparison</th>
<th>Overall Survival (OS)</th>
<th>Progression-free Survival (PFS)</th>
<th>Neutrophil engraftment</th>
<th>Graft-versus-Host Disease (GVHD)</th>
<th>Treatment-related Mortality (TRM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized trial</strong></td>
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<tr>
<td>Arakelyan et al, 2008 (5)</td>
<td>VABEM-RT n=82</td>
<td>5 year: 86.8% (95%CI, 79-94)</td>
<td>5 year: 78.9 (95%CI, 70-87.8)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>1997-2004 GOE-LAMS H97-HR</td>
<td>ABVD-TEAM + ASCT n=76</td>
<td>85.9% (95%CI, 77.7-94.1)</td>
<td>74.9 (95%CI, 65-84.7)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td><strong>Prospective cohort studies</strong></td>
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<tr>
<td>Majhail et al, 2006 (6)</td>
<td>RIC → UCB n=9</td>
<td>2 year: 51% (95%CI, 16-86)</td>
<td>2 year: 25% (95%CI, 0-55)</td>
<td>10% (95%CI, 6-28)</td>
<td>Grade 3-4: 33%</td>
<td>100d/180d: 11%/21%</td>
</tr>
<tr>
<td>2000-2005</td>
<td>RIC → MSD n=12</td>
<td>48% (95%CI, 19-77)</td>
<td>20% (95%CI, 0-44)</td>
<td>7% (95%CI, 5-12)</td>
<td>p=0.02</td>
<td>33%</td>
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<tr>
<td><strong>Retrospective cohort studies</strong></td>
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<tr>
<td>Morabito et al, 2006 (7)</td>
<td>CC n=24</td>
<td>4 year: 33%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>1988-2002</td>
<td>HDC n=27</td>
<td>81% p=0.02</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sureda et al, 2008 (8)</td>
<td>RIC n=89</td>
<td>5 year: 28% (95%CI, 18-38)</td>
<td>5 year: 18% (95%CI, 10-26)</td>
<td>NR</td>
<td>100d: 44% (95%CI, 35-57)</td>
<td>1yr: 38% (95%CI, 28-52)</td>
</tr>
<tr>
<td>1997-2001</td>
<td>MAC n=79</td>
<td>22% (95%CI, 13-36) p=0.003</td>
<td>20% (95%CI, 11-28) p=0.07</td>
<td>NR</td>
<td>100d: 38% (95%CI, 28-52) p=0.05</td>
<td>1yr: 33% (95%CI, 22-48) p=0.05</td>
</tr>
</tbody>
</table>

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 d1, 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, epidosorubicin) or EVA (etoposide, vincristine, adriamycin) plus IF-RT or for high-risk patients (six courses of ABVD, MOPPEBCAD (mechlorethamine, lomustine, vindesine, melphalan, prednisone, epidosorubicin, 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/m$^2$ 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 thiopeta (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.
Aggressive non-Hodgkin’s lymphoma
For aggressive non-Hodgkin’s lymphoma, three papers were retained: a meta-analysis reported by Greb et al (9), a CPG reported by Zelenetz et al (12) and an RCT reported by Baldissera et al (10). 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 (9) 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 (12) 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 (10), 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Comparison</th>
<th>Overall Survival (OS)</th>
<th>Progression-free Survival (PFS)</th>
<th>Neutrophil Engraftment</th>
<th>Graft-versus-Host Disease (GVHD)</th>
<th>Treatment-related Mortality (TRM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baldassera et al, 2006 (10)</td>
<td>VACOP-B 12 week n=27</td>
<td>47%</td>
<td>47%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>1998-2003</td>
<td>VACOP-B followed by HDS + ASCT 6 week n=29</td>
<td>40%</td>
<td>30%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Note: VACOP-B, etoposide 50 mg/m² IV d1 and 100 mg p.o. d2 and d3 weeks 3,7,11, doxorubicin 50 mg/m² weeks 1,3,5,7,9,11, cyclophosphamide 350 mg/m² IV weeks 1,5,9, vincristine 1.2 mg/m² weeks 2,4,8,10,12, bleomycin 10 U/m² weeks 2,4,6,8,10,12, prednisone 45 mg/m² p.o. daily for 1 week and every other day from weeks 2 to 12; HDS, cyclophosphamide 4 g/m² followed by etoposide 2 g/m²; ASCT, autologous stem cell transplantation.

For diffuse large B-cell lymphoma (DLBCL) specifically, two papers were retained, a CPG reported by Barosi et al (11), and another, a retrospective cohort study reported by Lazarus et al (13).

In the CPG reported by Barosi et al (11), 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 (13), 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Comparison</th>
<th>Overall Survival (OS)</th>
<th>Progression-free Survival (PFS)</th>
<th>Neutrophil Engraftment</th>
<th>Graft-versus-Host Disease (GVHD)</th>
<th>Treatment-related Mortality (TRM)</th>
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<td>1yr 5yr 1yr 5yr 1yr 5yr</td>
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<tr>
<td>Retrospective cohort studies</td>
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<tr>
<td>Lazarus et al, 2010 (13)</td>
<td>ASCT n=837</td>
<td>66% 49% NR NR NR NR</td>
<td>N/A N/A 12% 45%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995-2003</td>
<td>AlloSCT n=79</td>
<td>33% p&lt;0.05 22% p=ns</td>
<td>NR NR NR NR</td>
<td>N/A N/A 41% p&lt;0.001 18% p=ns</td>
<td></td>
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</tbody>
</table>

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.

Transplantation in T-cell lymphoma was reported in a retrospective cohort study reported by Lee et al (14). 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

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Comparison</th>
<th>Overall Survival (OS)</th>
<th>Progression-free Survival (PFS)</th>
<th>Neutrophil Engraftment</th>
<th>Graft-versus-Host Disease (GVHD)</th>
<th>Treatment-related Mortality (TRM)</th>
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<tr>
<td>Retrospective cohort studies</td>
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</tr>
<tr>
<td>Lee et al, 2008 (14)</td>
<td>ASCT + HDC n=47</td>
<td>56.2%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>ConCT + RT n=34</td>
<td>47.6% p=0.13</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Note: HDC, high-dose chemotherapy: various regimens used including CBV (etoposide, carmustine, cy), BEAM (carmustine, etoposide, cytarabine, melphalan), MEC (carmustine, 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 CHOEP (cyclophosphamide, doxorubicin, vincristine, prednisolone), dose-escalated CHOP (dCHOP), veiCHOP (velcade plusCHOP), CEP (Cy, etoposide, vincristine, prednisolone), CEP/ProMACE (CEP followed by Cy, doxorubicin, etoposide, prednisone), MACOPB (methotrexate, doxorubicin, Cy, vincristine, prednisone, bleomycin), CHOEP (Cy, doxorubicin, vincristine, etoposide, prednisone), ProMace, ProMace/Cytabom (ProMace plus cytarabine, 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 (etoposide, 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, dexamethasone), IMVP-16 (ifosfamide, methotrexate, etoposide), and VPD (etoposide, ifosfamide, cisplatin, dexamethasone). For suitable patients, IFRT was offered for localized disease following CT.

Follicular lymphoma

For follicular lymphoma, three papers were retained: a systematic review reported by Oliansky et al (15), a CPG reported by Zelenetz et al (12), and an RCT reported by Gyan et al (16).

In the systematic review reported by Oliansky et al (15), 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 (12) 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 (16), 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**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Comparison</th>
<th>Overall Survival (OS) 9-year</th>
<th>Progression-free Survival (PFS) 9-year</th>
<th>Neutrophil Engraftment</th>
<th>Graft-versus-Host Disease (GVHD)</th>
<th>Treatment-related Mortality (TRM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gyan et al, 2009 (16)</td>
<td>ASCT + HDC n=86</td>
<td>76% (95%CI, 67-85)</td>
<td>64% (95%CI, 54-75)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>GOE-LAMS 064 1994-2001</td>
<td>ConCT + immunotherapy n=80</td>
<td>80% (95%CI, 72-89)</td>
<td>39% (95%CI, 28-50)</td>
<td>p=0.004</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Note:** ASCT, autologous stem cell transplantation; HDC, High-dose chemotherapy; VCAP (vindesine, cyclophosphamid, 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 X 10^5 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 X 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 not changed significantly 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.

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 (17), and an abstract report summarizing the CIBMTR experience (18). 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 (19). 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. 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](http://www.clinicaltrials.gov)) (updated August 30, 2011)

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Title, details</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00469729</td>
<td>Efficacy and Safety Study of StemEx®, to Treat Subjects With High Risk Hematologic Malignancies, Following Myeloablative Therapy (ExCell) Study ID: GC P#02.01.001 Status: recruiting Updated: June 19, 2011</td>
</tr>
<tr>
<td>NCT00928018</td>
<td>Tacrolimus/Sirolimus/Methotrexate Versus Tacrolimus/Methotrexate or Cyclosporine/Mycophenolate Mofetil for GVHD Prophylaxis After Reduced Intensity Allogeneic Stem Cell Transplantation for Patients With Lymphoma Study ID: 09-073 Status: recruiting Updated: June 22, 2011</td>
</tr>
</tbody>
</table>

**Aggressive-Histology NHL Including Diffuse Large B-Cell Lymphoma and Aggressive T-Cell Lymphomas (AH-NHL)**

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Title, details</th>
</tr>
</thead>
</table>

**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.

ACKNOWLEDGEMENTS AND AUTHORSHIP
The Stem Cell Transplant Steering Committee and the Working Group would like to thank the following individuals for their assistance in developing this report:

- Dr. C. Tom Kouroukis, Mr. R. Bryan Rumble, Dr. John Kuruvilla, Dr. Michael Crump, Dr. Jordan Herst, and Dr. Caroline Hamm for taking the lead in drafting this recommendation report.
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- Ashley Keen for conducting a data audit.
- Bruce Histed for copyediting.
- Stephanie Pow, Claire Shanahan, and Sherrie Hertz, CCO Staff for project support.
REFERENCES

APPENDIX A. Literature search strategy

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

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 2 (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

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

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.

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

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.

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.

1Stem 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].