The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-Cell non-Hodgkin's lymphoma: an evidence-based review


Authors' objectives
To evaluate evidence on the role of cytotoxic therapy with hematopoietic stem cell transplantation (SCT) in the treatment of diffuse large-cell B-cell non-Hodgkin's lymphoma (DLCL).

Searching
MEDLINE, and the National Institute of Health NLM website were searched for studies published in English between January 1980 and December 2000. The search used the MeSH term 'Non-Hodgkin's lymphoma', limited to 'Drug Therapy' or 'Therapy'. The following sources were handsearched: abstracts published by the American Society of Hematology in Blood; American Society of Clinical Oncology abstracts in the Journal of Clinical Oncology; the European Group for Blood and Marrow Transplantation abstracts (1997 to 2000 meetings) in Bone Marrow Transplantation; and abstracts published in Annals of Oncology by the International Conference on Malignant Lymphoma (1999 meeting).

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not explicitly defined a priori in terms of the study design. Dose-escalation and dose-finding studies were excluded, as were reviews, editorials, case reports and letters. The primary studies included randomised controlled trials (RCTs), non-randomised controlled trials, cohort studies, case-control studies, uncontrolled studies and multiple time series.

Specific interventions included in the review
Studies that did not examine cytotoxic therapy were excluded, as were studies that examined therapy for relapse after SCT and studies of second transplantation. Many different chemotherapy regimens were examined. These included: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B); and etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (VACOP-B). In addition, the following transplantation techniques were included: double/tandem haematopoietic SCT; myeloablative allogeneic SCT; nonmyeloablative allogeneic SCT; autologous bone marrow transplant (BMT); autologous peripheral blood stem cell transplantation (PBSCT); purging; stem cell mobilisation methods; conditioning regimens; and high-dose sequential therapy.

Participants included in the review
Patients with DLCL were eligible if DLCL was defined according to the following criteria: the revised European-American Classification of Lymphoid Neoplasms or the World Health Organization classification of diffuse large B-cell lymphoma (see Other Publications of Related Interest nos. 1-2); International Working Formulation subtypes F, G and H; Keil Classification centroblastic, centro-blastic-centrocytic, centrocytic, and immunoblastic B-cell; and Rappaport classification diffuse B-cell lymphoma. Studies involving SCT were only included if DLCL patients accounted for at least 70% of the study population, unless the results were stratified by histology subtype. Patients with HIV-associated lymphomas were excluded.

Outcomes assessed in the review
The inclusion criteria were not defined a priori in terms of the outcomes. Studies that did not assess overall survival (OS), disease-free survival (DFS) or event-free survival (EFS), with the exception of studies of stem cell mobilisation techniques, were excluded.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Assessment of study quality
The strength of the evidence was graded according to study design. The grades ranged from 1 (the highest grade) corresponding to evidence from at least one proper RCT, to grade 4 (the lowest grade) corresponding to inadequate evidence owing to methodology problems (see Other Publications of Related Interest no.3). Other aspects of study design (sample size, duration of follow-up and treatment plan) were also evaluated (see Other Publications of Related Interest no.4). The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Information such as the outcomes assessed, median follow-up and sample size were tabulated. Additional information was provided in the text of the review.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the characteristics of the participants and a narrative synthesis was undertaken. The strength of the evidence was graded from 1, the highest grade where the experimental treatment was significantly better (p<0.05), to grade 5 in which the control group was significantly better (see Other Publications of Related Interest no.4). The strength of the treatment recommendations was graded from grade 1, the highest grade where there was evidence of effective treatment, to grade 5 where the treatment had not been adequately evaluated (see Other Publications of Related Interest no.5).

How were differences between studies investigated?
Differences between the studies were mentioned in the text.

Results of the review
The number of studies and participants included in the review was unclear.

1. Treatment recommendation by disease response and International Prognostic Index (IPI) risk (where available). First chemotherapy-sensitive relapse: the treatment recommendation was graded 1 (effective treatment) and the level of evidence was 1 (at least one properly designed RCT). There was one RCT (215 patients) that compared autologous BMT with salvage chemotherapy. Treatment with autologous BMT improved the overall response rate (84% versus 44%), 5-year EFS (46% versus 12%; p=0.001) and 5-year OS (53% versus 32%; p=0.038).

Chemotherapy-resistant relapse and primary refractory disease: the treatment recommendation was graded 4 (inadequately evaluated treatment) and the level of evidence was 2 (well-designed non-randomised controlled trials, cohort, case-control, multiple time series, dramatic results in uncontrolled trials).

First complete remission in patients with low or intermediate-to-low IPI risk: the treatment recommendation was graded 3 (not an effective treatment) and the level of evidence was 1 (at least one properly designed RCT). There was one RCT with 916 patients, of which 520 patients achieved complete remission. There was no significant difference in the 3-year OS or DFS in this subgroup of 520 patients who were randomised to chemotherapy or BMT: OS was 71% with chemotherapy versus 69% with BMT (p=0.60), while DFS was 52 and 59%, respectively (p=0.46).

First complete remission in patients with high or intermediate-to-high IPI risk: the treatment recommendation was graded 1, but there were problems with the study methodology; the level of evidence was 2 (well-designed non-randomised controlled trials, cohort, case-control, multiple time series, dramatic results in uncontrolled trials).

First partial remission after full-course induction therapy: there was no evidence available.

Abbreviated induction therapy (less than 6 cycles of CHOP or less than 12 cycles of MACOP-B or VACOP-B): the treatment recommendation was graded 3, but there were problems with study methodology; the level of evidence was 1.
High-dose sequential therapy in untreated patients with intermediate- to-high or high IPI risk: the treatment recommendation was graded 1 and the level of evidence was 1. In the one crossover RCT (98 patients), patients receiving high-dose sequential therapy had significantly increased rates of 7-year EFS compared with patients receiving MACOP-B (76% versus 49%; p<0.004).

High-dose sequential therapy in untreated patients with low or low- to-intermediate IPI risk: the treatment recommendation was graded 4 (inadequate evidence) and there were problems with the study methodology; the level of evidence was 1.

2. Treatment recommendation for transplantation techniques.

The treatment recommendation was graded 4 (inadequate evidence) for double/tandem SCT and the level of evidence was 2. For myeloablative allogeneic SCT, the treatment recommendation and level of evidence were 4 (inadequate evidence) and 2, respectively; there was no evidence available for nonmyeloablative allogeneic SCT. The treatment recommendation was 1 for both autologous BMT and autologous PBSCT, while the levels of evidence were 1 and 3, respectively. For purging, the treatment recommendation was graded 4 (inadequate) and the level of evidence was 2. For the stem cell mobilization method, the treatment recommendation and level of evidence were 4 (inadequate) and 2, respectively. There was no evidence available for conditioning regimens. The treatment recommendation and level of evidence were both 1 for high-dose sequential therapy in patients with intermediate-to-high or high IPI risk, and 4 (inadequate) and 1, respectively, for high-dose sequential therapy in patients with low or low-to-intermediate IPI risk.

Authors' conclusions
The authors' conclusions were given in the form of recommendations that were not easy to interpret.

CRD commentary
The aims were stated and the inclusion criteria were defined in terms of the treatment, outcomes and participants. Several relevant sources were searched, but the methods used to select the studies were not described. Restricting the search to studies in the English language may have resulted in the omission of other relevant studies, and the lack of attempts to locate unpublished studies raises, as the authors acknowledge, the possibility of publication bias. Validity was not formally assessed, other than by using study design to allocate a level of evidence. Some relevant data were tabulated and additional information given in the text. No details were given of the methods used to assess validity or to extract the data. The data were appropriately grouped by the patients' characteristics and described in a narrative. However, the narrative synthesis was predominantly limited to descriptions of the individual studies and the studies were not really combined. It was not easy to extract meaningful information from the tables of treatment recommendations that form the authors' conclusions. Hence, it is difficult to comment upon the conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors state that research is required to answer the following. Should patients be offered SCT in first complete response/remission or wait until first chemotherapy-sensitive relapse? Should patients receive salvage therapy in first relapse to test for chemotherapy sensitivity, or proceed to SCT in untested relapse? What is the optimal timing of stem cell mobilisation? What is the role of post-SCT therapy? How in future will risk-adapted therapy involving SCT be defined? What is the role of in vivo versus ex vivo purging using chemical or antibody selection? Will allogeneic SCTs with nonmyeloablative conditioning regimens offer a graft-versus lymphoma effect without the toxicity of a myeloablative allogeneic SCT? What is the role of gene therapy as part of the conditioning regimen for SCTs? What is the role of ex vivo expansion in autologous and allogeneic SCTs? What are the optimal combinations of different treatment modalities as conditioning regimens to produce least toxicity and greatest therapeutic effect?

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