Feasibility and safety of autotransplants with noncryopreserved marrow or peripheral blood stem cells: a systematic review

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CRD summary
This review concluded that non-cryopreserved autotransplants are feasible and safe for patients undergoing high-dose chemotherapy for malignancy. The conclusions appear to be supported by the data but, owing to the absence of controlled evidence, the possibility of publication bias and the poor reporting of review methods, it is difficult to assess their reliability.

Authors' objectives
To examine the feasibility and safety of autologous non-cryopreserved stem-cell transplants to support patients receiving high-dose chemotherapy, and to describe high-dose regimens commonly used in this context.

Searching
MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, ClinicalTrials.gov, the American Society of Hematology (ASH) website, the American Society of Clinical Oncology (ASCO) website and Google were searched for studies published in any language since 1965; the search terms were reported. Abstracts from ASH and ASCO meetings were also checked, along with the reference lists of retrieved articles.

Study selection
Study designs of evaluations included in the review
Any study design was eligible for inclusion, provided that it reported sufficient details of the patient's diagnosis, age, high-dose drug regimen used, number of harvested progenitors, and the length and conditions of storage.

Specific interventions included in the review
Studies assessing the transplantation of autologous non-cryopreserved marrow, or of peripheral blood stem cells gathered by leucapheresis, were eligible for inclusion. Studies of growth-factor primed blood were excluded. In the included studies, bone marrow was collected from multiple aspirations of the posterior and anterior iliac crests and in some cases the sternum, usually without previous priming with haemopoietic growth factors; it was stored for 8 to 72 hours. Peripheral blood progenitor cells were stored for 1 to 6 days. In most studies the harvested product was stored at 4°C.

Participants included in the review
Eligible studies included patients treated with myeloablative chemotherapy for malignancy. The participants in the included studies were children or adults (age range: younger than 1 to 69 years) with malignancies including Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, germ-cell tumours and acute leukaemias.

Outcomes assessed in the review
Eligible studies had to report all of the following outcomes. The primary outcome was the graft failure rate. This was defined as lack of neutrophil recovery of over 0.5 x 10^9 cells/L by 28 days post-transplant and/or the need for transfusions to maintain platelets of over 20 x 10^9/L after100 days post-transplant; death in aplasia of a patient fulfilling these criteria was defined as graft failure. The secondary outcomes were neutrophil and platelet engraftment times and transplant-related mortality. Neutrophil engraftment time was defined as the number of days to attain a neutrophil count of over 0.5 x 10^9/L from the day of stem-cell infusion (day 0). Platelet engraftment time was defined as the number of days from day 0 to achieve an unsupported platelet count of over 20 x 10^9/L. Transplant-related mortality was defined as the cumulative total of transplant-related deaths at any number of days post-transplant. Where studies used different definitions of engraftment times these were reported. Late transplant complications were also reported.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality
The authors did not state that they assessed validity. However, one article which met the inclusion criteria was excluded from the review because it had been retracted by the publication journal due to methodological flaws, and another excluded article was contemporaneous and had similar authorship and institutional affiliation to the retracted article.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the extraction. Results were reported as the percentage of patients who experienced the outcome for dichotomous outcomes, and as median rates and ranges for continuous outcomes.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative. Study characteristics and outcomes were also summarised in the tables. For some outcomes, results of individual studies were pooled by simple addition.

How were differences between studies investigated?
Heterogeneity between the studies was discussed in the text. The results were grouped by the type of malignancy, dose regimen, autograft used and outcome of interest.

Results of the review
The review included 16 studies: two phase 2 studies (n=70) and 14 retrospective case series (n=546).

The authors described the studies as well-conducted. They noted that publication bias was possible and that there was marked methodological and clinical heterogeneity between the studies, with wide variation in baseline patient characteristics, drug regimens and outcome definitions. However, the graft failure rate was consistent among studies, despite this heterogeneity.

Graft failure rate: this was 0.36% (2 out of 553) among patients who received myeloablative therapy. Of the 616 patients, 56 who did not receive myeloablative treatment and 7 who died before engraftment were excluded from this analysis.

Neutrophil engraftment times: in studies of bone marrow transplantation that reported this outcome according to review-defined criteria (10 studies, 333 participants), engraftment times varied from 10 to 20 days (range: 5 to 103). In studies of peripheral blood stem-cell transplantation that reported this outcome according to review-defined criteria (6 studies, 212 participants), engraftment times varied from 9 to 14 days (range: 0 to 86).

Platelet engraftment times: in studies of bone marrow transplantation that reported this outcome according to review-defined criteria (4 studies, 190 participants), engraftment times varied from 18 to 28 days (range: 5 to 300). In studies of peripheral blood stem-cell transplantation that reported this outcome according to review-defined criteria (5 studies, 140 participants), engraftment times varied from 13.5 to 25 days (range: 0 to 102).

Transplant-related mortality: this was 3.65% (22 out of 316). There were no transplant-related deaths in 8 studies; rates varied from 2 to 13% in the other 8 studies.

Late transplant complications: one study with a median follow-up of 62 months reported this outcome (n=114). Two patients, both with Hodgkin’s lymphoma developed new haematological malignancies after 18 to 20 months’ follow up.

The review also reported findings in studies that used different criteria for engraftment.

Authors’ conclusions
Non-cryopreserved autotransplants are feasible and safe for patients undergoing high-dose therapy.

CRD commentary
The review question and inclusion criteria were clear. Several relevant sources and strategies were used in the literature.
search, but the authors acknowledged that publication bias may be an issue. The potential for reviewer bias and error also cannot be determined, as the review methods were not clear. The study populations and interventions varied, as did the outcome definitions in some studies; this suggests that the authors’ use of a narrative synthesis is appropriate. Overall, the conclusions appear to be supported by the data, but the absence of controlled evidence, the possibility of publication bias and the incomplete reporting of review methods, make it difficult to assess their reliability.

Implications of the review for practice and research

Practice: The authors state that non-cryopreserved autotransplants are a safe alternative to standard autotransplants and may be especially useful where cryopreservation of stem cells is not feasible. They noted that shorter versions of commonly used high-dose chemotherapy regimens have been used to avoid long periods of storage of stem cells.

Research: The authors did not state any implications for future research.

Funding
None stated.

Bibliographic details

PubMedID
17355952

DOI
10.1093/annonc/mdm069

Original Paper URL
http://annonc.oxfordjournals.org/cgi/content/full/18/4/623

Indexing Status
Subject indexing assigned by NLM

MeSH
Bone Marrow Transplantation /adverse effects; Cryopreservation; Humans; Leukemia /therapy; Lymphoma /therapy; Multiple Myeloma /therapy; Peripheral Blood Stem Cell Transplantation /adverse effects; Transplantation, Autologous

AccessionNumber
12007005597

Date bibliographic record published
07/01/2008

Date abstract record published
30/09/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.