



# Non-myeloablative bone marrow and peripheral stem cell transplantation

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## ***Conflict of Interest***

None

## **NB:**

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## *Questions*

- 1. What are the effects of non-myeloablative allografts in people who are not eligible for myeloablative treatment?**
- 2. What are the effects of non-myeloablative allografts in people who are eligible for myeloablative treatment?**

## *Summary*

This review examined the evidence for non-myeloablative allografts in people who are a) eligible for myeloablative treatment, and b) ineligible, because they are unable to tolerate the adverse effects of myeloablation.

We found that, to date, research is restricted to case series, in which there was wide variation in patient characteristics, indications for treatment, interventions, and clinical outcomes.

No firm conclusions can be drawn about the efficacy of non-myeloablative allografts on the basis of existing research. Results of individual studies provide very weak evidence that non-myeloablative treatment may improve short term outcomes in certain patient groups. However, because studies lacked reliable control groups, this conclusion rests on the assumption that patients managed supportively or with conventional treatments have a uniformly poor short-term prognosis. More robust studies are needed. Treatment should probably be given in the context of research protocols.

## **Background**

Myeloablative therapy, consisting of high dose chemo- or radiotherapy followed by bone marrow or peripheral blood stem cell transplantation, has traditionally been given to people with a variety of haematological and non-haematological cancers, and non-malignant haematological disorders. By causing pancytopenia, myeloablative therapy is associated with severe acute adverse effects until transplantation 'rescues' the patient's bone marrow by inducing non-cancerous, donor-type growth of normal blood cells (haematopoiesis). Chronic effects are also seen as a result of immunological reactions between graft and host. These adverse effects limit the use of myeloablative regimens in older people and in people with existing comorbidity.

Non-myeloablative therapy has recently been developed as a less toxic alternative to myeloablation, on the theory that abolition of abnormal cells may not solely depend on prior myeloablation by high dose therapy. It has been suggested that engraftment of donor cells may also help to destroy malignant cells in the recipient. On this basis, it is argued that perhaps conditioning regimens need not be myeloablative, providing that patients receive enough immunosuppressive treatment to allow donor engraftment. It is hoped that low dose, non-myeloablative regimens might prove suitable for people who are not eligible for myeloablative treatment, and that they may even prove a less toxic alternative in people who would otherwise undergo myeloablation.

Non-myeloablative regimens, however, may be associated with severe adverse effects, because they rely on immunosuppressive treatment to prevent graft versus host disease after transplantation. Such treatment predisposes recipients to infection and may also reduce the anti-malignancy effects of donor cells. These effects may outweigh the benefits of preserving host marrow function until donor marrow engrafts.

## **Search Methods**

Search date: September 2000 (updated August 2001, see postscript). Primary sources: Cochrane database of systematic reviews; Medline from 1966 onwards and Embase from 1980 onwards. Hand searching of references. Additional references were sought through personal communication. Search strategy is available on request. We sought studies that examined at least one clinical outcome of non-myeloablative conditioning regimens in humans. Studies that used total body irradiation were excluded (all were uncontrolled case series).

## **Evidence found**

We found no systematic reviews, and no reliably controlled studies. We found 21 case series, the largest of which included 39 cases.<sup>1</sup> One study used historical controls to compare a subset of outcomes, but provided no data to confirm that controls were matched with cases. In common with many other studies, it did not state in advance the outcomes to be compared. Five

series were written up in abstract form only.<sup>1-6.</sup>  
We found no evidence of duplicate publication of patient data, but the lack of detail in many reports means we cannot rule out the possibility of duplication.

Mortality following treatment ranged from 0% (n=4, eligibility for myeloablation not explicitly stated, median follow up about 10 months)<sup>7</sup> to 61% (n=39, participants ineligible for myeloablation, median follow up 7 months).<sup>1</sup> Ranges for other outcomes were also wide. It was difficult to compare other outcomes because of varying (or absent) outcome definitions, and inconsistent grouping of outcomes among studies.

It was not possible to compare incidence or severity of clinical outcomes with those achieved by myeloablative treatment, because studies were not controlled. It was not possible to stratify effects in terms of the indications for treatment.

### **Quality of Evidence Found**

Few case series stated inclusion or exclusion criteria in advance of study recruitment, leading to the risk of selection bias in reported cases. Patient characteristics and indications for treatment varied among series. Nineteen series examined effects in haematological malignancy,<sup>1-19</sup> which was usually advanced and refractory to conventional chemotherapy. Three studies examined effects in non-malignant disorders<sup>7,11,20</sup> and four in non-haematological malignancy.

<sup>13,16,18,21</sup> Overall, eight studies included only patients who were reported as ineligible for conventional myeloablative conditioning (due to age or comorbidity).<sup>1-3, 7,9,16,18,20</sup> One study included only patients eligible for myeloablation.<sup>10</sup> The remaining 20 studies were not explicit about eligibility, or included some participants who were eligible for myeloablation, and some who were not.

Pre- and post-transplant regimens varied among series. Fludarabine was the most common component of conditioning regimens (19/21 studies). The remaining two series used low dose cyclophosphamide/busulfan<sup>8</sup> and thiotepa/cyclophosphamide.<sup>16</sup> After transplantation, most series used cyclosporin, often in addition to methotrexate, steroids, or both. Three studies offered donor lymphocyte infusions if donor chimerism had not been achieved within a fixed period after transplant.<sup>2, 12, 20</sup>

Studies reported on engraftment (restoration of blood cell counts), chimerism (establishment of donor-type cells), haematological remission, clinical recovery, and mortality. None reported on quality of life. Follow up periods varied considerably within and among studies. The longest median follow up for mortality among studies was 36 months (one study).<sup>10</sup> All other series reported mortality after a median follow up of 15 months or less. Transplant related mortality was often not defined, and definitions varied among studies.

Few series explicitly stated primary and secondary endpoints in their methods, increasing the possibility of bias due to post hoc analysis.

We found no robust evidence on the effects of non-myeloablative treatment, nor of its comparative efficacy with myeloablative regimens. If it is accepted that short term prognosis is uniformly poor with conventional management in the patient groups studied, the case series would suggest that non-myeloablative allografts may improve short-term prognosis in some patients.

In the absence of controlled studies of any kind, however, this result must be regarded as tentative, and it may be that longer term outcomes would have been no worse had myeloablation or no treatment been attempted. Similarly, quality of life may not be improved by non-myeloablative allografts. In addition to lack of controls, studies lacked power, clear selection criteria, and prior definition of endpoints; and were heterogeneous with regard to patient selection, interventions, co-interventions, and outcomes. For these reasons, their results should be regarded as hypothesis-generating rather than definitive, while the effects of non-myeloablative treatment remain uncertain and experimental. This would support the use of non-myeloablative treatment only within research protocols.

### ***Postscript: Updated Search***

An update search was undertaken in August 2001. The update search strategy was identical to that

originally performed. A brief summary of results is presented based on information from study abstracts, although it is advised that the cited primary articles are consulted for further details.

We found 17 additional studies.<sup>22-38</sup> All were uncontrolled case series, the largest of which reported retrospectively on 92 patients reported in a national research registry.<sup>24</sup> Other series were smaller, most reporting results in under 30 patients. Duplicate publication of data cannot be excluded.

Patient characteristics varied among and within series. Indications for treatment included multiple myeloma, leukaemias, lymphomas, myelodysplastic syndromes, thalassaemia major, chronic granulomatous disease, failed first allograft and malignancy secondary to initial treatment. HLA status and relationship of donor and host differed among studies. Patient populations consisted mainly of people considered unsuitable for conventional allograft.

Pre-and post transplant treatment protocols also varied among and within studies. Fludarabine-based regimens were the most commonly used conditioning treatments, although co-administered drugs and supportive treatments differed.

Follow up was of generally short duration, as was the case with studies found in the initial search.

In summary, the update search has not altered the conclusions of the review. The research regarding

efficacy and safety of this treatment is still in an early phase. Studies are heterogeneous in terms of their populations and interventions and are uncontrolled. Results are promising, especially if it may be assumed that prognosis is consistently worse with alternative treatment strategies in the studied patient groups. However, the conclusion remains tentative pending larger, preferably controlled, studies with consistent and explicit inclusion and exclusion criteria, consistent co-interventions and longer follow-up.

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