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Comments and Critique

Bone Marrow Transplantation With Unrelated Volunteer Donors

FOR MORE than 20 years, bone marrow transplantation has been an accepted and successful method to treat a number of severe disorders, such as leukaemia, myelodysplasia, bone marrow failure, immunodeficiency, storage disorders, and haemoglobinopathies. The importance of bone marrow transplantation for severe diseases was acknowledged by awarding Donnall Thomas the Nobel prize in medicine. The number of allogeneic bone marrow transplants performed every year is continuously increasing. The cumulative number worldwide during 1985–1987 was about 10 000, as estimated by a survey made by the International Bone Marrow Transplant Registry (IBMTR) [1]. Based on the annual accrual rate to the main registries, i.e. the IBMTR and the registries of the European Group for Bone Marrow Transplantation (EBMT) [2], one can estimate that more than 40 000 allogeneic bone marrow transplants have been performed up to now.

Still, numbers of patients that could have benefited from a bone marrow graft will not undergo bone marrow transplantation because of the lack of suitable donors. So far, the great majority of bone marrow transplants have been performed with marrow from HLA (human leucocyte antigen)-identical sibling donors. One reason for this is that HLA-identity or near identity seems to be a requirement for successful bone marrow transplantation, and to find an HLA-compatible unrelated donor in the general population is extremely difficult. Simple mathematics makes it clear that since the number of possible HLA phenotypes is the product of the squares of the number of alleles at each locus, there are 4×10^{18} possibilities, i.e. more than the total world population today [3]. However, fortunately enough, some HLA phenotypes are much more frequent than others. For example, in the UK and Ireland the five most frequent HLA phenotypes occur in 3.16% of the population. These five phenotypes are made up by HLA-A1, -A2, and -A3, HLA-B7, -B8 and -B12 and HLA-DR2, -DR3, and -DR4. Beatty *et al.* [4] have estimated that 17% of whites have a phenotype which allows a 90% chance of finding a donor in a registry of 50 000, while 50% of the remaining 83% of the patients have less than 10% chance of finding a donor in such a registry. In a registry of 200 000 whites, Beatty's calculations indicated that it would be possible to find HLA-A, -B and -DR matched donors for 50–75% of the patients, and an HLA-A, -B, -DR, -DW-matched donor for 40–50%. However, there is a good chance of finding a donor in smaller local registries in countries with a geographically stable population derived mainly from a single ethnic group.

The first unrelated donor registry was established by the Anthony Nolan Fund [5]. This centre now has more than 145 000 HLA-A and B-typed donors. Recently, further registries have been built, and with support from the European Commission (Concerted Action Project) a network has been established by bone marrow transplant registries in the so-called *Bone Marrow Donors World Wide* [6]. This is a book that is updated regularly every 3–4 months. It now contains information about HLA-typed volunteer donors from 18 registries. In June 1991, there were 594 200 HLA-A and B typed volunteers, 148 572 of whom HLA-DR-typed. Therefore, the prospects for finding an HLA-A, -B, and -DR-typed donor are excellent for the most common haplotypes, and decent for more unusual ones. However, for some patients with very unusual haplotypes, the chances are still very small.

Despite the large number of registered volunteers, relatively few patients have so far received grafts from unrelated donors. One important obstacle is that the time from start of searching to bone marrow transplantation is too long. In the Anthony Nolan Panel the search time, defined as the time from search request to the day of bone marrow transplantation, is about 7 months [7], and in the Canadian registry the median time was 168 days [8]. Patients may relapse or die before the donor marrow is available. The network created by *Bone Marrow Donors World Wide* and the regular publishing of the book may help speed up the procedure. Other ways to speed up the time are the use of new HLA matching tests that are quicker and safer. For example, Clay *et al.* [9] recently described a PCR typing method that is even quicker than the RFLP typing. This method for HLA-DR typing may bring down the typing time to 8 h instead of 2 weeks. The technique appears to be easier and needs less equipment than the conventional HLA-DR typing. In the IMUST study, supported by the European Commission, Bradley *et al.* [10] will try to establish a search prognosis index for patients with specific HLA-haplotypes, and defined clinical characteristics. This might help in the decision-making process. Alternative treatment methods, e.g. autologous bone marrow transplantation in leukaemia, may be the choice if the chances of finding a donor are too small.

Having established registries, search prognosis indexes, and refined HLA typing methods, the most important question remains. Who will profit from an unrelated bone marrow graft? There is no clear answer to this question. The first attempt to perform an unrelated bone marrow transplantation was unsuccessful [11]. Despite identity for HLA-A- and -B and a negative MLR (mixed lymphocyte reaction) between donor and recipient, the patient succumbed 2 months after the transplantation without signs of engraftment. However, in the following years it became apparent that it might well be possible to perform successful bone marrow transplantation using unrelated donors [12–17]. Today, most experience has been gained from such transplants in chronic myelocytic leukemia. A four-centre group

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recently claimed a 29% 2.5-year survival for 102 patients of whom 54 were in first chronic phase and 48 in more advanced stages, either in acceleration or in blast crisis [18]. Graft-versus-host disease was a serious problem. 65% had grade II-IV, which was significantly higher than would be expected in a group transplanted with marrow from HLA-identical sibling donors. The importance of a good match was indicated by an actuarial survival of 46% in 44 patients who received marrow from a well-matched donor, compared with 27% in those who received marrow from not fully matched donors. These data seem to indicate that there is a place for bone marrow transplantation using unrelated donors in chronic myelocytic leukaemia, but it may require well-matched marrow.

The interpretation of results for acute leukaemia is much more difficult. However, in one study of 104 patients including both acute and chronic leukaemias, the relapse-free survival was 41% if unrelated marrow was used, which was not significantly different from 46% if HLA-compatible sibling marrow was used [19]. The acute leukaemias were either in second or higher grades of remission or in relapse, and the two groups were matched for disease stage and age. In a Canadian study [20] also including both acute and chronic leukaemia, the projected long-term survival was 40%. These results have to be compared with results with chemotherapy and autologous bone marrow transplantation in similar prognostic groups. Since long-term survival of about 40% has been claimed for autologous bone marrow transplantation of acute leukaemia in both first [21] and second [22] remission, it is at present not apparent that unrelated donor transplantation is superior. One of the objectives of the study planned by the Concerted Action Programme is to utilize EBMT registries for comparison between allogeneic transplantation using unrelated donors with both autologous transplantation and sibling-donor transplantation. Hopefully, this will clarify the place of unrelated marrow transplantation in acute leukaemia.

Even more difficult is to recommend unrelated bone marrow transplantation in patients with aplastic anaemia. Here, other methods such as treatment with ATG, cyclosporine, and high-dose prednisolone are effective in a great number of patients [23]. So far, results with unrelated bone marrow transplantation are difficult to judge. In general, the few results that are now available are less promising than for leukaemia [24–26]. It is possible that new and more intensive conditioning protocols might improve these results [25].

The Project Managing Group of the Concerted Action Project now tries to make recommendations for bone marrow transplantation using unrelated donors [27]. One reason for the seemingly poorer results with unrelated donor marrow as compared with sibling donor marrow is that transplantation with unrelated marrow is frequently done at a later stage of the disease. This is often due to the long search time for an unrelated donor. Therefore, one recommendation is that the decision to start a search for an unrelated donor should be taken early, before deterioration of the disease. There will also be a listing of those diagnostic groups that seem to benefit from unrelated bone marrow transplantation. Principally, any patient who is a candidate for identical sibling donor transplantation may be a candidate for unrelated bone marrow transplantation with matched marrow. The view of the Project Managing Group is that all patients who receive a bone marrow graft from an unrelated donor should be on a protocol and be reported to one of the large registries. Also, certain categories of patients should only be treated in centres that have a large experience for many years in bone marrow transplantation. These patients should be on qualified research protocols and reported to research registries.

During the next few years it is probable that the Concerted Action Project, as well as other projects, will more clearly define the place of unrelated bone marow transplantation in haematological and other disorders. Improvement of typing technique, more precise knowledge about the major and minor histocompatibility antigens, shortening of the donor search time, improvement in graft-versus-host prevention techniques, shortening of the risk period for infection by the use of haematopoietic growth factors, as well as the use of more effective antiviral and antibacteriological agents will probably increase the number of patients that can benefit from bone marrow transplantation using an unrelated donor.

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Should Surgery Remain the Initial Treatment of "Operable" Breast Cancer?

SURGERY HAS traditionally enjoyed a prominant role in the primary treatment of most stages of breast cancer. The value of surgery in providing diagnostic security and allowing access to important prognostic information appeared unassailable, and the contribution of surgery to the control of local and regional disease was unquestioned. During the past two decades, however, two important developments have led to a reassessment of the breast surgeon's role. Firstly, prospective clinical trials evaluating breast conservation in early stages of the disease have demonstrated convincingly that the use of breast irradiation allows the extent of primary surgery to be drastically reduced, while maintaining adequate disease control [1–4]. Secondly, the appreciation of breast cancer as a systemic illness has led to the scientific investigation and widespread application of adjuvant systemic therapies in high risk patients, promising for the first time to change the natural history of the disease [5]. More recently, the putative successes of hormonal and chemotherapies have prompted their frequent use as adjuvants even in patients traditionally viewed as having a "good" prognosis, e.g. node-negative patients [6, 7], thus at least partially obviating the need for an axillary staging operation.

WHICH TREATMENT SHOULD BE FIRST?

A logical outgrowth of the above considerations is the use of "up front" systemic therapy, following establishment of the diagnosis by fine-needle aspiration cytology or limited biopsy of the primary tumour. Such treatment, variously termed "neo-adjuvant", "induction", "preoperative", or "primary", most frequently involves the administration of several cycles of combination chemotherapy. Based upon excellent response rates observed in the treatment of locally advanced stage III breast cancer [8, 9], primary chemotherapy is now under intensive investigation for less extensive lesions (Table 1). This strategy offers both real and theoretical advantages. Firstly, the objective response of the tumour can be observed, allowing the treatment to be continued in the event of a favourable response, or otherwise to be abandoned or modified. The second concrete advantage is to offer the possibility of breast preservation to patients who are not candidates for classical breast-conserving techniques because of an unfavourable ratio between tumour

Table 1. Summary of objective response rates and rates of breast-conserving treatment in published studies of primary chemotherapy for operable breast cancer

Study [ref.]	*n*	Tumour size	Chemotherapy cycles	Objective response CR/PR (%)	Conservative procedures (%)
Mauriac [10]	134	T>3 cm	3 EVM + 3 MiTVi	33/?	63
Bonadonna *et al.* [11]	165	T>3 cm	3–4 CMF or 3–4 FAC or 3 FEC	17/60	88
Jacquillat *et al.* [12]	250	T1–T4	3–6 VeTMFP +/− A, +/− TAM	30/41	100*
Scholl *et al.* (pp.1668–1671)	95	T>2 cm	2 FAC	13/32	79*
Spielmann *et al.* [13]	119	T>2 cm	3 AVCMF	9/61	53
Hortobagyi *et al.* [14]	128	Stage II–IV	4 FAC	14/60	27

*Treatment included radiotherapy given immediately after primary chemotherapy. A = doxorubicin, V = vincristine, C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, E = epirubicin, Mi = mitomycin, T = thiotepa, Vi = vindesine, Ve = vinblastine, P = prednisone, TAM = tamoxifen.

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