Haematology and Blood Transfusion Vol. 31
Modern Trends in Human Leukemia VII
Edited by Neth, Gallo, Greaves, and Kabisch

Use of Autologous Bone Marrow Transplantation in Acute Myeloid Leukemia

A. K. Burnett [1]

A. Introduction

Progress in achieving initial remission of disease in acute myeloblastic leukaemia (AML) has taken place in recent years, with rates of 70%–80% being reported [1–3]. This has been effected by different scheduling of drugs rather than by the introduction of new chemotherapeutic agents. The ability of chemotherapy protocols to maintain remission is less easy to demonstrate. Unlike remission maintenance chemotherapy in acute lymphoblastic leukaemia (ALL), there is little evidence to suggest that continuous chemotherapy has prevented subsequent relapse for the majority of patients. Some improvements have been claimed for very intensive protocols, with better results being achieved in children [4, 5]. However, since the majority of patients with the disease are adults, alternative approaches are required.

Allogeneic bone marrow transplantation (BMT) has proved to be an effective remission maintenance strategy, with approximately 50% of patients becoming long-term survivors [6–8]. This approach, however, is not without its limitations. When the procedure goes well, it is probably much less toxic than conventional intensive chemotherapy, but in a proportion of patients who do become long-term survivors, morbidity can be significant and there are important late consequences. Procedure-related deaths due to the immunobiological problems of allograft represent a risk. About 30%–40% of patients transplanted succumb to problems such as pneumonitis, graft-versus-host disease (GVHD) or the consequences of immunosuppression. A crucial point is that the actuarial risk of relapse following allograft appears to be 15%–30%, which represents a substantially better antileukaemic effect than that achieved by any other approach. Such results are only achieved in first remission. When allografts are attempted at later stages of the disease, results are worse primarily owing to a higher rate of relapse. An important limitation of allograft with regard to the problem of cure in AML is that it is only applicable to younger patients (conventionally under 40 years of age) with a fully HLA-matched donor, thus restricting the technique to 10%–15% of those with the disease. The prospects for younger patients (under 20 years of age) are good, with 70% –80% surviving; but conventional chemotherapy is also offering improved results in these cases. It can be anticipated that morbidity and mortality of allograft patients will be reduced by such measures as T-cell depletion to abrogate GVHD [9], and cytomegalovirus-negative blood product support for seronegative recipients [10, 11].

The mechanism involved in the cures obtained by allograft may be complex. Two major factors may operate. Allografted marrow rescue has permitted the administration of ablative doses of cyclophosphamide and total body irradiation (TBI) to the patient's marrow, which may alone be capable of eradicating leukaemia. There may in addition be an antileukaemic effect exerted by the graft on any residual leukaemia [graft-versus-leukaemia (GVL) effect]. Such an ef-

[1] Glasgow Royal Infirmary, Castle Street, Glasgow G4 OSF, UK

fect has been shown to operate in lymphoid leukaemia models in mice [12, 13] and was part of the rationale behind introducing BMT into clinical practice.

Autologous remission bone marrow represents a source of replacement haemopoietic stem cells following ablative chemotherapy or chemoradiotherapy. Potential advantages offered by autologous BMT (ABMT) are: (a) there would be an additional option available to patients who lack a donor; (b) procedural morbidity and mortality may be less; not only would GVHD be eliminated as a complication but syngeneic data suggest that pneumonitis and immunosuppression would be less; (c) if toxicity was limited, this approach could be offered to older patients and would thus represent an option for more patients with the disease. Theoretical objections must also be recognised, the first of which relates to loss of the GVL effect. This mechanism may operate in AML in remission in man, but such evidence is indirect and the effect may not be great. It should be borne in mind that the often-quoted experimental data refer to lymphoid models usually involved in transplantation across histocompatibility boundaries. An association of an antileukaemic effect of acute GVHD, based on statistical prediction, in man is not significant for AML in remission, although there is apparent an effect of AML in relapse and ALL in remission and relapse [14]. Perhaps the most useful parallel is the relapse rate in twin transplants for AML in first remission, where half of a relatively small number of patients with various preparative protocols developed recurrent disease usually within the first 12 months after transplant [15].

The second objection is that orthodox assumptions about the nature of remission suggest that the inevitability of relapse indicates that while the patient may fulfil the clinical criteria of remission, residual cells remain which are responsible for relapse. Remission marrow therefore will contain some residual leukaemic cells, and relapse is therefore probable. This raises the important issue of the importance of cleansing (or "purging") the bone marrow.

If the twin data are accepted at face value, they have three important implications for autograft: (a) there will predictably be a higher relapse rate, perhaps at least 50% in autograft, owing to lack of a GVL effect; (b) further risk of relapse may occur if contamination of the autologous marrow is relevant; and (c) morbidity and procedural mortality will be low.

Purging of residual leukaemia in vitro in the context of AML presents special problems. There is little evidence to suggest that density separation is of value. Specific monoclonal-antibody-based techniques are not available at present, and most attention currently centres around pharmacological treatment in vitro [16]. This originated from experimental data in a rat myeloid leukaemia model of efficacy which used a cyclophosphamide metabolite (4-hydroperoxycyclophosphamide) because the tumour was very sensitive in vivo to cyclophosphamide [17]. An unsatisfactory aspect of such an approach is that there is no way of assessing effectiveness in vitro in any individual case.

B. Choice of Ablative Protocol

On the basis of allogeneic experience, the timing of the autograft is predictably going to influence outcome. In relapsed disease and second remission allograft, even with the advantages of an uncontaminated graft and the postulated GVL effect, relapse rates are high; consequently, autograft is unlikely to be of benefit. Subsequent clinical studies confirm such an impression. For optimum results, use in first remission is logical.

Cyclophosphamide and TBI constitute the standard preparative protocol for allograft and represent a useful benchmark. There is some evidence to suggest that substitution of cyclophosphamide by melphalan may have enhanced antileukaemic effect [18]. Although increased TBI has little effect on reducing the relapse rate in allograft of relapsed disease, it may offer some advantage if used in remission. Chemotherapy can be an effective alternative preparative regime for allograft.

A number of studies involving chemotherapy-based protocols with ABMT are currently under way, but there is insufficient follow-up at present to indicate whether a TBI or chemotherapy protocol is superior. An interesting approach is that of double

autograft, whereby chemotherapy with ABMT is given on two occasions. A possible advantage of this approach, apart from the fact that it intensifies treatment, is that a degree of "in vitro purging" may be achieved [19].

C. Results of Autograft in First Remission

In our own experience in Glasgow, with the use of unpurged marrow, 22 patients have received an autograft in first remission.

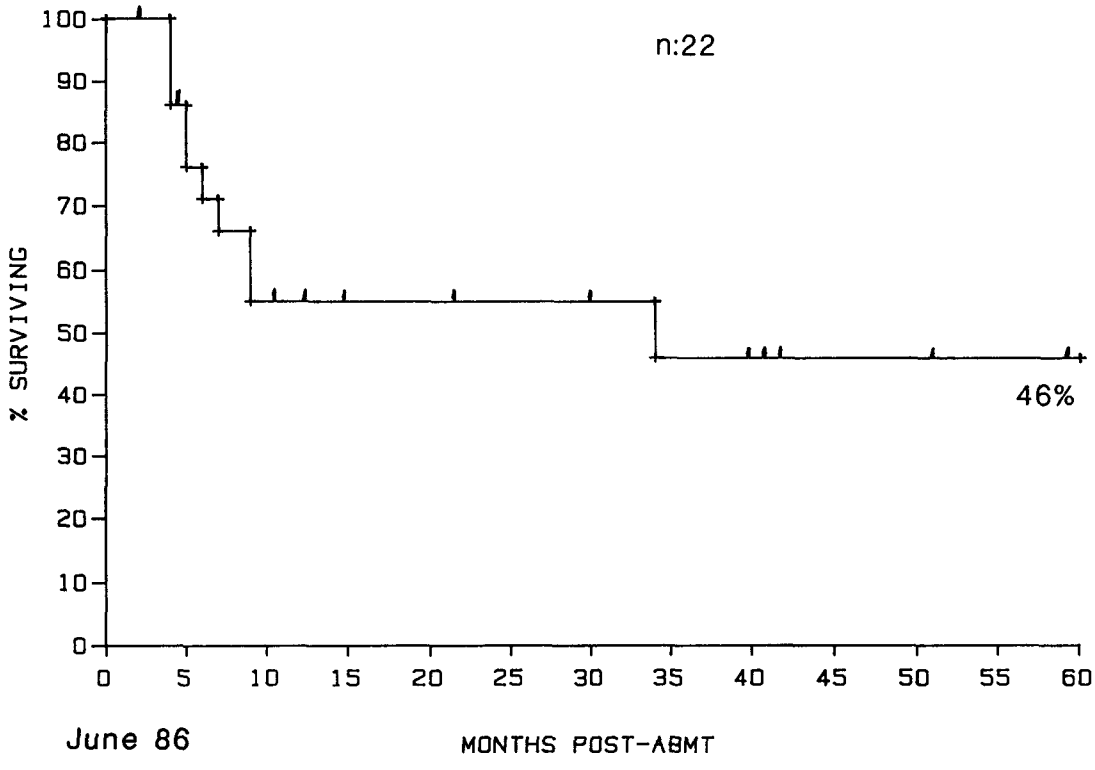

Fig. 1. Survival of patients receiving ABMT for AML in first remission (Glasgow)

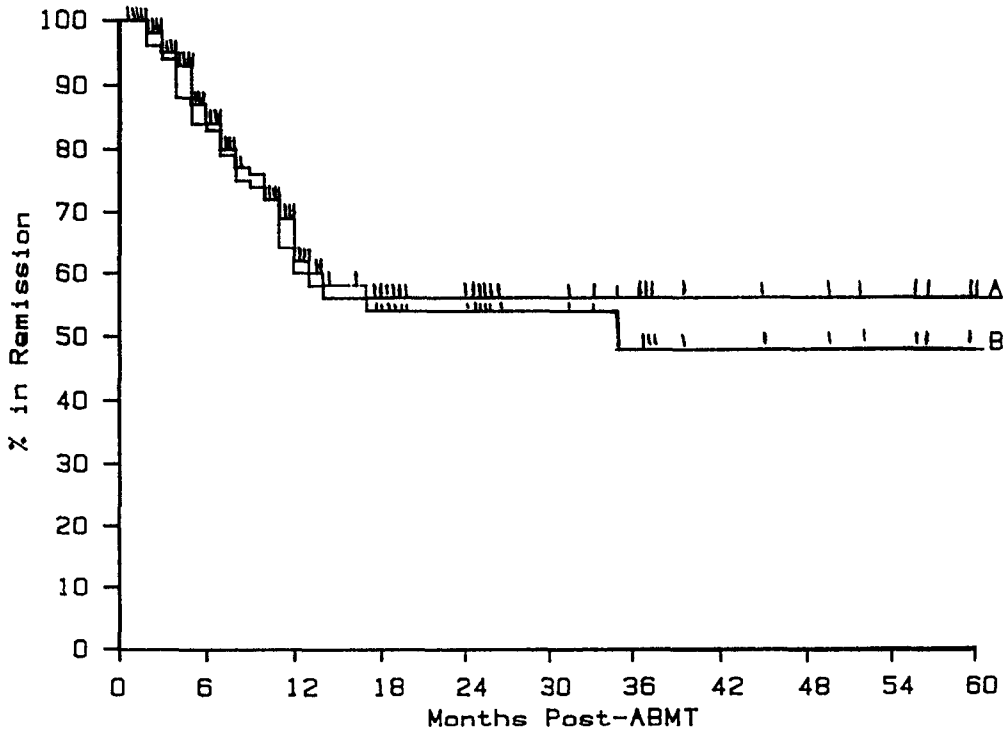

Fig. 2. Multi-centre study [20] of ABMT in first remission. *A*, leukaemia-free survival; *B*, overall survival

These patients ranged in age from 13 to 53 years (median 36). The first 13 patients received cyclophosphamide and single fraction TBI (950 cGy) and autologous marrow stored at 4 °C for 54 h. The next 9 patients received melphalan (110 mg/m^2) and fractionated TBI (6 × 200 cGy) with cryopreserved marrow. Nine patients have relapsed, all within 12 months of transplant, 12 continue in remission and 8 have been in remission for over 2 years. There was no procedural mortality, and morbidity was acceptable. One patient died of a cerebral haemorrhage in complete remission 35 months after ABMT. The actuarial survival at 4 years is 46% and leukaemia-free survival 57% (Fig. 1).

In a review of data from other European centres using unpurged bone marrow, 90 cases were assessed [20]. Of these cases, 5 died of non-leukaemic, usually infective causes, 3 within 3 months of autograft. The age range of patients was 10–57, but 33 patients were over 35 years old and may therefore be considered outside the acceptable age range for allograft. A variety of cytoreductive protocols were used: single-pulse high-dose chemotherapy, double autograft, and cyclophosphamide and TBI; 53 patients received TBI, and 37 a chemotherapy protocol (including 14 as double autografts). Twenty-seven patients relapsed, all but 2 within 1 year of autograft. The leukaemia-free survival at 3 years after ABMT was 56% (Fig. 2).

Relatively few data are available to assess whether purging confers additional benefit. Such comparisons as have been made show no advantage.

D. Conclusions

Available studies suggest autologous transplantation may have a contribution to make to remission maintenance in AML in first remission. Prolonged follow-up of more patients is awaited with interest, but in the meantime it is important to be aware of possible selection bias in these patients. In particular, they were in remission for variable periods prior to autograft and may have selected themselves as having more responsive disease; similarly, patients who relapsed prior to autograft would be excluded from the protocol. In the multi-centre study [20], when leukaemia-free survival was stratified according to time elapsed prior to autograft, there were improved prospects for those autografted at 4–8 months (58%) compared with those at < 4 months (38%). This could obviously be due to the selection bias referred to above, but it may also indicate that chemotherapy prior to autograft plays an important role.

These results are of importance in the future evaluation of purging techniques, since the leukaemia-free survival is similar to that observed in syngeneic transplants. This may suggest that the question of residual leukaemia in the graft is unimportant. It will also be difficult to demonstrate, at least in first remission, significant benefit from purging.

References

1. Rees JKH, Gray R, Hayhoe FGJ (1985) Late intensification therapy in the treatment of acute myeloid leukaemia. (abstract). Proc Am Soc Clin Oncol C621
2. Preisler HD, Rustum Y, Henderson ES et al. (1979) Treatment of acute non-lymphocytic leukaemia: use of anthracyclin – cytosine arabinoside induction therapy and comparison of two maintenance regimens. Blood 53:455–464
3. Gale RF, Foon KA, Cline MJ et al. (1981) Intensive chemotherapy for acute myelogenous leukaemia. Ann Intern Med 94:753–757
4. Weinstein HJ, Mayer RJ, Rosenthal DS et al. (1983) Chemotherapy for acute myelogenous leukaemia in children and adults: VAPA Update. Blood 62:315–319
5. Creutzig U, Riefim RH, Langermann HJ (1985) Improved treatment results in childhood acute myelogenous leukaemia: a report of the German Co-operative Study AML-BRM-78. Blood 65:298–304
6. Thomas ED, Buckner CD, Clift RA (1979) Marrow transplantation for acute non-lymphoblastic leukaemia in first remission. N Engl J Med 301:597–599
7. Powles RL, Morgenstern G, Clink HM et al. (1980) The place of bone marrow transplantation in acute myelogenous leukaemia. Lancet 1:1047–1050
8. Zwaan FE, Hermans J, Barrett AJ et al. (1984) Bone marrow transplantation for

acute non-lymphoblastic leukaemia: a survey of the European group for bone marrow transplantation. Br J Haem 56:645–653
9. Prentice HG, Blacklock HA, Janossy G et al. (1984) Depletion of T lymphocytes in donor marrow prevents significant graft-versus-host disease in matched allogeneic leukaemics marrow transplant recipient. Lancet I:472–476
10. Bowden RA,Sayers M, Flournoy N et al. (1986) Cytomegalovirus Immune Globulin and Seronegative Blood Products to Prevent Primary Cytolomegalovirus Infection after Bone Marrow Transplantation. N Engl J Med 314:1006–1010
11. McKinnon S, Burnett AK, Crawford RG et al. (1986) Prevention of CMV infection in allogeneic bone marrow transplant recipients by using CMv-negative blood products. Bone Marrow Transplantation 1:67(Suppl)
12. Barnes DWH, Loutit JF (1975) Treatment of murine leukaemia with x-rays and homologous bone marrow. Br J Haem 3:241–252
13. Boranic M (1971) Time pattern of anti-leukaemic effect of graft-versus-host reaction in mice. J Natl Cancer Inst 4:421–432
14. Weiden PL, Flournoy N, Thomas ED et al. (1979) Anti-leukaemia effect of graft-versus-host disease in recipients of allogeneic marrow grafts. N Engl J Med 300:1068–1073
15. Gale RP, Champlin RE (1984) How does bone marrow transplantation cure leukaemia? Lancet II:28–30
16. Santos GW, Colvin OM (1986) Pharmacological Purging of Bone Marrow with Reference to Autografting. Clin Haematol 15; 1:67–83
17. Sharkis SJ, Santos GW, Colvin M (1980) Elimination of acute myelogenous leukemic cells from marrow and tumor suspensions in the rate with 4-hydroperoxycyclophosphamide. Blood 55:521–523
18. Goss GD, Powles RL, Barrett A et al. (1985) Melphalan and total body irradiation (TBI) versus Cyclophosphamide plus TBI prior to bone marrow transplantation in acute myeloid leukaemia in first remission. Exp Haematol 13; 12–13 (Suppl 17)
19. Anderson CC, Linch DC, Goldstone AH (1986) Double autografting: a potential curative regimen for acute leukaemia. Minimal residual disease in acute leukaemia 1986. Hagenbeck B, Lowenberg A (eds) Martinus Nijhoff, Amsterdam, pp 221–233
20. Burnett AK, McKinnon S (1986) Autologous bone marrow transplantation in first remission AML using non-purged marrow – update. Minimal residual disease in acute leukaemia 1986. Hagenbeck B, Lowenberg A (eds). Martinus Nijhoff, Amsterdam, pp 211–220