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*Commentary*

# Supralethal Dose Therapy for Sensitive Cancers

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(A COMMENT ON: PHILIP T, BIRON P, HERVÉ P *et al.* Massive BACT chemotherapy with autologous bone marrow transplantation in 17 cases of non-Hodgkin's malignant lymphoma with a very bad prognosis. *Eur J Cancer Clin Oncol* 1983, **19**, 1371–1379.

THE TREATMENT of sensitive cancers with high-dose cytoreductive therapy followed by rescue of the hematopoietic system by the infusion of bone marrow cells is an idea which was initially explored in the late 1950s. Some of the earliest published reports involved the use of cryo-preserved autologous marrow [1]. In these early studies of autologous bone marrow transplantation the dose of cytoreductive therapy was not usually high enough to suggest a significant therapeutic advantage over conventional regimens. Over the ensuing years, concerns about the possible presence of occult tumor cells in autologous marrow and the demonstration that an adoptive graft vs tumor effect might be associated with graft vs host disease (GVHD) led to an emphasis on the use of allogeneic bone marrow transplantation in acute leukemia. While these studies of allogeneic marrow transplantation utilized pre-transplant cytoreductive regimens that were truly supralethal with respect to marrow function, the specific contribution of such supralethal pulses of therapy in the reported cures was obscured by the possible role of GVHD in providing a post-transplant antitumor effect. It was, therefore, not until the publication of the pioneering studies of Fefer and his colleagues on identical twin transplants in acute leukemia [2] that interest was re-awakened in the possible role of autologous marrow transplantation in the treatment of cancer. These studies demonstrated that cures could be obtained in relapsing and refractory patients with acute leukemia given supralethal dose therapy in a setting where GVHD was unlikely to play a role in the antitumor effect. Few patients possess an identical twin to donate marrow. The report by Philip and his co-workers [3] in this issue of the journal adds to the growing body of evidence that this approach may be more generally employed—with significant success—by the use of cryopreserved autologous marrow.

There are two principal requirements that must be met if supralethal dose therapy associated with autologous marrow transplantation is to be successfully applied to the treatment of cancer. First, the reinfused marrow must be free of clonogenic tumor cells. Second, the supralethal dose therapy must have a significant chance at clearing the tumor cells from the patient without producing lethal or irreversible extramedullary toxicity.

Although the presence of bone marrow involvement at the time of death in the 6 treatment failures reported by Philip *et al.* [3] raises concern that tumor may be reinfused with the cryo-preserved marrow in some patients, the successes observed in others of this group clearly demonstrate that clonogenic tumor is absent from the marrow of significant numbers of patients with non-Hodgkin's lymphoma (NHL), despite failure of primary therapy or clearly adverse prognostic factors. A recent review of autologous marrow transplantation in 64 patients with NHL confirms the success rate observed in Philips' study [4]. It is noteworthy that two of the reported long-term survivors had marrow involvement at diagnosis which was cleared by induction therapy prior to marrow harvesting. In contrast to these results, there is little evidence that relapsing or refractory acute leukemia patients can achieve

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significant long-term relapse-free survival using supralethal dose therapy and autologous marrow reinfusion [5]. Although some of the observed relapses are due to a failure of the supralethal dose therapy to clear tumor, some must be due to the reinfusion of tumor with the autologous remission marrow. Possible solutions to this latter problem of tumor cell contamination are suggested by animal model studies in which tumor cells were completely eliminated from tumor–marrow cell mixtures by *in vitro* immunologic or pharmacologic treatment [6]. Clinical application of *in vitro* treatment of marrow with either monoclonal antibody or 4-hydroperoxycyclophosphamide is currently under study [7, 8], but it is too early to assess the results.

In the long run the development of more successful, less toxic supralethal cytoreductive regimens is likely to be a more complex and difficult task than purging occult tumor from harvested marrow. Strictly speaking, the Applebaum version of BACT used by Philip and his colleagues is not supralethal to normal marrow, since two patients exhibited prompt hematologic recovery without marrow reinfusion. It would be tempting to try to improve the success rate of BACT by increasing its intensity, but the existence of about a 25% treatment-related mortality precludes simple dose escalations. In the non-lymphohematopoietic solid tumors the situation has been worse, since the extramedullary toxicities have been significant and the response rates have been far less encouraging [4, 6]. Thus, while phase III controlled studies comparing different supralethal dose regimens may provide a basis for progress in NHL and acute leukemia (provided there is a successful solution of the tumor purging problem), such an approach is unlikely to produce advances in the treatment of the non-lymphohematopoietic solid tumors. In this latter instance, a reasonable strategy would be to focus on therapeutic laboratory models to develop cytoreductive agents and combinations whose limiting toxicity is more narrowly restricted to the hematopoietic system and to then extend this work to the clinical setting in a series of phase II studies.

## REFERENCES


1. KURNICK NB, MONTANO A, GERDES MD *et al.* Preliminary observations on the treatment of post irradiation hematopoietic depression in man by the infusion of stored autologous marrow. *Ann Intern Med* 1958, **49**, 973–986.
2. FEFER A, CHEEVER MA, THOMAS ED *et al.* Bone marrow transplantation for refractory acute leukemia in 34 patients with identical twins. *Blood* 1981, **57**, 421–430.
3. PHILIP T, BIRON P, HERVÉ P *et al.* Massive BACT chemotherapy with autologous bone marrow transplantation in 17 cases of non-Hodgkin's malignant lymphoma with a very bad prognosis. *Eur J Cancer Clin Oncol* 1983, **19**, *1371*–1379.
4. PHILIPS GL. Current clinical trials with intensive therapy and autologous bone marrow transplantation (ABMT) for lymphomas and solid tumors. In: *Proceedings of UCLA Symposium on Bone Marrow Transplantation, Park City, Utah, February* 1983. In press.
5. GALE RP. Bone marrow transplantation in leukemia. In: GALE RP, FOX CR, eds. *Biology of Bone Marrow Transplantation.* New York, Academic Press, 1980, 11–27.
6. KAIZER H, SANTOS GW. Autologous bone marrow transplantation in treatment of leukemia, lymphomas, and other cancers. In: ARIEL I, ed. *Progress in Clinical Cancer.* New York, Grune and Stratton, 1982, Vol. 8, 31–43.
7. RITZ J, BAST RC, CLAVELL LA *et al.* Autologous bone marrow transplantation in CALLA-positive lymphoblastic leukemia after *in vitro* treatment with J5 monoclonal antibody and complement. *Lancet* 1980, **ii**, 60–63.
8. KAIZER H, TUTSCHKA PJ, STUART R *et al.* Autologous bone marrow transplantation in acute leukemia and non-Hodgkin's lymphoma: a phase I study of 4-hydroperoxycyclophosphamide (4HC) incubation of marrow prior to cryopreservation. *Haematol Blood Transf* In press.