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Perspectives and Commentaries

The Case for High-Dose Chemotherapy: Is it Chemotherapy's Last Gamble?

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THE PACE of development of new agents with exceptional effectiveness against human cancer has not kept up with the expectations of the public or the medical oncologists whose numbers have increased in the last twenty years. Experimental animals bearing transplantable tumors, mostly leukemias, have been the "model" of human cancers in screening and developing of drug administration schedule. This approach has been more productive of agents for the treatment of hematologic malignancies than the more common solid tumors. Nonetheless, this system of transplantable tumors also demonstrated that with some agents there was a very steep dose–response curve, especially when drug-sensitive, highly proliferative tumors were treated with escalated doses [1]. It was also obvious that extrapolation of these doses to man was not always possible because the toxicity to visceral organs that was not always predicted by the animal models. The principle of optimal or maximally-tolerated-dose chemotherapy has been more firmly rooted in the therapy of hematologic cancer, most especially the acute leukemias, where total obliteration of the leukemic marrow was the desired end point.

There probably would not be disagreement among oncologists with principle that more drug against an inherently sensitive tumor could result in a greater anti-tumor effect. The possible exceptions to this may be localized Burkitt's lymphoma, whose cure rate was not increased by repeated high-dose cyclophosphamide compared to a single dose and localized choriocarcinoma which can be cured by rather conventional doses of methotrexate. In almost all other circumstances, the dose of an effective chemotherapeutic agent determines the therapeutic impact on the disease. An important question would be whether an increased dose of a marginally effective agent would result in an anti-tumor response and would that response be clinically meaningful, given the likely toxicity of escalated dose treatment. Enough "preliminary" studies have been performed in order to give a framework upon which to offer comment whether there is a case for high-dose chemotherapy with the currently available drugs.

The impetus for the use of high-dose chemotherapy was derived from the experience with high-dose chemoradiotherapy in allogeneic transplantation for acute leukemia and from early studies at the Royal Marsden Hospital that showed that autologous reinfusion of the patient's own marrow would tolerate the myelosuppressive effects of high dose of melphalan [2].

There are few drugs which can be escalated without incurring visceral toxicity if the myelotoxicity was ameliorated by autotransplantation. At present, the alkylating agents are the most available for escalation because of the differential between the myelosuppressive and visceral toxic doses on escalation. The most commonly used have been cyclophosphamide, melphalan and BCNU. Other alkylating agents are under investigation, such as the platinum analogues, thiotepa, the brominated hexitols. Other agents include etoposide (VP-16), cytosine arabinoside, and methotrexate with citrovorum factor rescue. The use of autologous marrow reinfusion has offered the opportunity to explore the use of high doses of these agents against a variety of tumors. In most

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instances, the use of experimental high-dose protocols with autologous marrow reinfusion have been used in the setting of demonstrated refractoriness or relapse from conventional chemotherapeutic agents. As might be expected, these preliminary experiences showed that patients can tolerate the higher doses with recovery of peripheral counts, usually within 2–4 weeks. The antitumor effects were noteworthy, however, but were of short duration [3, 4]. The most extensive experience in previously untreated patients is that of high-dose melphalan for the treatment of metastatic melanoma. The response rate was 50%, but they were short-lived, varying from 3–5 months [2, 5, 6].

Considering that some patients required at least a month of hospitalization and extensive blood product support, the increased response rate was probably not clinically useful. The effectiveness of high-dose chemotherapy and autologous marrow reinfusion for other advanced solid tumors has been equally disappointing, with rare exceptions. The problems are multiple and include the facts that (1) most patients with solid tumors are usually over 50 years of age and tolerance to high doses may be limited, (2) most solid tumors that affect man are primarily refractory to conventional-dose chemotherapy, such as lung and GI cancers, and the "responses" achieved are, as in the melanomas, usually partial and not clinically useful, and (3) prior therapy in responsive tumors, such as small cell carcinoma of the lung and breast cancer, may contribute to the refractoriness to subsequent high-dose therapy. An emerging investigation entails the use of multiple alkylating agents in high dose. The approach has a basis in experimental animal tumor systems and cell culture demonstrating the lack of cross-resistance among some of the alkylating agents of differing chemical structure [3, 7], the hope being that the totality of the toxicity would be mainly myelosuppression and that each agent could be given in a maximal dosage to its unique visceral-limiting toxicity. This approach will require a careful Phase I investigation to determine the life-sparing maximal doses of these agents.

Trials of high-dose chemotherapy in previously untreated or "sensitive" solid tumors, such as breast cancer and small cell carcinoma of the lung, otherwise in remission are only now underway. One trial suggested that high-dose chemotherapy with marrow reinfusion as consolidation may increase the disease-free survival of patients with small cell carcinoma [8, 9]. Similarly, preliminary trials in patients with previously treated metastatic breast cancer suggest a high response rate in patients refractory or in relapse from conventional-dose chemotherapy [3]. The duration of these responses are quite short, usually in the order of a few months. Ultimately, an investigation will be required to establish the benefits of high-dose chemotherapy as compared to optimally tolerated conventional chemotherapy on the survival of patients in metastatic cancer. The case for use of the high-dose approach in the adjuvant setting would be strengthened by the demonstration of its superiority over currently effective regimens in previously untreated patients with metastatic disease. These issues are important since a headlong rush into high-dose chemotherapy for solid tumors with autologous marrow infusion by general hospitals outside of an investigational setting is premature since (1) the approach has not shown to be any more effective than current treatment, (2) it is toxic and more than occasionally lethal, and (3) it is very costly palliation, if indeed it is palliative.

At this point, I will offer the usual plea for clinical trials wherein some of the above issues can be addressed in carefully monitored settings. Patient selection is obviously extremely important. The second plea would be to avoid these trials in patients with far-advanced, heavily-pretreated disease.

Malignant diseases of the hemopoietic system have been better candidates for the use of high-dose chemotherapy or chemoradiotherapy as they are, as a rule, more responsive to cytotoxic drugs, especially the alkylating agents. Preliminary results of the use of high-dose therapy with autologous bone marrow reinfusion would suggest the potential for the salvage of some patients in relapse from conventional treatment. The regimens used have been primarily high-dose cyclophosphamide followed by high-dose whole body radiation. The latter is the basic transplantation regimen, originally developed by the Seattle group that was shown capable of curing patients with relapsed lymphoma when isogeneic bone marrow was reinfused [10]. This and other pilot trials using the same or similar regimens suggest a fraction of patients who have relapsed from prior optimal therapy may have second prolonged unmaintained remissions. The follow-up time is probably still too short to consider the possibility of cure. The prolonged disease-free survival unmaintained with any therapy in some patients with poor prognosis lymphomas, however, is very encouraging [11–15]. It is noteworthy that these initial trials suggested that patients refractory to conventional chemotherapeutic agents with bulky disease are unlikely to achieve durable remissions.

The intensive regimen with autotransplantation is most effective when used in the remission. It behoves investigators to identify patients at high risk of relapse from initial remission in order to study the benefits of high-dose therapy given as

Table 1. *Autotransplantation in advanced Hodgkin's disease*

Series	Regimen	Total patients	CR	Relapse	Died NED	Alive NED (duration)	Comments	References
Dumont, 1985	TACC, BACT, others	18 11 refractory 1 no prior rx 6 relapse	9	5 (2–5 months)	1 (3 months)	3 (19+, 37+, 60+)	9 died in 4–35 days	*Blood Transfusion and Immunohaematology*, **28**, 531–538, 1985.
Carella *et al.*, 1985	CVB	13 5 refractory 8 relapse	8	2 (2,3 months)	—	6 (2,4,8,12,25,34)	—	*Eur J Clin Oncol*, **23**, 607–613, 1985.
Jagannath *et al.*, 1986	CVB	30 23 refractory 7 relapse	15	3 (5,5,8 months)	—	12 (3+–44+, median 7 months, 4=12 months)	—	*Ann Intern Med*, **104**, 163–168, 1986.
Wolff *et al.*, 1985	CTX, TBI (IF rx)	20	13	—	5	8 (5+–38+)	—	*Blood*, **66**, 256a, 1985.
		81	45	10	6	29 (2+–60+)		

consolidation. This has not been studied in large series, but initial experience in adult acute lymphoblastic leukemia consolidated with high-dose cyclophosphamide, BCNU, and VP-16 was disappointing with only 2 of 14 patients alive in unmaintained remission [16]. The use of autotransplantation as consolidation in the therapy of non-Hodgkin's lymphoma may be more successful [12, 15, 17]. It is possible to identify patients with diffuse large cell lymphoma who will have only a small survival benefit from conventional combination chemotherapy despite achieving a clinical complete remission. Clinical criteria will segregate patients into groups of widely-differing prognosis, varying from close to 80% to as little as 20% long-term survival. This was recently defined from the m-BACOD and CHOP-Bleo regimens from their respective institutions [18, 19]. The initial published experience of high-dose chemotherapy with or without radiation in Hodgkin's disease reflects these issues (Table 1). The salvage complete remission rate is high with 55% of patients in an unmaintained remission [20–22]. Depending on selection of patients, these results may be surpassed in non-Hodgkin's lymphoma.

The issue of tumor cell contamination of the normal-appearing bone marrow specimen used for autotransplantation has not been approached in the clinical trials of solid tumors since the vast majority of responses are only partial and relapses have been early and usually in sites of prior disease. The issue is somewhat more complicated in the hematologic cancers which are either derived from, or commonly invade, the bone marrow. In these diseases, purging of potentially residual malignant cells has employed some innovative techniques employing cytotoxic monoclonal antibodies directed against differentiation antigens or cytotoxic chemicals with preferential effect against malignant cells. But, even in the malignant lymphomas, the trials have not, to date, demonstrated the necessity for marrow surgery. However, the known propensity for cryptic bone marrow involvement and the emerging prolonged survival seen in these patients makes the issue more pressing. The early trials showed that the purging techniques did not impair recovery of bone marrow function [24–27]. The latter is especially important in the use of autotransplantation in the treatment of the leukemias. The first clinical trial employed anti-CALLA (common acute lymphoblastic leukemia antigen) monoclonal antibody to purge the bone marrow of second remission acute lymphoblastic leukemia prior to intensive chemoradiotherapy [28]. In the hemopoietic tumors, there are some clear leads which spell a potential curative salvage value for high-dose chemo- or chemoradiotherapy. Clinical trials in solid tumors will also require the optimal circumstances of minimal tumor burden that has not been extensively exposed to antineoplastic agents in order to demonstrate a potential benefit of high-dose therapy. In any event, this

therapy is costly in resources and morbidity, and the number of patients benefitting may be limited unless and until less toxic agents are developed which have higher therapeutic indices.

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