Autologous Bone Marrow Transplantation:

Climbing the Dose-Response Curve

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Daumier, Honoré. The Doctor and the Nurse. (June, 1840)
"How is the patient?--Alas, he died this morning at 6 o'clock.
--Ah, than he didn't take my medicine.--But he did, sir.
--Then he must have taken too much.--No, Doctor.
--Then, he didn't take enough of it."

Although the lithograph reproduced here first appeared in the pages of le Charivari almost 150 years ago, the situation depicted by Daumier is still relevant to one of the critical issues in modern oncology. Indeed, oncologists continue to debate the optimal dose for all of our modern day anti-neoplastic chemotherapy drugs and regimens. While we agree that many patients with metastatic disease will benefit from chemotherapy, the optimal drug dose, i.e. the one that results not only in maximal response rates and prolongation of survival but also in the lowest possible morbidity and mortality, is still a subject of controversy.

One school of oncologists, citing studies of animals with experimental tumors and mostly retrospective analyses of human patients, has argued strongly that increased doses of chemotherapy invariably result in increased rates of complete response and cure for many tumors (Frei and Canellos, 1980; DeVita et al. 1987). As a consequence, these authorities have looked for ways to minimize the toxicity of particular regimens while continuing to give escalating drug doses.

One limited approach to this problem, for example, is to use regional perfusion or intra-arterial therapy of isolated metastases, to achieve local drug concentrations that are higher than those that could be tolerated with systemic administration. Similarly, radiation therapy delivered to an area of tumor involvement has been employed as a "sensitizer" to selectively increase the local effect of concurrently administered chemotherapy.

However, the subject of today's Grand Rounds, autologous bone marrow transplantation (ABMT), represents a general approach to the problem of excessive mortality from high-dose chemotherapy that has applicability to a broad range of patients. Indeed, the number of autologous transplants performed world-wide has been rising rapidly in the last few years. Given that the cost of this procedure is $30,000 to $70,000 per patient, it seems appropriate to review the theoretical basis for this technique and the actual results obtained to date in a variety of different tumors.

What is autologous BMT? Simply put, autologous means from the same individual. Thus, ABMT involves first collecting bone marrow cells from the patient prior to the chemotherapy treatment. Then, the cells may be stored at 4°C for several days or frozen in liquid nitrogen and preserved for months to years. Following completion of the drug treatment, the bone marrow cells are thawed and infused back into the patient in an attempt to restore bone marrow function and limit the duration of pancytopenia with its attendant risks of sepsis and bleeding.

Thus, one major tenet of ABMT is that marrow suppression is the major limitation to increased doses of chemotherapy. Indeed, almost all clinicians are familiar with the oncology patient who

is admitted 10-14 days after receiving high doses of chemotherapy with fever and agranulocytosis. Although most patients survive these episodes with the help of broad spectrum antibiotics, attempts at further increases in the dose of chemotherapy have invariably led to unacceptable increases in the number of fatal septic episodes. In fact, it is not uncommon with very aggressive treatment programs to observe no improvement or even a decrease in overall patient survival, despite an increase in the number of complete tumor responses. In these situations, early mortality secondary to increased bone marrow toxicity and sepsis is generally the explantation for the lack of an overall survival benefit.

Therefore, the major purpose of autologous BMT is the early restoration of bone marrow function following doses of chemotherapy that would normally result in very long periods of aplasia. One obvious requirement for this success of this technique, however, is that the patient's bone marrow be normal and free of tumor infiltration. Clearly, infusion of large numbers of tumor cells contaminating the patient's bone marrow could well vitiate any long-term benefits of high-dose chemotherapy. Thus, a potential disadvantage of ABMT is the risk of bone marrow contamination with residual leukemia or tumor cells. As we shall see, a variety of techniques have been employed in an attempt to "purge" the bone marrow of neoplastic cells.

How does autologous BMT differ from allogeneic BMT? In contrast to ABMT, the major purpose of allogeneic transplants is to completely replace the patient's abnormal bone marrow with normal marrow from another individual. However, as shown in Table 1, the use of allogeneic marrow introduces problems of graft rejection and graft-versus-host disease (GVHD) which are essentially

Table I Linch and Burnett, 1986.

Advantages and disadvantages of ABMT.

Advantages	Compared with	Disadvantages
Applicable to older patients No limitations due to donor availability No graft rejection No graft-versus-host disease	**Allogeneic bone marrow transplantation**	Contamination of infused marrow with residual leukaemia or tumor Potential loss of 'graft-versus-leukaemia' effect
Intensification of therapy Curtailment of treatment period	**Conventional therapy**	Contamination of infused marrow with 'untreated' residual leukaemia or tumor

non-existent in autologous grafts. In part because of the increased mortality of acute and chronic GVHD in older patients, allogeneic transplants have been most successful in younger patients and many centers exclude patients over the age of 40, thus excluding approximately 70% of cancer patients. However, because ABMT does not result in severe GVHD, these older patients may still be good candidates for high dose chemotherapy with autologous bone marrow support. Finally, allogeneic BMT also requires a histocompatible sibling as a bone marrow donor, which is available for only 25-40% of patients regardless of age. Thus, for patients without a histocompatible donor, ABMT may also be the only option.

The lack of graft versus host disease in autologous BMT also suggests a possible disadvantage of this technique as compared to allogeneic grafts, the lack of a graft versus tumor effect. Does such an effect exist? As we shall see, there is impressive data in the leukemias that a significant fraction of patients are cured not just by the chemotherapy regimen but also by an ongoing graft versus leukemia reaction. Although there is little data to suggest a similar effect exists in lymphomas and solid tumors, it is conceivable that similar benefits could exist for allogeneic transplants in other tumors.

To summarize what has been said thus far, the major assumptions underlying the increasing use of autologous BMT are:

(1) Transplantation of autologous bone marrow can accelerate bone marrow recovery after high dose chemotherapy.

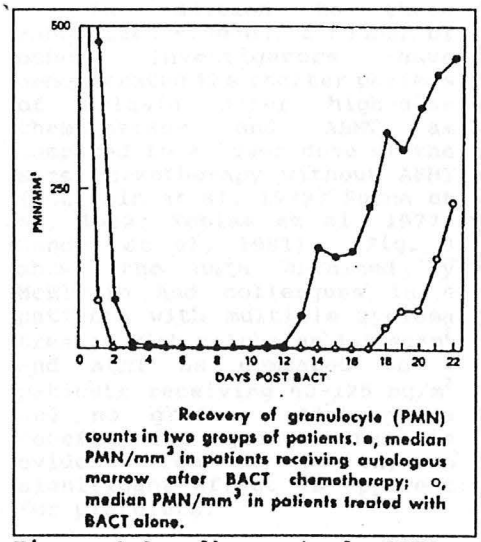
(2) Amelioration of hematologic toxicity will permit a marked intensification of therapy without increased mortality.

(3) Higher doses of chemotherapy will result in higher response ratesand an increased number of long-term survivors in both hematologic malignancies and solid tumors.

(4) Purging techniques can successfully remove residual leukemia, lymphoma, or tumor cells from bone marrow.

Before considering some of the data underlying these assumptions, it should be noted at the outset that few prospective controlled clinical trials which test the validity of these concepts have been reported. Of course, ethical considerations limit the clinical investigator's ability to rigorously test all of these concepts in patients. Where necessary, then, we will consider data from animal studies which have been considered sufficiently conclusive to eliminate the need for comparable human studies.

I. Is marrow rescue really necessary?

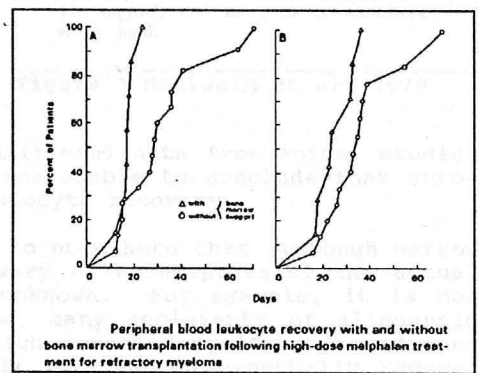


Recovery of granulocyte (PMN) counts in two groups of patients. ●, median PMN/mm³ in patients receiving autologous marrow after BACT chemotherapy; ○, median PMN/mm³ in patients treated with BACT alone.

Figure 1 Appelbaum et al, 1978

A number of studies in man have established that the recovery of granulocytes in the peripheral blood is accelerated in patients receiving high dose chemotherapy and autologous bone marrow transplantation as compared to patients receiving only high dose chemotherapy. Appelbaum and colleagues (1978) reported that in patients with malignant lymphoma receiving the chemotherapy regimen BACT[1], the median time to recovery of 100 granulocytes was 8 days in 9 patients receiving cryopreserved marrow compared to 16 days in 9 controls (Figure 1). In addition, patients receiving bone marrow rescue had a median of 7 days with fever >38.5° as compared to 15 days for those not given marrow support. However, the incidence of proven septic episodes was the same in both groups. Similar data have been reported in abstract form by Takvorian and associates (Takvorian et al, 1981).

However, not all data has been equally impressive. For example, Barlogie et al, 1987 recently presented data on 23 patients with refractory multiple myeloma who received melphalan at a dose of 80-100 mg/m^2 of whom 9 were rescued with autologous bone marrow. As can be seen in Fig. 2, patients receiving bone marrow demonstrated a faster and more uniform recovery of total leukocytes to 200/ul (A) and 500/ul (B). On the other hand, the recovery of granulocytes and platelets was not accelerated in



Peripheral blood leukocyte recovery with and without bone marrow transplantation following high-dose melphalan treatment for refractory myeloma

Figure 2 Barlogie et al, 1986

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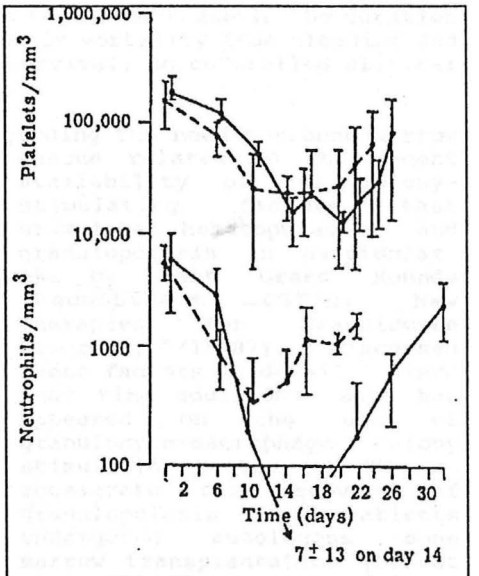
[1] (BCNU 200 mg/m^2, Ara-C 100 mg/m^2 q12hr X 8 doses, cyclophosphamide 45 mg/Kg q24hr X 4 doses, and 6-thioguanine 100 mg/m^2 q12hr X 8 doses)

this study by marrow support.

In addition to these randomized studies, a number of other investigators have demonstrated the shorter periods of aplasia after high-dose chemotherapy and ABMT as compared to a lower dose of the same chemotherapy without ABMT (McElwain et al, 1979; Sarna et al, 1982; Tobias et al, 1977; Zander et al, 1981). Fig. 3 shows the data obtained by McElwain and colleagues in 8 patients with multiple myeloma treated with melphalan 140 mg/m^2 and ABMT as compared to 4 patients receiving 60-125 mg/m^2 and no graft. Although a benefit for granulocytes is evident from day 10 on, no significant effect is apparent for platelets.



Effect of marrow autotransplantation to 8 patients (- - - -) on platelet and leucocyte recovery after i.v. melphalan (140 mg/m^2) compared with 4 patients receiving lower doses of melphalan (60-125 mg/m^2) and no graft (——). Bars show ±s.d.

Figure 3 McElwain et al, 1979

Finally, a number of groups have demonstrated that the number of bone marrow progenitors for granulopoiesis (GM-CFC) that are infused at the time of transplantation correlates significantly with the time to hematopoietic recovery (Spitzer er al, 1980; Roodman et al, 1987; Rowley et al, 1987). Thus, after review of this data, and in view of additional data from animal studies in dogs and primates, it seems reasonable to conclude that autotransplants can accelerate granulocyte recovery.

However, it is of interest to note here that although marrow grafts lead to more rapid recovery of hematopoiesis, the actual duration of graft function is unknown. For example, it is now clear that with sufficient time, many recipients of allogeneic transplants who have received high doses of cyclophosphamide and more than 900 rad of total body irradiation eventually recover significant degrees of autologous hematopoiesis (Yam et al, 1987). Although it is not possible to distinguish the endogenous recovered bone marrow cells from those used for the autologous graft, by analogy to the situation in allogeneic grafts, it is probable that most of the high-dose regimens used for ABMT do not eradicate all

of the bone marrow stem cells. Thus, it is unclear if ABMT is absolutely required for the recovery of hematopoiesis. Moreover, while it seems reasonable to assume that a decrease in the duration of aplasia will result in a decrease in mortality from bleeding and sepsis and an increase in patient survival, no controlled clinical trials have yet proven this point.

An additional reservation regarding the need for bone marrow rescue relates to the recent availability of the colony-stimulating factors that stimulate hematopoiesis, and granulopoiesis in particular. At my last Grand Rounds (Recombinant CSF's: New Therapies for Granulocyte Disorder, 7/16/87), I discussed these factors in detail. Since that time additional data has appeared on the use of granulocyte-macrophage colony stimulating factor (GM-CSF) to accelerate the recovery of granulopoiesis in patients undergoing autologous bone marrow transplantation (Brandt et al, '1988). Fig. 4 demonstrates the effect of an infusion of GM-CSF on 4 patients receiving CPA chemotherapy[2] and ABMT as compared to 24 historical controls receiving the same chemotherapy and ABMT. The results of this study demonstrated that GM-CSF increases the rate of peripheral leukocyte and granulocyte recovery once the blood counts begin to rise at about day 9-10, but does not affect the overall duration of complete aplasia.

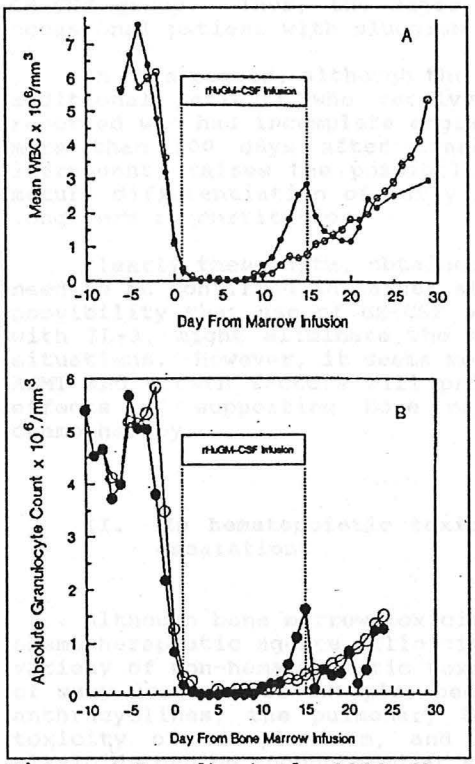


Figure 4 Brandt et al, 1988 Mean WBC and granulocyte counts in 4 patients treated with GM-CSF (solid circles) and 24 controls (open circles)

More recently, Nemunaitis et al (1988) have reported the experience of the Seattle transplant group with GM-CSF in patients undergoing autologous

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[2] (cyclophosphamide 1875 mg/m^2 q24hr X 3 doses, cis-platinum 165 mg/m^2, BCNU 600 mg/m^2)

transplants for lymphomas. When compared with 86 disease-matched and treatment-matched historical controls, 8 patients receiving >60 ug/m^2/day of recombinant human GM-CSF demonstrated more rapid recovery of neutrophil counts (10 days vs. 16 days to absolute granulocyte count >100/ul) and half the number of febrile days (6 vs. 12). Indeed, a careful examination of the data reveals a major overlap in the time to marrow recovery. Thus, some patients in the control group recovered granulocytes as early as 8 days after transplantation, equivalent to the earliest time observed in the GM-CSF group. Thus, the major effect of GM-CSF may be on the occasional patient with sluggish or delayed recovery.

In this regard, although the treatment was well tolerated, two additional patients who received a lower dose of GM-CSF were reported who had incomplete engraftment with persistent cytopenia more than 100 days after transplant. This result, although infrequent, raises the possibility that GM-CSF can promote premature differentiation of early stem cells and actually diminish long term reconstitution.

Clearly these data, obtained with small numbers of patients, need to be confirmed in larger studies. Moreover, they raise the possibility that use of GM-CSF or G-CSF, possibly in combination with IL-3, might eliminate the need for ABMT altogether in some situations. However, it seems more likely that the combination of ABMT and growth factors will prove to be complementary in their effects of supporting bone marrow recovery after high dose chemotherapy.

II. Is hematopoietic toxicity the limiting factor in dose escalation?

Although bone marrow toxicity is a major side-effect of many chemotherapeutic agents, clinicians are also very familiar with a variety of non-hematopoietic toxicities that limit the usefulness of many drugs. For example, because the cardiac toxicity of the anthracyclines, the pulmonary toxicity of bleomycin, the renal toxicity of cis-platinum, and the neurotoxicity of the vinca alkaloids can be encountered at standard drug doses, the potential of these agents for dose escalation has traditionally been thought to be limited.

On the other hand, considerable attention has focused on the alkylating agents, including melphalan, thiotepa, cyclophosphamide, and the nitrosoureas, such as BCNU. These agents not only produce predominantly hematopoietic toxicity at routine clinical doses, but also have the advantage of being non-cross-resistant in many clinical settings. For example, the nitrosoureas and cyclophos-

phamide are not cross-resistant in the treatment of lymphomas, and cyclophosphamide and melphalan are not necessarily cross-resistant in the treatment of multiple myeloma.

Because many of the patients who are candidates for ABMT have had previous chemotherapy, the success of ABMT depends critically on the availability of agents with continued activity in patients whose tumors exhibit the "multidrug resistant phenotype". This important problem of multi-drug resistance in clinical oncology has recently been reviewed at these Grand Rounds (10/7/88) by Dr. Eugene Frenkel, and thus will not be considered in any detail here. However, as pointed out by Dr. Frenkel in his Grand Rounds, tumor cells that are resistant to multiple chemotherapy drugs frequently maintain sensitivity to BCNU, cyclophosphamide, methotrexate, and other alkylating agents. Other newer agents that have also been investigated for use in ABMT include VP-16 (etoposide), amsacrine (AMSA), and mitomycin C.

With increased use of ABMT and high doses of these agents, however, it has become clear that additional and sometimes previously unexpected non-hematologic toxicities have become evident (Table 2). For example, although the well-known urothelial toxicity of cyclophosphamide that results in hemorrhagic cystitis can be virtually eliminated with use of the sulfhydryl containing compound, 2-mercaptoethane sulfonate (MESNA), a unique form of hemorrhagic myocarditis has been associated with high-dose cyclophosphamide (>100 mg/kg), frequently with a fatal outcome (Appelbaum et al, 1976; Gottdiener et al, 1981).

Similarly, melphalan, which has been used extensively for ABMT because its short half-life makes possible rapid re-infusion of bone marrow, has produced dose-limiting GI toxicity at about 200 mg/m^2. Pulmonary toxicity has been the most frequent side-effect limiting BCNU therapy in ABMT, particularly in patients with pre-existing pulmonary disease or previous thoracic irradiation. Veno-occlusive disease of the liver, as well as hemorrhagic colitis and pancreatic toxicity, have been observed with high doses of mitomycin C (>60 mg/m^2). Severe mucositis is a problem with high doses of VP-16, and the alkylator thiotepa has produced dose-limiting neurologic toxicity with stupor and coma occurring at doses greater than 900 mg/m^2. In addition, at doses above 900 mg/m^2, thiotepa has also produced an unusual dermatologic toxicity, manifesting as skin bronzing followed by desquamation.

Although these non-hematologic toxicities are severe, they often occur at drug doses many times that dose which produces life-threatening bone marrow depression. However, in clinical practice, particularly with regimens containing multiple drugs, toxicity to liver, lung, and other organs have limited the total dose escalation to 2-3 fold greater than that which can be used without bone marrow transplantation (Armitage and Gale, 1989). Is a 2-3

Table 2

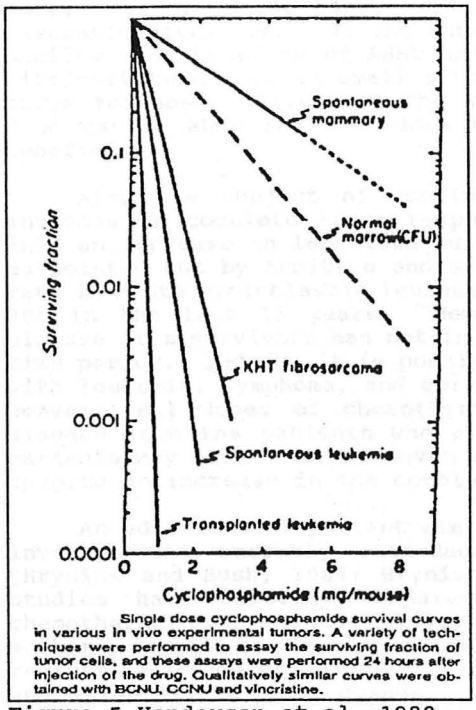
Drug	Toxicity	Normal Dose mg/m2	High Dose mg/m2	Ratio
BCNU	Pulmonary fibrosis Encephalomyelopathy	200-300	1200	4-6X
CTX	Carditis Cystitis	1500	11000	7-8X
Melphalan	Gastrointestinal ITP AIHA	45-60	200	3-4X
MitoC	Veno-occlusive liver disease GI hemorrhage	15	60	4X
Thiotepa	Skin desquamation Neurologic Mucositis	75	900	12X

fold increase in drug dose sufficient to result in major clinical benefit for the patient? As we shall see, the answer to this critical question probably depends on the dose-response curve of each individual tumor.

III. Will more cures result from higher doses of chemotherapy?

Much of the data cited by proponents of high-dose chemotherapy and ABMT involves animal studies demonstrating steep dose-response curves for experimental tumors treated with single agents and/or radiation. An example of this data is shown in Fig. 5, which is a synthesis of similar figures in Frei and Canellos, 1980 and Henderson et al., 1988.

Using a variety of experimental tumors in mice, ranging from leukemias, fibrosarcomas, and mammary neoplasms, investigators have



Single dose cyclophosphamide survival curves in various in vivo experimental tumors. A variety of techniques were performed to assay the surviving fraction of tumor cells, and these assays were performed 24 hours after injection of the drug. Qualitatively similar curves were obtained with BCNU, CCNU and vincristine.

Figure 5 Henderson et al, 1988

repeatedly demonstrated a linear relationship between tumor cell survival and chemotherapy dose. Particularly in hematopoietic tumors, these studies invariably show a steep dose-response curve with at least an additional log of tumor cell kill resulting from a doubling of drug dose. On the other hand, in a solid tumor model, spontaneous mammary cancer, the curve is clearly much less steep. In fact, normal marrow stem cells are more sensitive than the tumor cells to killing by the drug, suggesting a role for ABMT in this situation.

However, the relevance of these animal models to human tumors is unclear. Many of these experimental tumors are associated with a viral etiology and thus host immunity could conceivably augment drug-mediated tumor cell killing. In addition, some of these models involve cell lines which have been passaged in vitro for many generations. Such lines, however, may be relatively homogeneous and respond more uniformly to a drug than highly heterogeneous human tumors. Finally, even a tumor kill of 10^{-4} may be far from sufficient to achieve long-term cure in a patient whose tumor burden generally exceeds 10^{10} cells and may reach 10^{12} cells in advanced malignancy.

As we shall see in discussing the clinical indications and data for ABMT, the actual dose-response curve in human tumors is unknown and still the subject of much controversy. However, the benefits obtainable with ABMT and high-dose therapy depend critically on the shape of that curve. For example, as depicted in Fig. 6, if the curve is linear and steep well beyond the range of conventional clinical dosage (i.e. curve A), then high-dose therapy should provide substantial increase in tumor response and possible

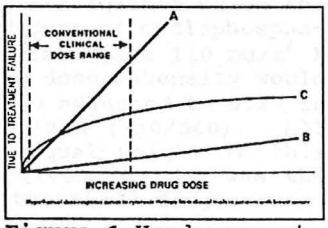


Figure 6 Henderson et al, 1988

cure. On the other hand, curves B and C illustrate much less favorable situations. If the curve (B) is linear but the slope is shallow, the benefits of ABMT and high-dose therapy will be more difficult to detect in small studies. On the other hand, if the curve reaches a plateau at the upper end of the normal clinical dose range, ABMT and high-dose chemotherapy are unlikely to be beneficial.

Also the subject of continuing controversy is whether an increase in complete tumor responses will necessarily translate into an increase in long-term survival and/or cure. For example, as pointed out by Armitage and Gale (1989), the complete response rate in acute myeloblastic leukemia has increased from 25% to about 70% in the last 15 years. However, the proportion of 5 year disease free survivors has not increased significantly in the same time period. Indeed, it is possible that the fraction of patients with leukemia, lymphoma, and germ cell tumors that are cured with conventional doses of chemotherapy have biologically different disease from the patients who eventually relapse. These latter patients may not be curable even with higher-doses of chemotherapy despite an increase in the complete response rate.

An additional important element of the subsequent discussion involves the recently introduced concept of "dose-intensity" (Hryniuk and Bush, 1984; Hryniuk et al, 1987). Because so few studies have directly compared different doses of the same chemotherapeutic agents delivered on the same schedule, these authors sought to develop a method for comparing similar drug regimens which nevertheless differed significantly in the frequency and intensity of drug dosage. In an attempt to equalize these differences, then, the comparison was based on the relative intensity of treatment over time, expressed as $mg/m^2/week$. The actual numbers were derived by the average dose given over the first eight weeks of therapy.

For example, in comparing different studies that employed the CMF regimen of cyclophosphamide, methotrexate, and 5-fluorouracil, the authors assigned a relative intensity of one to the highest dose of a given agent used by a standard regimen against which the others were compared. Thus, if the standard dose of cyclophosphamide were 560 $mg/m^2/week$ and a different regimen gave 120 mg/m^2 X 5 doses that were repeated every 28 days, the dose intensity would first be calculated as 150 $mg/m^2/week$ and then adjusted to 0.27 in comparison to the standard highest dose regimen (150/560). All three drugs in the regimens were accorded equal weight in this comparison and final dose intensity for a given regimen was the average of the values obtained for each of the three drugs.

Although this method obviously involves numerous major assumptions, the results obtained from such analyses have been quite influential in strengthening the arguments of those who favor

high-dose treatment and ABMT. One objection to this concept is that it minimizes the significance of treatment duration, i.e. whether the drugs are given for 4 months, 6 months, or a year (Dembo, 1987). However, with the exception of acute lymphoblastic leukemia, the evidence suggests that the major benefit of drug treatment occurs within the first few months, particularly for tumors with a high growth fraction. While not denying that some patients can continue to respond to treatment beyond this time, this point of view suggests that rapidity of response and the intensity of the early treatment is most crucial in determining the likelihood of prolonging survival and achieving cure.

IV. Is purging effective and/or necessary?

Bone marrow involvement with tumor cells is not an infrequent problem in the lymphomas, breast cancer, and small cell lung cancer. In addition, patients with leukemia in complete remission who are destined to relapse, i.e. the great majority, are presumed to have residual leukemia cells in their bone marrow throughout the course of their disease.

In order to avoid or minimize the chance of re-infusing tumor cells into these patients during ABMT, a variety of methods have been developed which are capable of removing or killing at least 2-3 logs of malignant cells. At the same time, these methods must spare the majority of the normal bone marrow progenitors that are essential to early recovery from bone marrow aplasia. As shown in Table 3, "purging" techniques generally either rely on monoclonal antibodies specific for the malignant cells, or on incubation with drugs which selectively kill malignant cells.

Table III Deeg et al, 1988

Marrow Purging Techniques for Autologous Marrow Transplants

Technique	Examples
Physical	Density gradients
Immunologic	mostly using monoclonal antibodies + complement + toxins † magnetic beads
Pharmacologic	4-HC/ASTA-Z

To obtain cell killing with monoclonal antibodies, complement is added to promote cell lysis in vitro, or the monoclonal antibodies can be coupled to toxins, such as ricin, to create immunotoxins. Alternatively, antibodies have been coupled to magnetic particles and after attachment of the antibody to the target population of tumor cells, the particle-antibody-cell complex is selectively removed by passage of the cells over a magnetic field. With this latter technique, which has been used particularly in childhood neuroblastoma with bone marrow involvement, more than 4 logs of tumor cells can be removed with no apparent damage to the normal hematopoietic stem cells. One limitation to the effectiveness of monoclonal antibodies, however, is the presence of cells with a low density of the target antigen. A possible solution to this problem

is the simultaneous use of multiple monoclonal antibodies.

The drug which has been most widely used for purging is 4-hydroperoxycyclophosphamide (4-HC), a derivative of cyclophosphamide. Mafosfamide, or ASTA-Z-7557, which has been used particularly in Europe, is another analog of cyclophosphamide which appears to undergo decomposition in vitro to 4-HC. Clinical trials with purging with this drug have been largely in ABMT for acute myelogenous leukemia (Yeager et al, 1987, 1989) and will be discussed in section VII-A. Some investigators have combined both monoclonal antibodies and 4-HC (Ramsay et al, 1989).

Despite the widespread use of purging, particularly in transplantation for leukemia and lymphoma, no randomized trials have tested whether purging actually works. Although some retrospective comparisons of results obtained in multiple different transplant centers have suggested an advantage for purging, others have not found any benefit (Burnett, 1989). In addition, there is no evidence that one purging method is superior to any other. In light of this lack of data, the role of purging will not be discussed further, but the use and method of purging will be indicated for each of the studies considered in this review.

With this background in hand, it is now appropriate to review a) the clinical evidence for increased responses with increased drug dosage, and b) the results obtained thus far with ABMT and high-dose therapy in a variety of clinical settings. The review will begin with lymphomas, including both Hodgkin's disease and non-Hodgkin's lymphomas, then discuss the acute leukemias and chronic granulocytic leukemia, and conclude with several solid tumors with an emphasis of breast cancer. To limit this discussion, pediatric tumors such as neuroblastoma and Ewing's sarcoma and a number of less responsive adult tumors where the experience with ABMT is still limited will not be covered. If the reader is interested, several recent reviews on ABMT which discuss these other settings have appeared within the last year (Armitage and Gale, 1989; Cheson et al, 1989; Pick, 1988).

V. Is ABMT of value in Hodgkin's disease?

Considerable clinical data suggests Hodgkin's disease exhibits a steep dose-response curve. For example, more than 20 years ago, Henry Kaplan (1966) published data from patients treated with radiation therapy alone. As shown in Fig. 7, the rate of tumor recurrence in a radiation field was closely related to the total radiation dose. Indeed, for doses above 4000 rad, the risk of tumor recurrence was essentially zero.

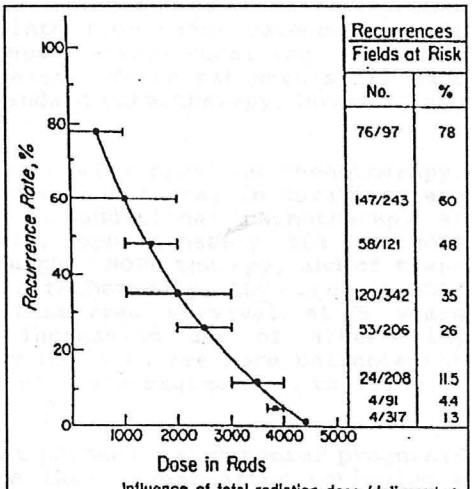


Figure 7 Kaplan, 1966

More recently, DeVita et al (1987) applied the principles of dose intensity discussed above to the analysis of results obtained with MOPP[3] chemotherapy for Hodgkin's disease. As shown in Fig. 8, relative to the original MOPP regimen, which is assigned an intensity of 1.0, other versions of MOPP with less intensive use of the same drugs (assessed as mg/m^2/week) appear to have resulted in a significantly lower disease-free survival. The results obtained with the most intensive MOPP regiment have been updated in a recent paper by Longo and colleagues (Longo et al, 1986), and represent more than a 10 year follow-up. Even within that single series, a retrospective analysis demonstrated that reductions in vincristine dose correlated significantly with reductions in complete response rate and disease-free survival.

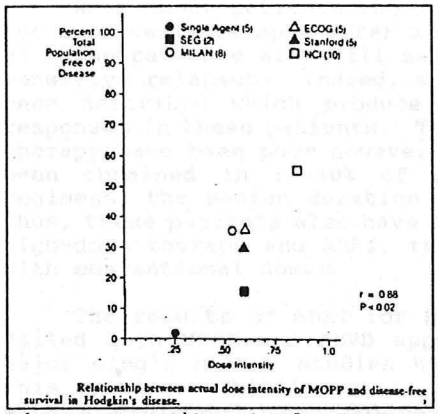


Figure 8 DeVita et al, 1987

Despite the excellent results obtained with the original MOPP

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[3] (Nitrogen mustard, vincristine, procarbazine, prednisone)

regimen, with alternative non-cross-resistant regimens such as ABVD[4], and with alternating cycles of MOPP and ABVD, approximately 30% of patients will eventually relapse and require further treatment. These relapses fall into four major categories. Of course, some patients will relapse after receiving radiation therapy alone for early stage disease. These patients still have a substantial salvage rate with standard chemotherapy, however, and are not candidates for ABMT.

Patients who relapse after receiving previous chemotherapy, but whose initial remission was more than 1 year in duration, are also candidates for treatment with additional chemotherapy at conventional doses. For example, approximately 50% of MOPP failures enter a second CR after further MOPP therapy, and of these 50% are disease-free at 5 years. Alternatively, ABVD used in MOPP failures has yielded a 38% disease-free survival at 5 years (Santoro et al, 1982). With increasing use of alternating MOPP/ABVD therapy, however, we may begin to see more patients who have already been exposed to both of these regimens at the time of first relapse.

Two additional categories that portend a much poorer prognosis are patients who (1) relapse less than 1 year after achieving a complete remission, or (2) either never achieve a complete remission or who demonstrate no response to the salvage chemotherapy regimens described above. This last group has been termed resistant relapses. The prognosis of these patients with additional chemotherapy is sufficiently poor that they are considered candidates for ABMT.

What about patients who responded to both MOPP and the ABVD, but eventually relapse after a second round of chemotherapy? Many of these patients are still sensitive to treatment and are termed sensitive relapses. Indeed, a number of third-line regimens have been described which produce a significant number of complete responses in these patients. The long-term results with third line therapy have been poor however. Although complete responses have been obtained in 15-40% of patients failing two chemotherapy regimens, the median duration of these responses has been short. Thus, these patients also have been considered to be candidates for high-dose therapy and ABMT, rather than for further chemotherapy with conventional doses.

The results of ABMT for Hodgkin's disease patients who have failed both MOPP and ABVD appear to be quite promising. Three major single center studies have been described in detail as of this writing. Phillips et al (1988) have reported on 26 patients with a minimum 3 year follow-up, of whom 27% are disease free following high-dose cyclophosphamide, total body irradiation, and

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[4] (Adriamycin, bleomycin, vinblastine, DTIC)

ABMT. Gribben et al (1989) have published data on 44 patient with refractory Hodgkin's disease, of whom 22 never achieved a complete remission with conventional therapies. With a minimum follow-up of 1 year and a median follow-up of 2 years, 50% of these patients are in complete remission following BEAM[5] chemotherapy and ABMT. Finally, Jagannath et al (1989) have reported on 61 patients with Hodgkin's disease, all of whom had failed both MOPP and ABVD and 59 of whom were in relapse at the time of their ABMT. As shown in Fig. 9, following high dose chemotherapy with CBV[6], 38% of the patients are disease free with a minimum 2 year and median 3 year follow-up. It should be noted that patients with bone marrow involvement were excluded from these studies.

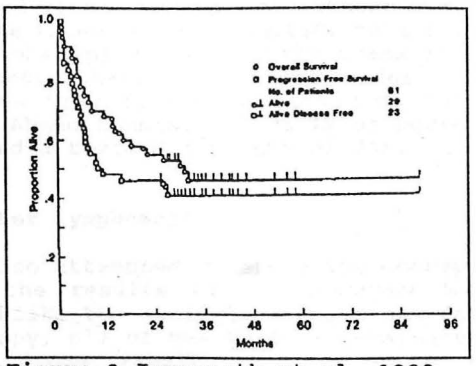

Figure 9 Jagannath et al, 1989

Although these results seem to be superior to what can be achieved with further chemotherapy at conventional doses, no randomized trials have been reported that compare the results of ABMT with third line salvage regimens. Clearly, such a study may be necessary to definitively assess the value of ABMT in Hodgkin's disease.

One additional reasons for caution in interpreting the results of these studies is that the number of sensitive or "untested" relapses included in each series is clearly critical to the success of the study. For example, when Jagannath et al (1989) divided their patients into two groups, 32 with resistant relapses and 29 with sensitive or untested relapses, a major difference in outcome was readily apparent. At 2 years, only 20% of the resistant group were alive, while 75% of the other group were alive, albeit some with active disease. Consistent with this data is the recent report of Ahmed et al (1987, 1989) describing a series of 23 patients, of whom 18 were resistant relapses. Although these patients were treated with a CBV regimen similar to that used by Jagannath, only 2 patients are alive and disease free more than a year after ABMT.

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[5] (BCNU 60 mg/m^2, VP-16 75 mg/m^2 , cytosine arabinoside 200 mg/m^2, melphalan 30 mg/m^2)

[6] (cyclophosphamide 1.5 g/m^2 q24hr X 4 doses, BCNU 300 mg/m^2, VP-16 100-150 mg/m^2 q12hr X 6 doses)

Finally, the results obtained with ABMT were not without early mortality. The results from these three centers suggests that from 5-20% of the patients may die from complications of the transplant procedure, despite graft support. Data from other older and smaller series suggests that the true figure is closer to 20%. Although the series reported by Ahmed consisted largely of poorer prognosis patients, they reported a toxic death rate of 26%.

VI. Is ABMT of value in other lymphomas?

DeVita et al (1987) have also attempted to apply the concept of dose-intensity to analyze the results of chemotherapy for diffuse large cell lymphoma. Unlike the analysis carried out for Hodgkin's disease and MOPP therapy, all of the regimens evaluated in this situation use different drugs, ranging from 4-8 out of a total of 9. To compare these different drug treatments, the authors assigned a value of 1.0 to the regiment MACOP-B[7] and then calculated a relative dose intensity for other regimens based on all nine drugs. The results of this questionable methodology, shown in Fig. 10, appear to show that the long-term survival of each treatment is directly related to its degree of dose-intensity.

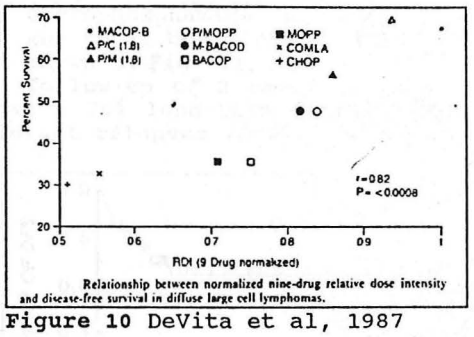

Figure 10 DeVita et al, 1987

Needless to say, the retrospective analysis carried out by DeVita, while provocative, has been severely criticized. Armitage and Cheson (1988), for example, argue strongly in a recent review that there is no evidence to show convincingly that the newer regimens being used to treat large cell lymphoma are better than the oldest and probably least toxic regimen, CHOP[8]. Instead, they point out that differences in patient characteristics such as age and tumor burden may explain the apparent differences in cure rates reported with different regimens. To settle this question, a large randomized trial is now underway to compare CHOP to three other newer and more toxic regimens is now underway.

Regardless of the evidence for the value of dose-intensive therapy in the aggressive non-Hodgkin's lymphomas, a significant minority of patients will never achieve a complete response with

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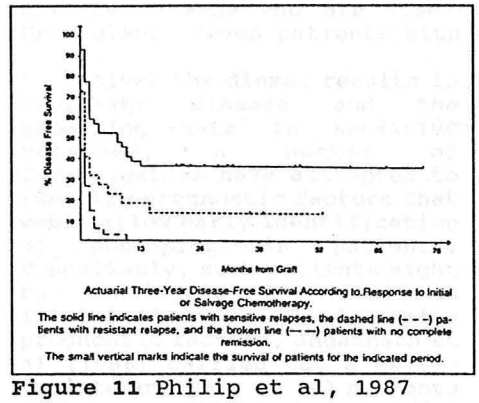
[7] (methotrexate, adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin)

[8] (Cyclophosphamide, adriamycin, vincristine, prednisone)

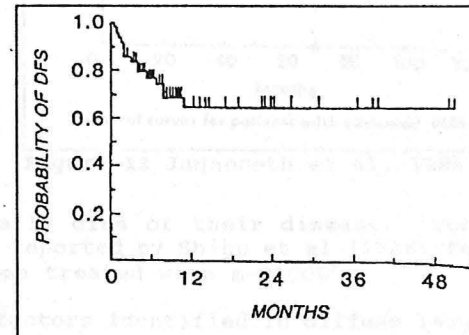
initial therapy. In addition, patients who relapse after receiving adequate doses of one of the major regimens for this disease rarely are cured of their disease with further conventional treatment. Similar to the situation in Hodgkin's disease, patients who relapse after achieving a complete response may be further classified as still sensitive to additional treatment (sensitive relapse) or resistant to additional treatment (resistant relapse).



Actuarial Three-Year Disease-Free Survival According to Response to Initial or Salvage Chemotherapy.
The solid line indicates patients with sensitive relapses, the dashed line (– – –) patients with resistant relapse, and the broken line (— —) patients with no complete remission.
The small vertical marks indicate the survival of patients for the indicated period.

Figure 11 Philip et al, 1987

The value of these distinctions is apparent in the results reported by Philip et al (1987) describing 100 patients with diffuse lymphomas of intermediate to high-grade (large cell, immunoblastic, and lymphoblastic). Two-thirds of these patients were treated with a variety of high-dose chemotherapy regimens, such as BEAM, CBV, and BACT, while one-third received high-doses of single agents such as cyclophosphamide or melphalan and total body irradiation. As shown in Fig. 11, with a minimum follow-up of 2 years, patients with sensitive relapses (n=44) had a 36% long-term disease free outcome, while patients with resistant relapses (n=22) had only a 14% disease-free survival. Patients who never achieved a complete remission with initial conventional therapy (n=34) had the worst outcome, with none surviving more than a year. It should be noted that none of these patients had bone marrow involvement.



Kaplan–Meier Estimate of the Probability of Disease-Free Survival (DFS) in 49 Patients Undergoing Autologous Bone Marrow Transplantation for Poor-Prognosis Non-Hodgkin's Lymphoma.
Each tick mark represents a surviving patient in complete remission.

Figure 12 Takvorian et al, 1987

Consistent with these results, Takvorian et al (1987) reported on 49 patients, of whom 33 had bone marrow involvement at some time during the course of their disease. In contrast to the previous study, however, all of these patients were sensitive relapses, who in fact had minimal disease after second line therapy at conventional doses. Following treatment with high dose cyclophosphamide and total body irradiation, ABMT was performed with bone marrow that

had been treated in vitro with anti-B1 monoclonal antibody and complement in an attempt to "purge" malignant B cells. As shown in Fig. 12, this favorable group of patients appear to have a high probability of long-term disease-free survival, although the median follow-up at the time of the report was short. Only two treatment related deaths occurred. Some confirmation of these results may be seen in the abstract report of Gorin and associates (Desbois et al, 1988) describing 7 of 16 patients with sensitive relapses and diffuse disease who are disease free more than 36 months from transplant. Seven patients with resistant disease are all dead.

Given the dismal results in resistant disease and the promising data in sensitive relapses, a number of investigators have attempted to identify prognostic factors that would allow early identification of poor-prognosis patients. Conceivably, such patients might be candidates for ABMT as initial therapy. To determine prognostic factors, Jagannath et al (1986) carried out a multivariate analysis of 102 patients with large cell lymphoma treated with the CHOP-Bleomycin regimen. As shown in Fig. 13, patients could be divided into three very different groups based simply on the serum LDH, a marker of total tumor burden, and on the presence of large bulky mass disease. Patients without either of these adverse factors had an excellent outcome after conventional treatment, but patients with both adverse prognostic findings all eventually dies of their disease. Very similar findings have also been reported by Shipp et al (1986) for patients with large cell lymphoma treated with m-BACOD[9].

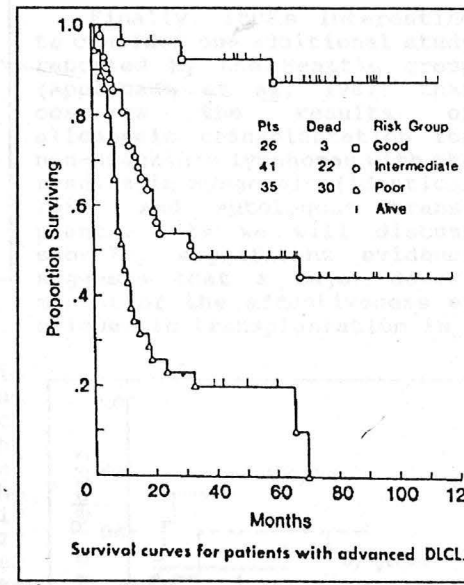


Figure 13 Jagannath et al, 1986

In view of the prognostic factors identified in diffuse large cell lymphoma, Gulati et al (1988) have recently reported early results for 27 previously untreated patients with either bulky tumor masses >8x8 cm or an LDH>500 IU/ml (nl<225). After receiving intensive chemotherapy without ABMT to obtain initial complete or partial remission, 14 responding patients (6 CR, 8 PR) were

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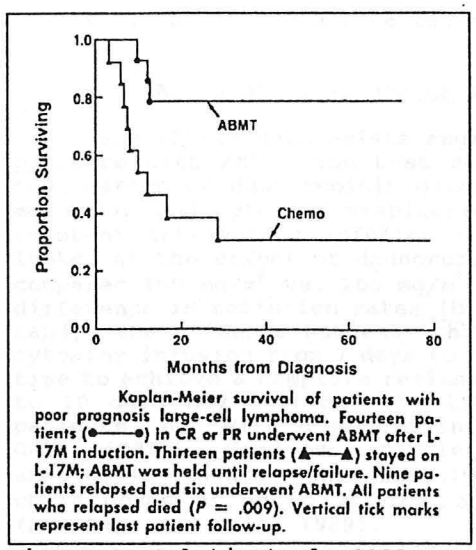
[9] (methotrexate, bleomycin, Adriamycin, cyclophosphamide, vincristine, and decadron)



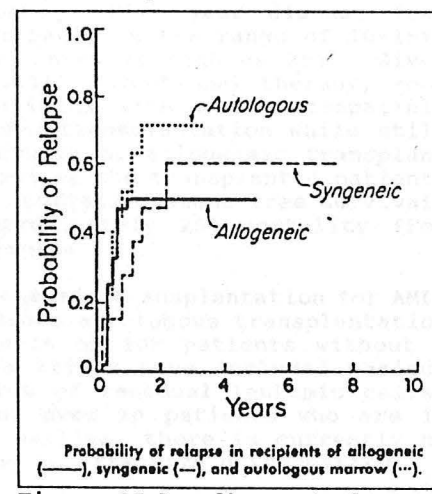
Kaplan-Meier survival of patients with poor prognosis large-cell lymphoma. Fourteen patients (●——●) in CR or PR underwent ABMT after L-17M induction. Thirteen patients (▲——▲) stayed on L-17M; ABMT was held until relapse/failure. Nine patients relapsed and six underwent ABMT. All patients who relapsed died (P = .009). Vertical tick marks represent last patient follow-up.

Figure 14 Gulati et al, 1988

the acute and chronic leukemias is the occurrence of a graft versus leukemia reaction. Whether such an effect may be important in the lymphomas, however, is unknown. However, as shown in Fig. 15, the probability of relapse is essentially the same in 27 autologous, 13 syngeneic, and 60 allogeneic marrow transplants carried out in Seattle. While certainly far from conclusive, these data suggest that a graft versus lymphoma effect is not a major factor in determining long-term survival after transplantation in these patients.

willing to receive immediate high-dose therapy with DAT[10] chemotherapy and ABMT. After at least 3 years of follow-up, 11 of the 14 patients are disease-free, as shown in Fig. 14. Results of this type will clearly need to be subjected to definitive evaluation in truly randomized prospective trials.

Finally, it is interesting to consider one additional study reported by the Seattle group (Appelbaum et al, 1987) that compares the results of allogeneic transplantation for non-Hodgkin's lymphomas with the results in syngeneic (identical twin) and autologous transplants. As we will discuss shortly, significant evidence suggests that a major determinant of the effectiveness of allogeneic transplantation in



Probability of relapse in recipients of allogeneic (——), syngeneic (—), and autologous marrow (···).

Figure 15 Appelbaum et al, 1987

[10] (daunomycin, ara-C, thioguanine)

VII. What is the role for ABMT in the leukemias?

A. Acute myelogenous leukemia (AML)

Very little data exists regarding the dose-response curve in patients with AML. The best results have been obtained with a combination of daunorubicin given daily for three doses at 30-70 mg/m^2/day and cytosine arabinoside given at 100-200 mg/m^2/day by constant intravenous infusion for seven days. No studies have looked at the effect of daunorubicin dose, and the one study that compared 100 mg/m^2 vs. 200 mg/m^2 of cytosine arabinoside found no difference in remission rates (Dillman et al, 1986). On the other hand, some evidence suggests that shortening the duration of the cytosine infusion from 7 days to 5 days is associated with a longer time to achieve a complete remission, while increasing the duration to 10 days may increase the likelihood of a remission in some patients, but with a marked increase in toxicity (Champlin and Gale, 1987). Used as a single agent at higher doses, cytosine arabinoside induces approximately 25% complete responses at 1 g/m^2, while doses of up to 24 g/m^2 achieve 50-75% complete responses (Armitage and Gale, 1989).

What is certain in the treatment of AML, however, is that 25-30% of patients will still not achieve an initial complete remission, and that the majority of patients who do will still relapse within the first 1-2 years. Five year disease free survival rates in adult AML are probably in the range of 10-15%, although some groups have achieved rates as high as 25%. Given this relatively low rate of cure with conventional therapy, some centers have considered young patients with a histocompatible sibling as candidates for allogeneic transplantation while still in 1st remission. Indeed, the results of allogeneic transplantation are encouraging, with only 25% of the transplanted patients relapsing by 3 years of follow-up. Overall disease-free survival, however, is about 50% due to approximately 25% mortality from infection and graft versus host disease.

In light of the success of allogeneic transplantation for AML, a number of investigators have pursued autologous transplantation as an alternative for older patients or for patients without a sibling donor. In general, these trials have included various methods for purging the bone marrow of residual leukemic cells, which are almost certainly present even in patients who are in complete remission. As discussed earlier, there is currently no evidence demonstrating that purging is effective or necessary.

More problematic for the success of autologous transplants is the lack of a graft versus leukemia effect. In allogeneic grafts, the presence of graft versus host disease is clearly associated with a decreased incidence of relapse (Weiden et al, 1981;

Butturini, Bortin, et al, 1987). Similarly, depletion of T cells from allogeneic bone marrow grafts decreases the incidence of graft versus host disease but increases the likelihood of relapse (Mitsuya et al, 1986). In addition, the results of syngeneic transplantation for AML (identical twins) demonstrate a 50-60% relapse rate at both Seattle (Fefer et al, 1986) and in an retrospective analysis of the world-wide experience (Gale and Champlin, 1984).. Thus, it seems unlikely that autologous BMT can achieve better than a 40-50% relapse free survival without the benefit of a graft versus leukemia effect.

Because of the uncertain value of ABMT in AML in 1st remission, where a small but significant number of patients may already be cured by conventional chemotherapy, the Hopkins groups has emphasized ABMT in patients with AML who are in second or even third complete remission. These patients are rarely cured by conventional anti-leukemic therapy. Yeager et al (1986) initially reported their results with 25 such patients who were treated with high-dose cyclophosphamide and busulfan or high-dose cyclophosphamide and total body irradiation, and then grafted with autologous marrow that had been purged ex vivo with the alkylating agent 4-hydroperoxycyclophosphamide. Five patients died of transplant-related toxicity, 9 patients relapsed, and 11 (44%) patients remained in remission with a median follow-up of >400 days.

More recently, these authors have updated their results in a larger series of 53 patients in second remission and 10 patients in third remission (Fig. 16). The results continue to be very encouraging, as all 11 original patients were still in complete remission with a minimum follow-up of 2 years. Since the duration of second remission may relate to the length of the 1st remission, it should be pointed out that the median duration of 1st remission in these patients was 15 months (range 2-96). It is also interesting to note that these results are not much worse than those obtained with 11 patients transplanted in 1st remission, suggesting it may be possible to wait until the 1st relapse to consider this procedure. Combined data from the European experience with ABMT in 61 patients with 2nd remission AML (Burnett, 1989) has yielded a plateau at 40% disease-free survival, although with a short period of follow-up. Interestingly in the European experience, purging had no effect on these results.

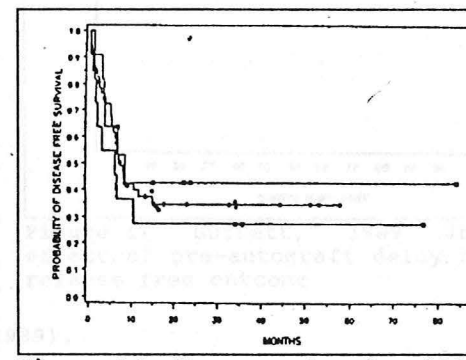


Figure 16 Yeager et al, 1989 Results of ABMT for AML in CR1 (top; n=11), CR2 (middle;n=53), CR3 (bottom; n=10).

Other centers have reported smaller series of patients who have undergone ABMT for AML in 1st remission. However, these series must be interpreted with great caution due to possible selection artifacts caused by long pre-autograft delays. For example, in reporting the combined European experience for AML in 1st remission, Burnett noted that the median time to autograft was more than 5 months, and more than 10% of the patients were transplanted more than a year after diagnosis. When the survival of these patients is stratified by pre-autograft delay, it is clear that patients with more than a 12 month delay do significantly better (Fig. 17). Clearly, those patients destined to do poorly never receive an autograft, while those who have a long first remission include an increasing percentage who are already cured.

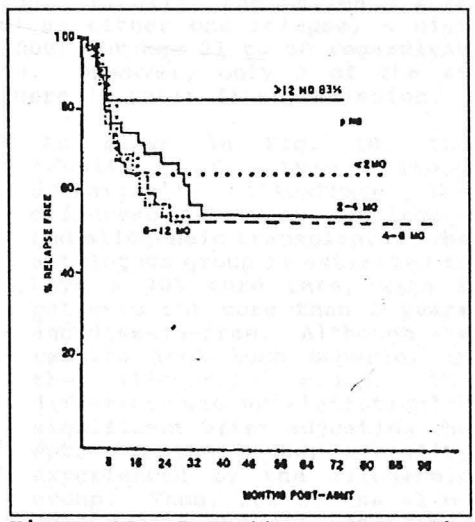


Figure 17 Burnett, 1989 The effect of pre-autograft delay on relapse free outcome

Thus, with this selection artifact in mind, the significance of much of the data reported for AML is less clear. Indeed, when the disease-free survival reported in the collected European data is compared with age-matched and delay-matched (i.e. only those patients who have not relapsed in the first 8-12 months) controls receiving intensive chemotherapy without autologous BMT, the results are not clearly significantly improved by transplantation (Preisler, 1987). Encouraging results in 19 patients, 11 of whom are disease-free with a median follow-up of 34 months have also been reported by the group at M.D. Anderson (Spinolo et al, 1989).

B. Acute lymphoblastic leukemia

Experience with autologous BMT for poor prognosis ALL in 1st remission or ALL in 2nd remission is limited. It is clear, however, that the likelihood of achieving cure after an initial relapse in ALL, and particularly adult ALL, is extremely low with conventional chemotherapy. Thus, many centers have been willing to consider patients in second remission as candidates for high-dose chemotherapy and ABMT. However, much of the data has been reported by pooling both pediatric and adult cases. Not surprisingly, given the higher cure rate of ALL in children with chemo-

therapy alone, the results of ABMT in ALL may be significantly better in children than in adults.

Despite the inclusion of approximately two-thirds pediatric cases, the best studies are those of the Minnesota group, initially reported in the New England Journal as a comparison between allogeneic transplants for patients with a matched donor, and autologous transplants for unmatched patients (Kersey et al, 1987). For the autologous transplants, the bone marrow was purged with a panel of monoclonal antibodies to B cells (Ba-1,2,3) and complement. Conditioning for both groups was either high-dose cyclophosphamide and fractionated total body irradiation or cytosine arabinoside and single dose total body irradiation. Finally, the patients were selected for "high-risk", defined as either one relapse, a high white count at presentation (>50,000), or age 21 to 50 regardless of white count or relapse status. However, only 3 of the 45 patients in the autologous group were in their first remission.

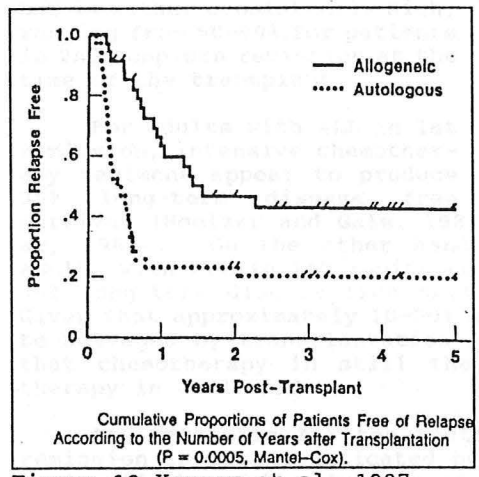


Figure 18 Kersey et al, 1987

As shown in Fig. 18, the results of this study dramatically illustrate the differences between autologous and allogeneic transplants. The autologous group is estimated to have a 20% cure rate, with 9 patients out more than 2 years and disease-free. Although the results look much superior in the allogeneic group, the difference was not statistically significant after adjusting the data for the higher mortality experienced by the allogeneic group. Thus, 26% of the allogeneic patients died of transplant complications, while only 4% of the autologous patients died during the initial hospitalization. On the other hand, 79% of the autologous grafts were considered likely to eventually relapse when the data were analyzed in a statistical model.

In contrast, in the allogeneic group, of those who developed graft-versus-host disease, only 37% were estimated to have relapse as a cause of treatment failure, while those who did not develop GVH had an estimated 75% relapse rate, strikingly similar to the autologous group. One other relevant point is that the duration of the first remission, i.e. >18 mo or <18 mo, was not a prognostic factor in this study, although others have found a major difference in success rate for allogeneic transplants when patients were categorized by length of 1st remission (Butturini, Rivera et al 1987).

The same authors have updated these data at a recent meeting (Ramsay et al, 1989). The results are essentially unchanged with an additional year of follow-up, although one patient in the autologous group has apparently relapsed between 3 and 4 years after transplant. Ramsay has also summarized the data obtained by a variety of other centers with autologous BMT in ALL in both 1st and 2nd relapse (Table IV). In order to make this comparison more meaningful, the median age of the patients in each group has been added to the table. As can be seen, the centers treating the older patients (UCLA, Hopkins) report significantly lower estimates of disease free survival at two years, just over 10% in both cases. Once again, the relapse rate for autologous BMT is rather consistently high, ranging from 50-90% for patients in 2nd complete remission at the time of the transplant.

Table IV Ramsay et al, 1989

Survey of Autologous BMT for ALL
Kaplan-Meier Estimates at Two Years

CENTER	NUMBER OF PATIENTS		DISEASE FREE SURVIVAL		RELAPSE RATE	
		Median Age	1st	2nd/3rd	1st	2nd/3rd
Besancon	44	12	57%	---	55%	48%
Boston	30	7	---	30%	---	---
Hopkins	29	22	20%	11%	75%	89%
Lyon	10	10	---	---	---	50%
Minnesota	69	9	---	22%	---	76%
Seattle	41	15	53%	28%/0%	35%	68%/88%
UCLA	10	30	---	12.5%	---	83%
Westminster	18	18	28%	45%	80%	50%

For adults with ALL in 1st remission, intensive chemotherapy regimens appear to produce 35% long-term disease free survival (Hoelzer and Gale, 1987; Linker et al, 1987; Hoelzer et al, 1988). On the other hand, allogeneic transplantation for adults with ALL in 1st remission appears to produce approximately 40% long-term disease free survival (Gale and Butturini, 1989). Given that approximately 10-20% of chemotherapy relapses can still be salvaged by transplantation in 2nd remission, Gale has argued that chemotherapy in still the treatment of choice as initial therapy in adult ALL.

Any rationale for the routine use of autologous BMT in 1st remission is also complicated by the lack of a graft versus leukemia effect. While the loss of this effect may be partially compensated for by the reduced mortality due to transplant complications and severe GVHD, some degree of GVH is probably important in decreasing the risk of relapse. Thus, ABMT for adult ALL in 1st remission would not seem indicated at the present time. Recent data suggests, however, that it is possible to define a poor prognosis group of adults, based on high initial white count, null ALL phenotype, older age (>35), and longer time to achieve a complete remission (> 4 wks) (Hoelzer et al, 1988). Patients with none of these adverse factors had a probability of being in complete remission at 5 years of greater than 60%, while those with 2 or more factors had a probability of less than 20%. These authors are currently randomizing poor risk patients to further chemotherapy alone vs. bone marrow transplantation, allogeneic or autologous.

C. Chronic granulocytic leukemia (CGL)

Allogeneic BMT for CGL in chronic phase has proven to be capable of achieving a long-term survival of 55-65% and a disease-free survival at 5 years of greater than 50% (Thomas and Clift, 1989). Moreover, if patients are transplanted within the first year after diagnosis, the results may be substantially better. Although nearly all of these patients are Philadelphia chromosome negative, the availability of the polymerase chain reaction to detect very small numbers of residual Ph positive cells will undoubtedly identify some patients who have not relapsed by clinical or cytogenetic criteria, but who still harbor the Ph positive clone. The long-term significance of such a finding, however, is unknown.

The possibility of achieving similar results with autologous BMT for CGL patients who are older or who do not have a sibling donor is complicated first by the lack of a graft versus leukemia effect. Although good results have also been obtained in small numbers of identical twins, with 9 of 14 currently alive and disease-free with follow-up ranging from 7-12 years (Thomas and Clift, 1989), data from T-cell depletion studies in much larger numbers of patients suggest that graft versus disease and an associated graft versus leukemia effect are also important in CGL (Goldman, 1989). Thus, although depletion of T cells dramatically decreased the incidence of severe GVH, it also resulted in a much higher risk of relapse in patients transplanted for CGL.

More serious, however, is the problem of eliminating Philadelphia positive cells from the bone marrow. Two recent approaches to this latter problem are of interest. First, a small percentage of patients with Ph positive CGL have become cytogenetically normal after prolonged therapy with alpha-interferon. Although these patients do have residual Ph cells detectable by the polymerase chain reaction technique, harvesting and storage of the "remission" marrows in these patients is currently being carried out in anticipation of ABMT at a later stage of the disease.

Second, Eaves and colleagues (Barnett et al, 1988) have shown that bone marrow from patients with CGL frequently becomes Ph negative after 1-2 weeks of culture in vitro. Apparently, Ph positive cells die off under these conditions and only Ph negative cells persist. This group has now reported treating three patients in chronic phase CGL with VP-16, cyclophosphamide, total body irradiation and autologous bone marrow cultured in vitro for 10 days. One patient died of transplant related toxicity, one patient relapsed at 3 months, and one patient is in remission with normal cytogenetics at 7 months post transplant. Clearly these results are extremely preliminary, and must be viewed in context of previous data on short-term cytogenetic remissions achieved in CGL

with chemotherapy alone. Nevertheless, this technique suggests an approach for separating normal residual marrow stem cells from abnormal Ph positive stem cells. A similar approach has been reported by Dexter and colleagues for purging bone marrow of patients with AML and cytogenetically abnormal clones (Chang et al, 1986; Testa et al, 1987).

Finally, a number of groups have used bone marrow harvested from patients in the chronic phase of CGL to treat the accelerated or blast crisis phase of the disease with ABMT and high-dose chemotherapy (Phillips et al, 1984; Thomas et al, 1984; Preisler et al, 1984; Haines et al, 1984; Reiffers et al, 1986; Lemonnier et al, 1986). Although many of these patients were able to achieve a second chronic phase of their disease, and some were found to have a proportion of cytogenetically normal cells after transplant, the durations of these second chronic phases have been short and long-term survival is extremely rare.

VIII. What is the role of ABMT in solid tumors?

A. Germ cell tumors

Because the germ cell tumors are highly responsive to chemotherapy, few patients have been treated with ABMT because most can be cured with first or second line chemotherapy regimens (Einhorn, 1987). The recent introduction of the cyclophosphamide analog, ifosfamide, for the treatment of testicular cancer has resulted in improved rates of salvage, approximately 40% at minimum two years follow-up, for patients who relapse after initial therapy (Loehrer, Einhorn, and Williams, 1986). Clearly, then, high-dose therapy and ABMT are probably indicated only as a third line approach to treating refractory testicular tumors.

Possibly because patients with refractory testicular neoplasms have been heavily pre-treated, the reports of high-dose therapy and ABMT have generally been disappointing. Complete remission rates have been about 20% overall, and the duration of these responses have less than a year in duration (Herzig et al, 1987; Wolff et al, 1984; Postmus et al, 1984; Pico et al, 1986; Sleijfer et al, 1986; Mulder et al, 1988). Conceivably, the identification of poor prognosis patients who fail initial chemotherapy might allow the selection of less-heavily pre-treated patients who are destined to fail conventional therapy.

B. Small cell lung cancer

Four studies have attempted to randomize patients to low and high doses of chemotherapy for small cell lung cancer. Although one of these studies showed a statistically significant difference

in response rates and survival, the doses used in the low-intensity arm were relatively small, and no complete responses were seen in this arm (Cohen et al, 1977). Two other studies failed to find differences in survival or response rates between low and high doses of cyclophosphamide (Figueredo et al, 1985) or methotrexate (Hande et al, 1982). One final study showed an increase in the complete response rate in small numbers of patients treated with higher doses of cyclophosphamide, but the survival was the same in both arms (O'Donnell et al, 1985). Overall these studies suggest that there is not additional benefit to doses of cyclophosphamide greater than 300-400 mg/m^2/week (Murray, 1987).

Recently, Murray (1987) has applied the concept of dose-intensity delivered over the 1st 6 weeks of therapy to retrospectively analyze the results obtained with CAV[11] chemotherapy for small cell lung cancer. Analyzing over 2000 patients published in 25 separate studies, a logistic regression analysis confirmed the lack of a correlation between cyclophosphamide dose-intensity and outcome. On the other hand, the dose-intensity of adriamycin was highly significantly associated with response in extensive stage disease. For patients receiving CAE[12] therapy, the correlation for adriamycin extended to both response rate and median survival time.

Given the high response rate of untreated small cell lung cancer to standard chemotherapy, a number of investigators have treated small numbers of patients with high-dose therapy and ABMT. Many of these studies have looked at the utility of ABMT as late "intensification" treatment following conventional induction therapy. In general, the results of ABMT used in this manner in uncontrolled studies has not been encouraging. Even though these studies were generally limited to patients achieving complete or partial responses with initial therapy, the 2 year survivals were very low and not clearly superior to conventional treatment (Ihde et al, 1986; Smith et al, 1985; Sculier et al, 1985; Cunningham et al, 1985). Spitzer et al (1986) have described 5 patients with a disease-free survival of more than 4 years out of 13 patients with limited stage disease who initially achieved a complete response with traditional induction therapy.

One randomized trial has compared the value of intensification with ABMT in small cell lung cancer (Humblet et al, 1987). Of 101 patients, 45 were randomized to either continued conventional therapy or late intensification with ABMT. Patients with extensive stage disease had the same overall survival regardless of therapy, and no long-term survivors were seen in either treatment group. Of the 32 patients with limited-stage disease, relapse occurred at

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[11] (cyclophosphamide, adriamycin, vincristine)

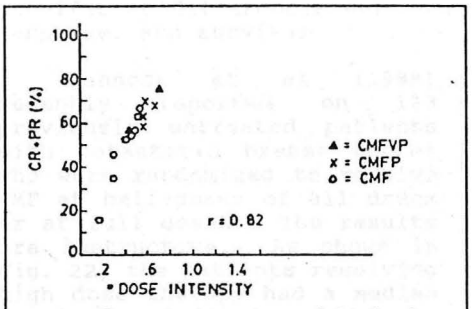
[12] (cyclophosphamide, adriamycin, VP-16)

a median of 10 weeks in the conventional arm and 35 weeks in the ABMT arm, a significant difference. Nevertheless, the median overall survival times were not significantly different (60 weeks and 84 weeks, respectively). Three patients survived more than 2 years in the ABMT group, however, while no patient survived beyond one year in the conventional treatment arm.

In analyzing this last trial, it is important to note that relapses generally occurred at the sites of previous disease and not in the bone marrow. This suggests that bone marrow involvement with small cell lung cancer is not the reason for the poor results of ABMT in this disease. However, purging of tumor cells from the marrow may become more important if regimens are improved to yield increased control of primary tumor sites. One logical step to take in ABMT for small cell lung cancer would be to treat selected patients with ABMT at the time of diagnosis, before the development of drug resistance. Such a study should be carried out, however, as a randomized trial with conventional treatment.

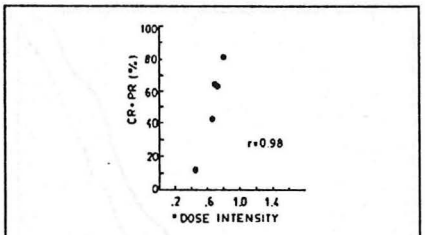
C. Breast cancer

Although the concept of dose-intensity has already been introduced in this Grand Rounds, the original use of this method of analysis was in breast cancer (Hryniuk and Bush, 1984). As shown in Figs. 19 and 20, the rate of complete and partial responses in metastatic breast cancer appears to be strongly correlated with the dose-intensity calculated for the CMF[13] and FAC[14] regimens commonly used in



Response rate v average relative dose intensity of CMF. Calculations are from doses actually delivered after reductions for toxicity. Dose intensities are relative to the regimen of Cooper and Holland.[1] $P = < .001$.

Figure 19 Hryniuk and Bush, 1984



Response rate v average relative dose intensity of CAF. Calculations are from doses actually delivered after reductions for toxicity. Dose intensities are relative to the regimen of Bull and Tormey.[14] $P = .01$.

Figure 20 Hryniuk and Bush

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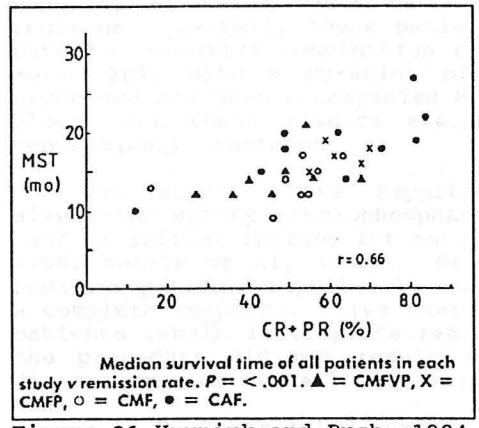
[13] (cyclophosphamide, methotrexate, 5-fluorouracil)

[14] (5-fluorouracil, adriamycin, cyclophosphamide)

breast cancer. Moreover, as shown in Fig. 21, this correlation also holds for median survival times, although the slope of the curve appears to be less significant. While this analysis is certainly provocative, Henderson et al. (1988) have argued forcefully that this analysis is flawed. Analyzing data from all trials using CMF for adjuvant therapy of both pre- and post-menopausal breast cancer, Henderson et al (1988) found a very low correlation between dose-intensity and the time to disease relapse. Indeed, in the premenopausal group the correlation was negative.



Median survival time of all patients in each study v remission rate. $P = < .001$. ▲ = CMFVP, X = CMFP, ○ = CMF, ● = CAF.

Figure 21 Hryniuk and Bush, 1984

A small number of randomized clinical trials have looked at the issue of dose-response in metastatic breast cancer. Hortobagyi et al (1987) randomized 59 previously untreated patients with metastatic breast cancer to a conventional dose of FAC or to FAC with substantially higher doses of adriamycin and cyclophosphamide given in a protected environment. No significant differences were seen in response rates, duration of response, and survival.

Tannock et al (1988) recently reported on 133 previously untreated patients with metastatic breast cancer who were randomized to receive CMF at half-doses of all drugs or at full doses. The results are instructive. As shown in Fig. 22, the patients receiving high dose therapy had a median survival of 15.6 months as compared to 12.8 months in the low dose group. However, when the data were corrected for an imbalance between the two arms in the time from relapse to randomization, the effect was not statistically significant (P=0.12). Response rates were significantly different, however, with 30% responding in the high dose arm vs. 11% in the

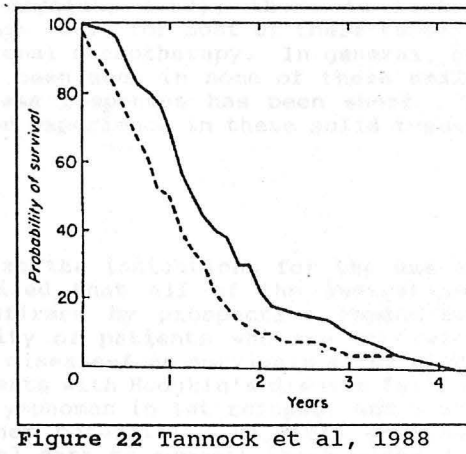


Figure 22 Tannock et al, 1988

low dose arm. Not surprisingly, the high-dose group experienced more vomiting, myelo-suppression, and alopecia.

Despite the conflicting data on the impact of increased dose-intensity on breast cancer, the use of autologous bone marrow transplantation for patients with metastatic breast cancer has increased in recent years. More than 300 women have been reported who have undergone ABMT (Antman and Gale, 1989). The great majority of these cases have been refractory to conventional regimens. Overall, these patients have had a complete response rate to intensive combination chemotherapy regimens and ABMT of about 20%, with a duration of 2-5 months. Given that this procedure has been accompanied by a mortality of 5-20%, it is not clear that these results are better than that achieved with conventional treatment.

Two studies have reported results with high-doses of alkylating agents (cyclophosphamide, cis-platinum, and BCNU) and ABMT as initial therapy for metastatic breast cancer (Eder et al, 1986; Peters et al, 1988). Of a total of 25 estrogen-receptor negative patients reported in these two studies, 14 (56%) achieved a complete response. Five toxic deaths occurred (20%), and four patients remain in complete remission at 19-55 months. Overall, the procedure did not result in an improvement in the median disease free or overall survival.

D. Other solid tumors

Patients with ovarian cancer, melanoma, colon carcinoma, glioma, and other solid tumors have also been treated with a variety of high-dose drug regimens and ABMT. With the exception of ovarian cancer (Levin and Hryniuk, 1987), there is little evidence for a steep dose-response curve for most of these tumors, which respond poorly to conventional chemotherapy. In general, an increased rate of responses has been seen in some of these small trials, but the duration of these responses has been short. A recent review details the limited experience in these solid tumors (Cheson et al, 1989).

IX. Conclusions

If one attempts to summarize the indications for the use of ABMT, it must first be emphacized that all of the indications suggested here need to be confirmed by prospective randomized trials. Nevertheless, a minority of patients who are otherwise incurable seem to have long-term disease-free survivals after high-dose therapy and ABMT, i.e. patients with Hodgkin's disease failing MOPP and ABVD therapy, diffuse lymphomas in 1st relapse, and acute leukemias in 1st relapse. Other potentially valuable settings which need substantial additional data to support their wider use are untreated diffuse lymphomas and leukemias in 1st remission that

have features associated with a poor prognosis. Most controversial is the value of ABMT in CGL, breast cancer, small cell lung cancer, and other solid tumors.

For the future, we can expect to see more randomized trials and a trend to using intensive therapy in the adjuvant setting for diseases like melanoma and breast cancer that have very poor prognostic features. For example, patients with inflammatory breast cancer and patients with Stage II disease and greater than 10 positive axillary nodes, both of whom have a poor prognosis, are being considered for ABMT at at least one center.

Relative to dose-response data for breast cancer, one major trial is underway to examine the dose-responsiveness of adjuvant therapy in this disease. Over 800 patients are enrolled in a CALGB study comparing adjuvant therapy with CAF at high dose for 4 months, moderate dose (two-thirds) for 6 months, and low dose (one-half) for four months. The results of this trial should be evaluable in another 4-5 years.

Another direction for the future that could prove valuable for ABMT is an in vitro method for determining the dose-response curve of various tumors with a variety of chemotherapy drugs (von Hoff et al, 1986). In a pilot study with the tumor cloning assay, in which individual tumor specimens are cultured in vitro and tested for killing with different concentrations of drug, von Hoff and associates were able to demonstrate a steep dose response curve for certain drugs. For example, melphalan in lymphomas (n=44) and cis-platinum in small cell lung cancer (n=38) exhibited steep dose-response curves. At the highest doses for these drugs, 100% of the patient samples had at least a 50% decrease in the number of tumor colonies surviving a 1 hr exposure to the drug. In contrast, most of the drugs tested in breast cancer (n=453) and other solid tumors had flat or shallow curves with increasing drug dose. Although this work is clearly preliminary, an improved understanding of each drug's dose-response characteristics in each tumor will be critical to exploiting the potential value of high-dose chemotherapy and autologous bone marrow transplantation.

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