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INTENSIVE THERAPY FOR MALIGNANT DISEASE*

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Unfortunately, many patients with cancer are not curable with our current standard therapies. Patients with malignancies that are not sufficiently localized for cure with surgery and/or radiotherapy can sometimes be cured with chemotherapy. However, even patients with what are termed chemotherapy sensitive malignancies are not always able to be cured. For example, only 30–40 per cent of patients with extensive diffuse large-cell (i.e. centroblastic and immunoblastic) lymphoma can be cured utilizing the most effective combination chemotherapy regimens[1]; approximately 30–40 per cent of patients with widely disseminated Hodgkin's disease will not be cured with an effective combination chemotherapy regimen[2] and essentially all patients with metastatic breast cancer will eventually die of their disease despite frequent response to chemotherapy.[3]

The existence of a high response rate, despite frequent relapses in responding patients, raises the hope that dose escalation might allow a greater fraction of cured patients. This depends on the existence of a dose-response relationship (i.e. higher doses kill more cancer cells) in the tumors in question. Standard doses for many chemotherapeutic agents are defined by the level at which toxicity becomes intolerable by producing too high a treatment related mortality. With predominantly myelosuppressive chemotherapeutic agents, transplantation of healthy hematopoietic progenitor cells and/or the use of hematopoietic growth factors might sufficiently ameliorate myelotoxicity to allow higher doses of therapy. This offers the possibility of delivering increasingly intensive therapy and, if a dose-response relationship really exists, of curing patients that could not be cured with standard dose schedules.

DOSE-RESPONSE IN CANCER CHEMOTHERAPY

It has been clearly demonstrated that there is a dose-response relationship to the use of chemotherapeutic agents in several cancers. The most convincing data have compared lower than usual doses of chemotherapeutic agents with present standard doses. For example, a randomized trial in patients with breast cancer that compared standard versus lower doses of cyclophosphamide, doxorubicin and fluorouracil showed a decrement in benefit with the lower doses.[4] There are numerous other reports purporting to show that patients who do not receive full doses of treatment have a poorer treatment outcome.[5–8]

While lower doses of chemotherapeutic agents seem to reduce the chances for benefit, it does not necessarily follow that higher doses will improve treatment response. To illustrate this point, three different (theoretical) dose-response curves that might exist for chemotherapeutic agents in a particular tumor are

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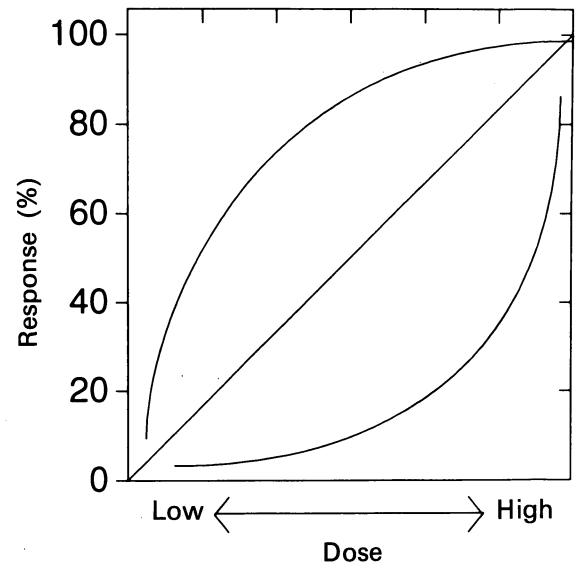

FIGURE 1

Theoretical dose-response curves for patients with a malignancy treated with a specified regimen.

demonstrated (Fig 1). It is most likely that the middle—i.e. linear—dose response curve does not seem to be correct. That is, increasing the doses above standard does not seem to cause a proportional increase in response. The lower curve would be the one most likely to show a benefit from dose escalation and increasingly intensive therapy. If this were the situation, then increasing the doses would cause a disproportionate increase in treatment response. Unfortunately, the available evidence suggests that the upper curve more accurately represents the current situation. That is, as doses are increased the response rate goes up, but at increasingly smaller increments. Thus, it appears that a considerable increase in dose is required for a useful increase in therapeutic response.

In patients with large cell lymphoma, increasing the number of drugs does not seem to improve treatment outcome.[9] However, there is some evidence that a dose-response does exist in the treatment of a number of malignancies. Some patients with chemotherapy resistant lymphomas have been cured with very high dose alkylating agent therapy and autologous bone marrow transplantation.[10] Unfortunately, the cure rate in truly resistant patients is only 10–20%. A recent trial in Hodgkin's disease demonstrated that higher doses of carmustine, etoposide, cytarabine, and melphalan produced a significantly better response and progression free survival in patients with Hodgkin's disease when compared to lower doses.[11] The results were sufficiently good that this randomized trial was stopped early.

Finally, very high doses of alkylating agents and/or total body radiotherapy have been demonstrated to cause disproportionately higher response rates in patients with breast cancer and follicular non-Hodgkin's lymphona.[12–16] However, the pattern of late relapses seen with these disorders precludes confident determination of the curability of this approach.

AUTOLOGOUS BONE MARROW TRANSPLANTATION

Autologous bone marrow transplantation involves the storage of the patient's own hematopoietic progenitor cells obtained before high dose therapy which are reinfused afterwards. This treatment was first widely utilized in the 1980s. It has become a more frequently applied treatment than allogeneic bone marrow transplantation and as many as 10,000 procedures might be performed annually world wide. The increasing utilization of this treatment approach relates to its documented curative potential in several malignancies (e.g. non-Hodgkin's lymphomas, Hodgkin's disease, acute leukemia, and germ cell tumors) and the fact that the treatment can be done increasingly safely. At the University of Nebraska Medical Center the treatment related mortality has fallen over the past decade from 30–35 per cent to approximately 1–2 per cent. This allows the utilization of this treatment approach in patients with an otherwise poor prognosis early in the course of their treatment.

There are a number of potential disadvantages to the use of autologous bone marrow transplantation. These include the reinfusion of malignant cells and the considerable cost of the procedure. A number of approaches have been tried to eliminate the possible reinfusion of malignant cells. These include in vitro treatment of the stored marrow to either destroy malignant cells or to concentrate stem cells.[17,18] In vitro marrow treatment has been accomplished using chemicals that are more cytotoxic to tumor cells than normal myeloid stem cells,[19] immunologic approaches using antibodies directed against the tumor cells,[20] and various other approaches.[21] All of these methods have been able to reduce the number of tumor cells in experiments in which a measurable number of tumor cells have been added to marrow. It is presumed therefore that it is possible to significantly reduce the number of tumor cells in an autologous bone marrow graft. However, it is unlikely that tumor cells are completely eliminated. It is also unclear what number of tumor cells in a graft will lead to relapse. It is reasonable to assume that there would be a threshold number required for inducing relapse just as there appears to be a threshold number to cause engraftment of myeloid stem cells. Available data suggests that in some clinical circumstances marrow 'purging' can reduce the incidence of relapse.[19,20] However, a definitive trial has not yet been done to answer this point.

Another approach that might reduce the number of tumor cells that are collected and reinfused involves the collection of hematopoietic progenitor cells from peripheral blood rather than from the bone marrow. This is an increasingly popular approach to autologous transplantation. When hematopoietic growth factors are used, with or without collection during the recovery phase from preceding chemotherapy, a limited number of apheresis procedures can collect adequate numbers of progenitor cells to allow transplantation.[22,23] At least in some illnesses, it appears that this approach is less likely to yield significant tumor contamination when compared to marrow transplantation.[24,25] Both approaches can yield durable engraftment. Because of the comparative ease for the patient of avoiding the operating room, and because of a presumed (but not absolutely proven) more rapid recovery from a perfusion of peripheral blood progenitor cells, this approach is becoming increasingly popular and is now probably performed more often than autologous bone marrow transplantation.

It has also been suggested that very high dose chemotherapy might be administered without the reinfusion of hematopoietic progenitor cells. With the advent of the wide spread use of hematopoietic growth factors, the possibility exists that some patients might be able to have hematopoiesis stimulated by the in vivo use of hematopoietic growth factors acting on residual, endogenous stem cells. It is quite clear that many patients have endogenous hematopoietic stem cells that survive high dose therapy. This is demonstrated by the recurrence of endogenous hematopoiesis in patients undergoing allogeneic bone marrow transplantation when T-cell depletion of the allogeneic graft is utilized.[26]

TABLE 1

Curability of selected malignancies with high-dose therapy and autologous hematopoietic progenitor cell transplantation

Curative potential	*Diseases*
Definite	Acute leukemia
	Aggressive non-Hodgkin's lymphoma
	Hodgkin's disease
	Germ cell tumors
Possible	Breast cancer
	Low-grade non-Hodgkin's lymphoma
	Chronic leukemias
	Multiple myeloma
Unlikely	Colon cancer
	Melanoma
	Lung cancer

While patients with severely damaged marrows are probably not good candidates for using only hematopoietic growth factors, it is apparent that patients can benefit from this approach when treated early in the course of their illness at a time of fairly normal marrow function. The dose and choice of cytotoxic agents utilized is probably also important. For example, patients receiving very high doses of busulfan or total body radiotherapy are probably not good candidates for this treatment approach. However, several investigators have demonstrated that very high doses of chemotherapeutic agents can be tolerated in patients with reasonably healthy bone marrows when high doses of hematopoietic growth factors are utilized post therapy.[27] The relative merits of the two approaches, early use and late use, need to be evaluated in specific clinical situations. Randomized clinical trials may answer some of these questions.

The adjuvant value of autologous bone marrow transplantation in effecting cure has been measured in several diseases. Several of these malignancies are listed in Table 1. As can be seen, in illnesses such as acute leukemia, aggressive non-Hodgkin's lymphomas, Hodgkin's disease, and germ cell tumors, patients can be cured. In other illnesses such as breast cancer and low-grade non-Hodgkin's lymphomas, the indolent and relapsing nature of the illness makes it harder to document cure. However, the results reported to date are encouraging. There are, unfortunately, a number of other illnesses in which the approach has not dramatically increased survival or cure of any significant number of patients. These malignancies, unfortunately, include some of the more common cancers such as those of colon and lung.

CONCLUSION

Very intensive therapy with chemotherapeutic agents and/or total body radiotherapy followed by autologous bone marrow transplantation can cure some patients with otherwise apparently incurable malignancies. This is certainly true for patients with hematologic malignancies, and probably true for certain patients with carcinomas. The application of this technology needs to be carefully considered since it does have risks. It is also very expensive.

When considering how to apply a new treatment approach, the application needs to be considered on different levels. To make an analogy with military activities, one has to consider both tactics and strategy. Tactics, in military terms, describe the activities of armies engaged in combat. These represent the 'details' of fighting. Analogous factors in intensive cancer therapy and autologous bone marrow transplantation include the treatment regimen utilized, whether or not attempts are made to remove potentially contaminating tumor cells from the autologous graft, details of supportive care, and the source of hematopoietic stem cells utilized. While important, these are not as likely to have a major impact on outcome as the strategy chosen for their use.

Strategy in military terms are the plans and maneuverings of armies before combat begins to allow themselves the best chance to prevail. In intensive cancer therapy using autologous bone marrow transplantation, the best analogy is probably to the selection of the patient and the timing of the treatment. That is, the difference between utilizing this treatment in patients with end stage, resistant tumors versus identifying high risk patients and incorporating the treatment early into their therapy. In general, a superior strategy will have more of an impact on outcome than superior tactics—although both are important.

Ultimately, the place of very intensive cancer therapy and autologous bone marrow transplantation in the treatment of patients with cancer will depend partly upon our ability to identify optimum strategies for its use, but also upon health care policies in our countries. This is an expensive and complicated treatment approach.

Whether or not we will be able to continue to apply this therapy to benefit patients with malignancies will depend upon national policy decisions about the use of this and other 'high tech', expensive, therapies.

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