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Perspectives and Commentaries

Perspectives for the Use of High-dose Chemotherapy in the Treatment of Solid Malignant Tumors

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(A COMMENT ON: Postmus PE, de Vriese EGE, de Vries-Hospers HG *et al.* Cyclophosphamide and VP 16-213 with autologous bone marrow transplantation. A dose escalation study. *Eur J Cancer Clin Oncol* 1984, **20**, 777–782.)

DURING recent years many investigators have been interested in the administration of high-dose chemotherapy for the treatment of solid malignant tumors. The optimal 'high dose' should be defined by phase I studies as the maximum dosage that can be administered without reaching excessive extra-hematological toxicity.

Recently, several such phase I and II studies have been published, leading to a rational approach to the intensification concept. The most investigated antineoplastic drugs are cyclophosphamide, melphalan, BCNU and etoposide (VP 16-213).

High-dose cyclophosphamide was already being studied in the early seventies [1] and much experience has been obtained in allogeneic bone marrow transplantation. The maximum recommended dose is 200 mg/kg, to be given usually four times over 2–4 days. The limiting extra-hematological toxicity is cardiac [2], with the possible occurrence of pericarditis and myocardial necrosis. Autologous bone marrow infusion is not necessary when cyclophosphamide is used alone. Two phase I studies in poor-prognosis tumors have been reported about melphalan [3, 4]. The extra-hematological limiting toxicity is mucosal with severe stomatitis, esophagitis and diarrhea. A maximum dose of 180 mg/m^2 has been recommended when the drug is administered as an i.v. bolus over three consecutive days. The usefulness of autologous bone marrow transplantation has not been determined and the effectiveness of a small primary dose of cyclophosphamide given 1 week before melphalan therapy in order to reduce the gut and marrow toxicities remains controversial. High-dose BCNU has also been studied in two recent publications [5, 6], at doses ranging from 600 to 2850 mg/m^2 (the conventional dose is about 240 mg/m^2). Interstitial pneumonitis occurring 1–3 months after the infusion of the drug was the most serious side-effect and was often fatal (10 deaths in 21 patients with pulmonary toxicity in two combined series); it was not predictable but the role of a cumulative dose of BCNU was probably important. Another serious toxic effect of high-dose BCNU is severe hepatitis with fatal liver necrosis when the dose is equal to or greater than 1200 mg/m^2. The autologous bone marrow infusion seems to shorten the bone marrow aplasia.

Etoposide, given over three consecutive days, was reported to have a limiting mucosal toxicity [7]. The maximum tolerable dose was 2.4 g/m^2; such a high dose of etoposide did not seem to be ablative but no patients were treated without autologous bone marrow infusion.

Other single agents that have been less extensively studied in high-dose regimens are AMSA and mitomycin.

Phase I studies of intensification have also been performed with combined chemotherapy. In

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patients with small cell lung cancer the EORTC Lung Cancer Working Party [8] has successfully used combinations of cisplatin–adriamycin–etoposide (CAV), adriamycin–etoposide–cyclophosphamide (AVE) and cyclophosphamide–etoposide (CE). With the first two regimens unacceptable mucositis was rapidly reached. With the use of cyclophosphamide and etoposide only, given 4 times over 48 hr, the drugs could be given at 200 mg/kg and 3 g/m^2 respectively without severe mucositis. Autologous bone marrow infusion was not necessary if the dosage was equal to or less than 200 mg/kg for cyclophosphamide and 2 g/m^2 etoposide. In a previous issue of *European Journal of Cancer & Clinical Oncology*, Postmus *et al.* used the same drugs on three consecutive days and recommended 7 g/m^2 of cyclophosphamide with 1.5 g/m^2 etoposide, in addition to autologous bone marrow transplantation. Limiting extramedullary toxicity was mucositis with 2.5 g/m^2 of etoposide.

An advantage of the combination of cyclophosphamide plus etoposide is that both drugs can be used at very high doses compared with conventional dosage. No extra-hematological additive toxicity has been documented; however, when etoposide was administered over 3 days severe mucositis occurred at relatively lower dosages.

It should be emphasized that with intensive treatments patients will become severely neutropenic and thrombocytopenic and should be managed in the same way as leukemics.

An important question relates to the role of the autologous bone marrow infusion. At Seattle [9] ten patients with resistant small cell lung cancer have been treated with a combination of cyclophosphamide (120 mg/kg over 2 days) and—in some cases—BCNU (500 mg/m^2 over 2 days) followed by a total-body irradiation (a midplane dose of 1000 rads given at 8 rads/min rate by two telecobalt sources) and autologous bone marrow infusion. This was a regimen similar to the conditioning therapy for allogenic bone marrow transplantation, known to be ablative and definitely requiring a bone marrow transplant. In that study autologous bone marrow infusion was able to reconstitute a normal hematological function, usually during the third post-transplant week.

When autologous bone marrow transplantation is used after standard myelosuppressive doses of chemotherapy, it does not influence bone marrow recovery [10]; with intensive chemotherapy without total-body irradiation, which is considered by most authors to be non-ablative, the role of the autologous transfusion on bone marrow recovery is unknown. Therefore it is important to determine whether autologous bone marrow infusion is useful or not. Firstly, it is a complicated procedure necessitating general anesthesia and special technical support. Secondly, the theoretical risk of transfusing malignant cells present in the marrow exists. Efforts to obtain the separation or the destruction of the neoplastic cells within the marrow prior to the transplantation are being actively investigated by several groups.

Pharmacokinetic studies performed in patients receiving intensive chemotherapy can provide new and interesting information. Some data are available for high-dose cyclophosphamide and etoposide [11]: considerable variation from one patient to the other, as far as cyclophosphamide (given at doses of 1.5–3.5 g/m^2) metabolism was concerned, was observed; and a high dose of VP 16 (400–800 mg/m^2) resulted in pharmacokinetic characteristics similar to those seen with lower doses.

At this time there are no clear indications for intensification of chemotherapy of solid tumors. Further phase II studies and randomized studies will be necessary to determine whether high-dose chemotherapy has a place in the treatment of non-hematological neoplasms. Theoretically, intensification can be used in different ways: induction, second-line (salvage) and late intensification (consolidation). The first two modalities are based on the concept that dose is an important factor for effective chemotherapy [12]; in sensitive tumors and within certain limits, higher doses are probably associated with higher response rates and survivals: examples of such neoplasms are small cell lung cancer, testicular carcinoma and neuroblastoma.

Late intensification has been proposed, theoretically, by Norton and Simon [13]. According to their mathematical model, small tumors—such as the microscopic residual disease in patients with clinically complete responses—that are less sensitive to chemotherapy should be treated with doses of chemotherapy capable of increasing the killing of neoplastic cells and thus the cure rate.

Two recent phase II studies have been performed in specific tumors testing induction intensification. Twenty-eight patients received high doses of melphalan for advanced malignant melanoma [14]; a 43% partial response rate was obtained with only a doubtful survival advantage. In another study 25 untreated patients with small cell lung cancer, including 21 with limited disease, were given high-dose cyclophosphamide (100–200 mg/kg over 4 days) followed by chest irradiation only [15]; this therapy resulted in an 84% rate of objective responses with 56%

complete responses; the median survival time was 69 weeks, with a projected 30% survival at 20 months. These results are encouraging if they are compared with those obtained with standard-dose treatments.

No comprehensive studies have been reported so far in specific tumors for 'salvage' and late intensification. However, the results obtained in phase I studies and in preliminary trials using arbitrarily chosen levels of 'high dose' can provide some indirect information, which suggests that no major advantages as far as survival is concerned were obtained in spite of a relatively high rate of objective response. The determination of the effectiveness of late and induction intensification over standard therapy will require carefully performed randomized studies.

In conclusion, high-dose chemotherapy has actually no routine indication in the care of a patient with a solid tumor; it remains an investigational approach. Trials employing a rational methodology have recently provided information about the optimal doses to be used. Phase II and randomized studies in patients with specific tumors are now necessary to determine the role, if any, of intensification of chemotherapy in the therapy of cancer.

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