Cancer Chemother Pharmacol (1982) 9: 127–133

Cancer Chemotherapy and Pharmacology

Review

Intensive Chemotherapy for Solid Tumours – Current Clinical Applications

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Summary. *The treatment of solid tumours with high-dose chemotherapy using alkylating agents either as single agents or in combination schedules has received increasing attention from clinical investigators in recent years. This has frequently been given in association with autologous bone marrow support, a technique which appears to ameliorate myelosuppression that might otherwise be dose-limiting, and which thus may allow dose escalation into a range previously not reached. Despite this ability, and in spite of much experimental evidence from drug-sensitive animal tumours that increasing doses result in increased response rates, no major impact has yet been made in the therapy of solid tumours using this form of therapy. In addition, the use of high-dose schedules has seen the emergence of extramedullary manifestations of drug toxicity which were not encountered at conventional doses.*

Nevertheless, there are some encouraging data from reports in certain tumours, including small cell lung cancer, testicular cancer, ovarian cancer, and lymphoma, and further studies are clearly indicated. These should probably be restricted to certain drug-sensitive tumours, and should include an examination of the role of high-dose chemotherapy as consolidation treatment, following conventional induction therapy for selected tumour types.

This form of treatment may yet provide an important contribution to the control of human solid tumours, but much further work, probably with combination drug schedules, is required.

Introduction

In discussing the case for intensive cancer chemotherapy in 1976, Tattersall and Tobias observed that '*studies of high-dose single agent therapy in man have been disappointing*', and questioned its usefulness in common human cancers [48]. Since then, efforts to improve results with this form of therapy have been intensified, generally with the use of autologous bone marrow support to ameliorate toxicity. The purpose of this review is to assess the current state of the art of intensive chemotherapy for solid tumours, and to attempt to place this therapeutic strategy in perspective.

Background

Studies in experimental tumours systems, which began about 20 years ago, have concluded that for drug-sensitive tumours a steep dose-response curve can usually be demonstrated. Frei and Canellos have recently reviewed these data [19], and they indicated that in general these observations also apply in clinical practice. This view has prompted several investigators to use chemotherapy in very high doses, in particular in patients with those solid tumours which are initially sensitive to conventional doses of cytotoxic drugs yet generally prove fatal in the end.

The rationale for this approach relates to the presence of drug-resistant tumours cells, which are a major factor in the ultimate failure of chemotherapy to control tumour growth in such patients. The mechanisms by which they are derived vary according to the drug involved and are beyond the scope of this review, but evidence from animal studies suggests that the development of drug resistance is dose-related, and that one important component of curative experimental drug schedules is the use of drugs in maximally tolerated doses [43].

Unfortunately, however, it has not proved possible to demonstrate as steep a dose-response relationship in drug-sensitive human tumours as has been seen in experimental systems. One reason is that it clearly is not practical to perform comprehensive dose-response studies in the clinical situation. Thus data from patients consist of fragments of the dose-response curve for each particular tumour type; and also the use of combination rather than single-agent schedules makes interpretation difficult. In addition, it is likely that factors such as the heterogeneity of human tumours and drug access, which will vary according to tumour vascularity, are of major importance. Within these limitations, however, the results from several studies in solid tumours such as breast cancer [27, 32], small cell lung cancer [13] myeloma [5], head and neck cancer [30], and ovarian cancer [26] do support the concept that, at least for these drug-sensitive tumours, increasing responses may result from increasing dose rates over the conventional dose range. Nevertheless, conflicting data exist [15, 52], and clearly it would be inappropriate to assume that a steep dose-response relationship can be demonstrated for all, or even most, drugs and tumour types. Moreover, where the data have indicated that such a relationship might be present, what remains unclear is how far this can be extrapolated into the dose range used in intensive chemotherapy to achieve the maximum response.

In general, increasing dose rates for cytotoxic drugs lead to increasing toxicity, although there is the important exception of methotrexate, which can be administered at high doses with leucovorin rescue and minimal toxicity, provided that a high level of supervision is maintained in association with plasma drug monitoring [6]. For the majority of drugs, however,

0344-5704/82/0009/0127/$ 01.40

including alkylating agents and anthracyclines, increased dose rates are limited by specific organ toxicity, bone marrow being the most common site where dose-limiting toxicity occurs. The use of bone marrow transplantation in the management of aplastic anaemia and acute leukaemias [46, 49] has aroused renewed interest in techniques of bone marrow harvesting with short- and long-term storage, and these have been adopted as a means of providing autologous bone marrow support for patients receiving high doses of cytotoxic drugs.

A common approach has been the aspiration of $2-5 \times 10^8$ nucleated cells/kg prior to chemotherapy, with reinfusion at a suitable time after the administered drug could be assumed to have been cleared from the circulation using available pharmacokinetic data. For high-dose chemotherapy completed over a period of hours, short-term storage of bone marrow at 4° C has proved adequate, but when high-dose chemotherapy has been prolonged over a period of days, cryopreservation of bone marrow has been required. Using these techniques for providing autologous bone marrow support, published evidence suggests that for certain high-dose chemotherapy schedules haematological recovery could be enhanced (see below).

As a result, investigators have continued to increase the doses of drugs whose major dose-limiting toxicity had been myelosuppression, beyond those conventionally used, to the range where (a) consistently increased response rates in drug-sensitive tumours might be expected, and (b) other dose-limiting toxicities become apparent.

The group of drugs which has received most attention in terms of high-dose schedules is that of the alkylating agents, particularly cyclophosphamide and melphalan. Although high-dose chemotherapy with autologous bone marrow support has been the subject of clinical trials for 20 years, large-scale clinical studies are sparse. In 1962 two studies were published detailing the use of high-dose alkylating agent chemotherapy. The first was a study of 31 patients with metastatic melanoma treated with high-dose melphalan (100 mg) in association with autologous bone marrow support [3]. Although no survival benefit was apparent, 11 patients demonstrated a marked tumour response and about 70% were described as having a subjective response. In the other series patients with a range of tumours were treated with cyclophosphamide at doses of 40–165 mg/kg, melphalan in doses of 0.96–2.3 mg/kg, or mustine in doses of 0.8–1.85 mg/kg together with marrow support [37]. Tumour regression described as 'good' was achieved in patients with advanced malignant melanoma, uterine carcinoma, and Ewing's tumour, but the benefit of autologous bone marrow support was unclear, and no advantage for this form of therapy over conventional doses of chemotherapy was claimed. In a study published in 1963 mustine was again used in a high dose (1 mg/kg) in 32 patients with lung cancer [21]. Toxicity was excessive, and the median survival of patients in this series was only 6 months, which is not significantly different from the results obtained using conventional drug doses.

Nine years later, Buckner et al. [11] reported a series of 26 patients with a variety of types of metastatic cancer, who received one or more courses of cyclophosphamide at doses of 60–240 mg/kg. Twelve of these received 120 mg cyclophosphamide/kg, six with autologous marrow support and six (non-randomized) without marrow support. No clear benefit for marrow support was apparent in this group, but an additional observation of importance was the frequent occurrence of electrocardiographic changes indicative of cardiac toxicity in five patients receiving 120 mg/kg. The sole patient who received 240 mg cyclophosphamide/kg died from cardiac failure 12 days post therapy. With regard to tumour response, encouraging results were obtained chiefly in those tumours known to be sensitive to alkylating agents at conventional dosage, including testicular cancer and ovarian cancer, and the same investigators published a further small series of nine patients with ovarian cancer treated with high doses of cyclophosphamide (120 mg/kg) without autologous bone marrow support [12]. Of these patients eight achieved at least a partial response. The data did suggest some advantage for this form of therapy; however, a subsequent randomized study by Young et al. failed to show any advantage for cyclophosphamide in doses of 80 mg/kg over conventional therapy with oral melphalan in advanced ovarian cancer [52].

At that stage it was thus not possible to draw firm conclusions as to the role of high-dose alkylating agent therapy in the management of drug-sensitive tumours. It did seem possible, however, that a significant benefit over conventional-dose therapy might be achievable provided that cyclophosphamide doses of 120–200 mg/kg were employed, implying (at least for ovarian cancer) the existence of a relatively shallow dose-response curve.

Recent Studies

Although the data from earlier clinical studies are inconclusive, investigators have continued to explore the use of high-dose chemotherapy, using both single-agent and combination schedules. These efforts have involved a wider range of drugs and tumour types, and as a result much useful information has been obtained, particularly in the areas of tumour responsiveness, pharmacokinetics of high-dose chemotherapy, and extramedullary manifestations of drug toxicity.

a) Single Agents

(i) Melphalan. As mentioned previously, melphalan was first used in high doses in association with autologous bone marrow support in 1962, but it has recently undergone extensive retesting at considerably higher doses. Related to this resurgence of activity has been the intriguing observation of Millar [35] that pretreatment of mice with small doses of 'priming' agents such as cyclophosphamide reduced the toxicity of subsequent large doses of alkylating agents (or irradiation). The mechanism underlying this phenomenon is not understood, but Hedley et al. [25] reported clinical data which suggested that cyclophosphamide priming accelerated bone marrow recovery in patients treated with high-dose melphalan; however, the extent of any possible protection from toxicity in organs other than bone marrow, e.g., gastrointestinal mucosa, remains unclear, and mucositis, which can be severe, remains a major dose-limiting factor in high-dose melphalan therapy.

Pharmacokinetic data on high-dose melphalan therapy have been reported by McElwain et al. [34], who have indicated that at a high dose (140 mg/m^2) melphalan is rapidly cleared from the circulation, with no detectable melphalan present in plasma after 2 h. Urinary excretion of unchanged melphalan appeared to be complete after 6 h. As regards clinical studies of the role of high-dose melphalan (140–260 mg/m^2), McElwain et al. [34] have reported data which suggest that in patients with advanced malignant

melanoma, autologous bone marrow support with reinfusion performed 8 h after treatment enhanced haematological recovery; in addition, responses to this chemotherapy in measurable tumour were seen frequently. In a follow-up assessment they reported that 27 patients had received this form of therapy, and 10 (37%) achieved a partial response, while two (7%) achieved a complete response [41]. However, survival advantage was slight and was limited to those patients receiving more than 200 mg/m^2, so that except for a selected group of patients with symptomatic visceral metastases from malignant melanoma this form of therapy was not recommended. The technique, again employing single-agent high-dose melphalan, has been somewhat more promising in childhood tumours, including advanced neuroblastoma [40] and Ewing's sarcoma [14], in both of which it is being assessed currently as a form of consolidation therapy following initial conventional chemotherapy. The initial studies do indicate a potential for long-term survival with this form of therapy in childhood tumours, and further studies are awaited with interest.

(ii) Cyclophosphamide. Since the earlier reports by Buckner et al. [11] there have been relatively few reports on the use of cyclophosphamide given in high doses as a single agent. This may have been due partly to the presence of major extramedullary dose-limiting toxicities. However, the recent demonstration that 2-mercaptoethane sulphonate can ameliorate the urothelial toxicity of isophosphamide has helped to renew interest in this form of therapy [10]. Isophosphamide and cyclophosphamide are activated in the liver to produce the antitumour metabolites isophosphoramide mustard and phosphoramide mustard respectively, and also acrolein, which although having little antitumour activity is responsible for urothelial damage. 2-Mercaptoethane sulphonate, a water-soluble sulphydryl-containing compound, inactivates acrolein and is now given routinely in several centres in conjunction with high doses of cyclophosphamide, with virtually complete abolition of urothelial toxicity.

However, the second major non-haematological toxicity of high-dose cyclophosphamide, i.e., cardiotoxicity, remains as the chief obstacle to further dose escalation with this agent particularly as, unlike with melphalan, mucositis is rarely seen. As reported initially by Buckner et al. [11], and subsequently confirmed by Applebaum et al. [1], cyclophosphamide in high doses appears to cause a unique form of haemorrhagic myocarditis, which may frequently be fatal. This complication has been seen at total doses as low as 160 mg/kg when the drug is used in combination with other agents, but it seems that when cyclophosphamide is used as a single agent lethal cardiac toxicity is unlikely to occur below total doses of 240 mg/kg; although one case of fatal myocarditis has been recorded following single-agent cyclophosphamide at the dose of 180 mg/kg [23]. The potential for this form of toxicity is thus an important consideration in the selection of patients for high-dose therapy, and it remains to be seen whether differences in high-dose cyclophosphamide scheduling, e.g., the use of infusions, can ameliorate this cardiac toxicity.

Pharmacokinetic studies on high-dose cyclophosphamide have not yet been reported, partly because of technical difficulties in measuring the active metabolites. At conventional doses, it appears that plasma clearance of phosphoramide mustard (the active secondary metabolite of cyclophosphamide) is biphasic, the longer half-life being 8.7 h [28]. Further information is required at higher doses, however, since cyclophosphamide itself is inactive, requiring hepatic conversion to active metabolites, and it cannot be assumed that such conversion will be carried out to the same extent at all dose levels. However, preliminary analysis of specimens taken from a group of six patients treated with high-dose cyclophosphamide (200 mg/kg over 12 h) indicated a mean serum half-life for unchanged cyclophosphamide of 4.9 h and a mean percentage of unchanged cyclophosphamide in urine of 9.8% of the administered dose, suggesting a degree of metabolism at the high dose similar to that found in standard doses (J. F. B. Stuart et al. personal communication).

The precise role of autologous bone marrow support in enhancing bone marrow recovery following high-dose cyclophosphamide given as a single agent remains in doubt. As mentioned, the studies of Buckner et al. [11] have suggested that such support does not significantly enhance recovery at doses of 120 mg/kg. Studies aimed at defining the role of marrow support for cyclophosphamide at higher doses (200 mg/kg) are currently under way, but it should be emphasized that when used in combination with high doses of other drugs, the requirement for such support is likely to be considerably greater.

With respect to the clinical applications of high-dose cyclophosphamide, one of the most interesting recent applications relates to the treatment of small cell lung cancer. In a recent report from University College Hospital in London, 16 patients (13 with limited disease small cell lung cancer) received high-dose cyclophosphamide (160 mg–200 mg/kg) as initial treatment, together with 2-mercaptoethane solphonate and autologous bone marrow support [44]. Seven showed a complete response and seven a partial response. The treatment was well tolerated, and was followed by a course of thoracic irradiation without any additional toxicity such as carditis. Although nine patients have subsequently relapsed (follow-up of 6–16 months), it is clear that the response rate to single-agent cyclophosphamide at this dose (81%) is superior to that obtained with conventional doses (30%–40%) [9] in small cell lung cancer. Since this tumour remains fatal in the majority of cases, the incorporation of this form of treatment into the overall therapeutic strategy is an intriguing prospect.

(iii) Bis-Chloroethylnitrosourea (BCNU). Although the alkylating agent BCNU has been in clinical use since 1964, it is only comparatively recently that trials of this agent at high dose with autologous bone marrow support have been documented. Phillips et al. [38] noted that autologous bone marrow support appeared to permit the use of BCNU at 5–10 times the conventional doses; however, extramedullary toxicity was noted and was occasionally severe. This group subsequently reported a series of 24 patients with refractory malignant disease involving the central nervous system (7 primary and 17 metastatic tumours) [18]. Three patients had a complete response and 12 a partial response following BCNU at the doses of 600–2,850 mg/m^2 given over 3 days with marrow reinfusion at 7 days. Toxicity, however, was formidable, particularly noteworthy being nine deaths secondary to extramedullary toxicity of BCNU. A separate report on the use of high-dose BCNU therapy [47] in which marrow was reinfused 24 h after a single dose of 600–1,400 mg BCNU/m^2 also indicated both a significant level of tumour response in previously untreated patients (including 4 responders out of 8 patients with recurrent glioma) and a significant level of extramedullary toxicity including gut necrosis, liver necrosis

and lung toxicity, leading to four deaths among 19 patients treated.

Early pulmonary toxicity after high-dose BCNU therapy has also been noted by the MD Anderson group [31], and in three of 14 patients treated, severe pulmonary fibrosis proved to be fatal. These data suggest that the role of nitrosoureas in high-dose chemotherapy studies will probably be confined to the use of rather lower doses in combination schedules (see below).

(iv) VP16 213. The first phase I study of high-dose VP16 was recently reported from Vanderbilt University, Tennessee, and dose escalation from 1,200 mg/m^2 to 2,400 mg/m^2 was performed in association with autologous bone marrow support in 29 patients [51]. VP16 was infused at a maximum rate of 500 mg/h and given over 3 consecutive days. Autologous bone marrow was reinfused 72 h after the last dose of VP16, at doses of 1,500 mg/m^2 and above, and bone marrow recovery occurred predictably at about 16 days at doses up to 2,400 mg/m^2. Mucositis, not normally seen with VP16 at conventional doses, was first observed at doses of 1,800 mg/m^2 and occurred in the majority of patients given 2,400 mg/m^2, which probably represents the maximum tolerated dose when the drug is given as a single agent. Other side-effects noted at this dose included mild nausea and vomiting, drug-associated fever, reversible acidosis, and a skin rash.

In this phase I study, objective responses to high-dose VP16 were seen in patients with acute lymphatic leukaemia, Hodgkin's disease, small cell lung cancer, germ cell tumours and also glioblastoma, and clearly this drug will assume an increasingly important role in combined-modality programmes of high-dose chemotherapy.

In this same group of patients, a pharmacological study of high-dose VP16 was also performed [24]. This indicated that the pharmacokinetics of the drug at doses of 400–800 mg/m^2 appear to be similar to those reported at lower doses, i.e., the decline from peak levels (which ranged from 27 to 114 μg/ml) was biexponential, with initial and terminal half-lives of 0.79 and 8.1 h, respectively. Renal clearance accounted for only a third of plasma clearance, and penetration into cerebrospinal fluid and pleural fluid was low (2%–7% of plasma levels.).

(v) Other drugs. Other recent studies of high-dose chemotherapy have included a phase I study of mitomycin C in 29 patients given doses of 60–120 mg/m^2 followed by bone marrow reinfusion 48 h later [29, 42]. Although two responses were seen (in metastatic colon carcinoma and in resistant diffuse lymphoma), extramedullary toxicity was formidable. This included gut necrosis and hepatic toxicity, and suggests that further studies with this drug are not indicated.

Meta-AMSA, a compound which is still undergoing evaluation at conventional dose levels, has also been examined in a pilot study of high-dose schedules. The data indicate that in association with autologous bone marrow support, doses of up to 1,000 mg/m^2 could be given safely; however, none of seven patients thus treated exhibited a significant response [53].

Finally, a phase I study has recently been reported of the combination of high-dose busulphan (16–20 mg/kg PO over 4 days) and cyclophosphamide (200 mg/kg IV over 4 days) in association with bone marrow rescue [33]. Although in this study of 18 patients haematological recovery was generally satisfactory at a mean of 18 days after treatment, non-haematological toxicity in the form of severe stomatitis and hepatic veno-occlusive disease (fatal in 2 cases) was seen regularly. These forms of extramedullary toxicity, not previously noted for cyclophosphamide, are presumably attributable to busulphan and appear to limit its usefulness in high-dose chemotherapy schedules at this stage.

(b) Combination Schedules

Randomized studies comparing high-dose single-agent with combination schedules are clearly difficult to perform, and using such criteria the possible superiority of combination schedules is likely to remain unproven. Nevertheless, it appears logical that to overcome potential biochemical drug resistance, which may develop through several mechanisms, combinations of drugs at high doses are likely to prove more successful. Thus various studies using this approach have already been reported, and when autologous bone marrow support is being employed investigators have clearly feel justified in the simultaneous use of more than one agent whose primary dose-limiting toxicity is haematopoietic. While this approach as stated above is certainly valid, it should be emphasized that only the availability of adequate single-agent data with respect to both tumour responsiveness and toxicity at high doses will make rational analysis of combination schedules possible.

The majority of high-dose chemotherapy schedules have included cyclophosphamide, and the other drugs used have varied widely according to the tumour type treated. Thus, Tobias et al. [50] reported a small series of 10 patients given high-dose cyclophosphamide with adriamycin and autologous bone marrow support. Although six of the nine evaluable patients (mainly ovarian cancer) exhibited at least a partial response, the numbers were too small to allow definite conclusions as to the advantage of this form of therapy over conventional chemotherapy to be drawn. In the following year, an important study published by Applebaum et al. [2] detailed the use of high-dose combination chemotherapy (cyclophosphamide, BCNU, cytosine arabinoside, and 6-thioguanine) in association with autologous bone marrow support in patients with relapsed Burkitt's lymphoma. Fourteen patients were treated, four of whom died shortly after treatment (3 from acute carditis). However, three patients achieved a prolonged complete remission and possible cures; despite the cardiac toxicity this represents one of the more promising results yet achieved for this form of therapy for an advanced drug-resistant solid tumour.

In 1979, the use of high-dose chemotherapy in a more heterogeneous patient population was reported by Gale et al. [20]. Treatment involved high-dose cyclophosphamide, usually in combination with high-dose adriamycin and vinblastine. In addition, some patients also received total-body irradiation and two also received methotrexate and 5-fluorouracil. The treatment of 10 patients was reported and toxicity was clearly unacceptable, with four patients dying of toxicity, three of respiratory failure, and one of cardiac failure. However, three patients (1 with testicular cancer, 1 with breast cancer, and 1 with lymphoma) did achieve a complete remission, which was maintained at the time of the report, and these patients had been judged unresponsive to conventional therapy.

A similar pattern of relatively encouraging response rates at the expense of considerable toxicity has been seen in the studies reported by the M D Anderson group in 1980 and 1981]7, 45]. These reports detail the treatment of a total of 26

patients, chiefly with small cell lung cancer, testicular cancer, and lymphoma. The drug combination used was one involving high-dose cyclophosphamide and VP16, with or without BCNU and adriamycin. Despite the fact that patients treated were frequently of low performance status, the majority of patients, all of whom had received extensive prior chemotherapy, showed an objective, albeit short-lived response. Although the results are encouraging, it is not possible to conclude that this form of therapy is clearly superior to conventional-dose treatment, since most of the responding patients had not received one of the drugs, i.e., VP16, in conventional doses prior to high-dose chemotherapy, and a proportion might have been expected to respond to that drug alone. The toxicity of this treatment was substantial, with a total of six patients dying as a result of infectious complications of myelosuppression following the chemotherapy; fungal infections in particular were noted to be an important problem. With the aim of reducing toxicity by using this schedule in previously untreated patients, this group recently reported the use of high-dose combination chemotherapy with autologous bone marrow support as initial treatment in a small series of 14 patients with small cell lung cancer [17]. Although the toxicity was acceptable, there was no obvious advantage, in terms of tumour response or survival, to this form of therapy over conventional chemotherapy, and this has prompted these investigators to consider the future use of this form of therapy as 'late intensification' rather than as initial therapy.

Other combination chemotherapy schedules used in high doses in conjunction with autologous bone marrow support have recently been reported in two studies [16, 22]. These include adults with malignant lymphoma and solid tumours, as well as children with a range of childhood tumours. The drugs used have varied according to the tumour type, although cyclophosphamide has been common to all the schedules. The other drugs used include thioguanine, cytosine arabinoside, CCNU, vincristine, actinomycin D, methotrexate, vinblastine, DTIC, and melphalan. This wide variability renders a comparative analysis of results difficult, although in general the best clinical results were obtained with non-Hodgin's lymphoma in adults, and rhabdomyosarcoma and retinoblastoma in children. However, several of these patients, particularly adults with lymphoma, were previously untreated, and in such cases clear superiority for high-dose over conventional dose therapy cannot be established. The reported toxicity was considerable, particularly in the series of children treated with high-dose chemotherapy. Apart from severe myelosuppression all patients had severe gastrointestinal toxicity, probably due to the combination of high-dose DTIC and adriamycin. In addition, one patient with neuroblastoma died 4 months after high-dose chemotherapy with disseminated lymphoma attributable to incidental Epstein-Barr virus infection thought to have been contracted from her father. While there is relatively little information on the long-term effects on the immune response in patients following high-dose chemotherapy, this case report prompts consideration of this potentially important manifestation of toxicity. Gale et al. [20] have documented impaired lymphocyte responsiveness to mitogens in their three long-term survivors following high-dose chemotherapy, and further studies along these lines are certainly indicated.

Overall, one of the most significant features of these studies of high-dose combination chemotherapy in solid tumours is the considerable heterogeneity noted for several important parameters, including the extent of prior therapy and the tumour types treated, as well as the wide variability in combination schedules used. Although hints of superiority, particularly in drug-sensitive tumours, emerge, firmer conclusions will need to be based on larger series of patients with specific tumour types treated with uniform drug schedules. In addition, further information is certainly required on the pharmacokinetic implications of these high-dose chemotherapy schedules, since it is certainly conceivable that major changes in the handling of one drug may result from the concurrent administration of high doses of one or more other compounds [39].

Future Trends

The impression gained from several of the studies reported in this paper is of a definite but limited advantage to high-dose chemotherapy over conventional-dose treatment in terms of response rates in certain tumour types. It remains uncertain, however, that such increases in response rate can be translated into improvements in actual cure rates for patients undergoing this intensive therapy, and the challenge for the future thus appears to be to use this advantage to the greatest benefit in patients with drug-sensitive solid tumours. Several investigators have concluded that this might best be achieved by reserving high-dose chemotherapy for the patients with minimal residual disease following conventional therapy. The hypothetical basis for such an approach comes from the mathematical concept propounded by Norton and Simon [36], which states that at minimum tumour size increased doses of chemotherapy are required to overcome relative drug resistance. Some clinical support for this 'late intensification therapy' comes from studies by Bodey et al. [8] on the treatment of adult acute leukaemia, in which such an approach appears to show some promise.

One solid tumour which certainly lends itself to this form of treatment is small cell lung cancer, which still proves fatal in most patients despite the achievement of a complete response with conventional chemotherapy in a considerable number. The feasibility of treating such patients with high doses of cyclophosphamide has recently been examined by Banham et al. in Glasgow [4]. Seventeen patients who had initially received conventional chemotherapy went on to receive up to 200 mg cyclophosphamide/kg with autologous bone marrow support. Preliminary analysis has shown that of these only two were already in complete remission at the time of high-dose therapy, and further tumour responses were seen in all the remaining 15 patients following high-dose cyclophosphamide. However, response durations were frequently short, and further clinical studies will certainly be required to demonstrate any advantage to this strategy in terms of prolonged survival over conventional treatment.

Conclusions

Experience with high-dose chemotherapy over the past 6 years has permitted the following conclusions to be drawn:

a) *High-dose chemotherapy*, which will generally involve alkylating agents either alone or in combination with other agents, yields highest response rates in those tumours which are initially sensitive to these drugs at conventional doses. Thus, solid tumours in which further studies of this form of treatment may be contemplated are ovarian cancer, small cell lung cancer, testicular cancer, lymphoma, and certain childhood tumours.

b) As reported here, *most of the studies using high-dose chemotherapy* have employed autologous bone marrow support as a means of ameliorating the bone marrow toxicity of this form of treatment. Although no randomized studies have been reported, the evidence suggests that when combinations of two or more myelosuppressive drugs are used at high doses, autologous bone marrow support does enhance haematological recovery, and appears to be clearly indicated. For single-agent therapy the situation is less clear, and the precise doses for each drug at which marrow rescue becomes of value remain to be defined.

c) As stated in the introduction, *other dose-limiting toxicities* are being encountered as bone marrow suppression is being ameliorated. For cyclophosphamide, cardiac toxicity is now clearly the major dose-limiting toxicity, while for melphalan and possibly BCNU, the site where dose-limiting toxicity appears to occur is the gastrointestinal mucosa. In addition, a form of severe pulmonary toxicity appears to limit the usefulness of BCNU, while hepatic toxicity in the form of veno-occlusive disease may well limit the usefulness of mitomycin C and busulphan at high doses.

d) Despite considerable activity in several centres, high-dose chemotherapy has not yet made a major impact on the *curability of solid tumours*. There are some examples, however, where the potential for real benefit clearly exists, but the most appropriate integration of this approach has still to be established. For certain common solid tumours the results of conventional chemotherapy appear to have reached a plateau, so that pending the arrival of new drugs or of novel therapeutic strategies based on a better understanding of tumour biology, high-dose chemotherapy will continue to hold promise.

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Received July 19, 1982/Accepted August 3, 1982