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**Acknowledgements**—The European School of Oncology gratefully acknowledges an educational grant from Chugai-Rhône-Poulenc, which made the meeting possible.

Pergamon

*European Journal of Cancer* Vol. 30A, No. 1, pp. 122–125, 1994
Elsevier Science Ltd. Printed in Great Britain

0964–1947(93) E0007-R

# Dose Optimisation and Dose Intensification in Malignant Lymphoma

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## INTRODUCTION

IT IS self evident that the response of malignant lymphomas to cytotoxic drugs is related to dose insofar as the adminstration of homeopathic dose does not effect remission. The issue, therefore, is whether steps to optimise the therapy given (full dose, on time) or to escalate the doses above that in standard protocols will improve the remission and survival rates.

The work of Skipper and colleagues [1,2] certainly provides a theoretical rationale for the belief that modest increments in cytotoxic drug delivery could effect greater responses: in a number of animal tumour cell lines, there was a log linear relationship between tumour cell kill and administered dose. It must be borne in mind, however, that there are a number of limitations in extrapolating from this type of data to the clinical setting. It can, for instance, be argued that animal tumour models poorly reflect human tumours. The original model used by Skipper assumes that the growth rate of tumours is exponential, which is not the case at all times; this is well illustrated by a consideration of the growth kinetics in multiple myeloma. This same model also assumes that cure is brought about by the elimination of all tumour cells by the cytotoxic agents, not taking into account any host anti-tumour mechanisms.

## DOSE OPTIMISATION

There is no feasible replacement for good clinical data, but, unfortunately, the availability of this type of data is limited. Several lymphoma studies have shown that those patients who do not receive full dose therapy [3, 4] have a lower response rate and survival, and it has been suggested that optimising such therapy with haematopoietic growth factors will improve the response rates. However, it should also be taken into account that failure to give planned therapy is related to the age of the patient, stage of the disease (e.g. marrow involvement) and overall performance status, all of which might predict, independently of drug delivery, for a poor outcome. Definite evidence of the benefits of dose optimisation cannot, therefore, be obtained from retrospective analyses. One randomised trial has been performed in ovarian carcinoma where patients were deliberately given half dose therapy, albeit for twice as long [5]. The responses and overall survival were reduced in the low dose

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Received 26 Aug. 1993; accepted 27 Sep. 1993.

intensity arm. This type of study is unlikely to be repeated deliberately in the lymphomas, but in a British National Lymphoma Investigation (BNLI) trial in advanced Hodgkin's disease comparing alternating LOPP (lomustine/vincristine/procarbazine/prednisone) and EVAP (etoposide/vincristine/doxorubicin/cisplatin) with the same drugs in a hybrid regimen, the change of scheduling in the hybrid regimen led to a lower effective dose, as judged by the incidence of neutropenia [6]. The response rate was also significantly reduced, and the trial was stopped prematurely. The results from such studies indicate that reduction of standard therapy for all patients is likely to lead to a lower response rate, but the situation is not analogous to the scenario where a few patients are forced to receive dose reductions, either for cytopenias or other organ failures. Any trial to address the effects of growth factors in these patients would have to incorporate a very large number of patients. In the interim, it seems reasonable to use growth factors in patients in whom giving planned therapy is proving difficult, although a healthy air of scepticism must be maintained.

## DOSE INTENSIFICATION

Escalation of dose intensity has been the major focus of therapeutic development in high grade non-Hodgkin's lymphoma (NHL) over the last 20 years. Comparison of the results of non-randomised trials [7] suggested that there was a close relationship between relative dose intensity and response rate. Third generation regimens such as ProMACE-CytaBOM (prednisone/doxorubicin/cyclophosphamide/etoposide; cytarabine/bleomycin/vincristine/methotrexate) and MACOP-B (methotrexate/doxorubicin/cyclophosphamide/vincristine/prednisone/bleomycin) appeared to give much better results than standard CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) therapy. However, selection bias can occur in non-randomised trials in single centres, particularly at the point of referral to those centres, and this should be taken into account in this type of analysis. A recently completed South Western Oncology Group (SWOG) trial compared the efficacy of CHOP with m-BACOD (bleomycin/doxorubicin/cyclophosphamide/vincristine/dexamethasone/methotrexate/folinic acid), MACOP-B and ProMACE-CytaBOM in large cell NHL; no significant differences were observed [8]. In the U.K., a trial in patients with histologically aggressive NHL comparing PACE-BOM (prednisone/doxorubicin/cyclophosphamide/etoposide; bleomycin/vincristine/methotrexate—a weekly regimen with similar relative dose intensity to MACOP-B) with CHOP, also revealed no differences in response rate or survival [9]. In high-grade NHL, there is little evidence, therefore, to support a policy of modest dose escalation. In histologically indolent NHL, there is even less evidence available. In Hodgkin's disease, it appears that alternating MOPP/ABVD-like (nitrogen mustard/vincristine/procarbazine/prednisolone/doxorubicin/bleomycin/vinblastine/DTIC) regimens are superior to MOPP alone [10, 11], but whether this in any way relates to the use of mutliple, theoretically non-cross-resistant agents, dose intensification, or merely the introduction of highly effective anthracylines, is not completely clear.

Greater levels of dose escalation have been possible with the aid of autologous bone marrow transplantation (ABMT) or peripheral blood stem cell support. Preliminary results have been very encouraging, but there is again a scarcity of hard data from randomised trials. We have published results from our centre of 155 patients with relapsed or resistant Hodgkin's disease treated with high dose BEAM (BCNU/etoposide/ara-C/melphalen) regimen and autologous bone marrow support [12]. The selection criteria were based on a retrospective analysis of British National Lymphoma Investigation (BNLI) data, and were designed to identify patients in whom the possibility of a 5-year survival was less than 35% [13]. Of the patients treated with BEAM, the actuarial overall survival at 5 years is 55%, with 50% of patients progression-free. Similar results were obtained in a small BNLI randomised trial comparing BEAM and ABMT with several courses of the same drugs at lower doses (mini-BEAM) [14]. The projected progression-free survival at 3 years in the BEAM recipients was 53%, and in those treated with mini-BEAM was 10%. It must be borne in mind, however, that only 20 patients were entered in each arm of this study, and any results from such a small study require confirmation in larger trials. No such trials have yet been reported.

There is a similar lack of randomised trial data examining very high-dose therapy in NHL. In histologically aggressive NHL, five separate scenarios for the use of high-dose therapy need to be considered. Firstly, those patients who fail to respond to first-line therapy or salvage therapy after relapse, and so have 'resistant disease'. In our experience, the long-term survival after BEAM and ABMT in this category of patients is less than 10%, and we do not, therefore, consider dose escalation to be effective. The second category to consider is those patients who respond to front-line therapy, but only achieve a partial remission (PR). An Italian study has randomised this category of patients to receive either very high dose therapy or repeated cycles of DHAP (dexamethasone/high dose cytarabine/cisplatin) chemotherapy [15]. The initial results show a significant advantage in favour of the high dose therapy, but it is not clear from the abstract reports whether this advantage holds true for an analysis based on 'intention to treat'. The third area for consideration is patients who have relapsed following a complete remission (CR), and this category of disease is being explored in the international 'Parma trial', the results of which are awaited with interest. The fourth scenario in which high-dose therapy merits consideration is as part of planned front-line treatment in patients with poor prognostic features at presentation. Several national/international trials are in progress but no data is yet available. Finally, a variant of the above situation is the use of high-dose therapy as consolidation of CR in poor risk patients. Relatively few patients in this group achieve a CR, yet a recent analysis by the BNLI suggests that the relapse rate, once CR has been established, is no greater than in the low-risk group [9]. It can thus be argued that high-dose therapy in remission could only benefit a minority of patients, as most at this stage are already cured, and any procedure-related deaths would thus significantly minimise any benefit accruing to the high-dose therapy. A randomised trial has been performed in this situation by the French/Belgian LNH group [16]. Although there was only one procedure-related death out of the 182 patients who received the high-dose therapy, there was no evidence that the escalated consolidation therapy reduced the relapse rate.

In conclusion, it must be said that the efficacy of dose optimisation and modest dose escalation in the malignant lymphomas is unproven. Even with very high dose therapy, the support for this strategy at the present time is not based upon hard evidence, although it is certainly the view of the author that in Hodgkin's disease, there is a clinically exploitable dose–response curve at the upper end of the dose intensity spectrum.

## THE ROLE OF GROWTH FACTORS

The issue with regard to growth factors is whether they will permit sufficient dose escalation to be of clinical value. There is evidence from randomised trials that rHuG-CSF and rHuGM-CSF (recombinant human granulocyte and granulocyte–macrophage colony-stimulating factors) accelerate neutrophil recovery after ABMT [17, 18], and this may translate into less antibiotic use and shorter stays in hospital. Growth factor mobilised peripheral blood stem cells (PBSC) seem even more efficacious in this regard, and are facilitating high dose therapy strategies [19]. Instead of being restricted to a single course of high dose therapy, which may not be the optimal way to dose intensify, many groups are now considering multiple cycles of high dose therapy with growth factor-mobilised PBSC support [20–22].

The role of the currently available growth factors without haematopoietic stem cell support is less clear. There is no doubt that rHuG-CSF and rHuGM-CSF will allow the planned dose to be given more frequently. In a study from Manchester [23], the use of rHuG-CSF with the VAPEC-B (vincristine/doxorubicin/prednisone/etoposide/cyclophosphamide/bleomycin) protocol for high-grade NHL led to a rise in the total dose given within the 12-week period from 83% of the planned dose in the control group to 95% in the rHuG-CSF group. In a German trial, using rHuGM-CSF after COP-BLAM III (vincristine/cyclophosphamide; prednisone/bleomycin/doxorubicin/procarbazine) therapy in high grade NHL, there was similar optimisation of doses given [24]. It seems unlikely that these relatively small dosage increments could have a detectable impact on overall survival, although in selected individuals there could be a very large impact dose delivery, and for these few patients there could be a major survival impact. Thousands of newly diagnosed patients with NHL would be required to carry out a randomised trial in this small subset of patients. In addition, it is uncertain that sufficient clinicians would withold growth factors if therapy was significantly delayed or large dose reductions were required due to neutropenia. Interestingly, in the rHuGM-CSF study after COP-BLAM III therapy [24], a significant increase in response rate was noted in the poor risk patients who received rHuGM-CSF. There were, however, a disproportionately large number of drop-outs in the rHuGM-CSF arm, and the analysis was not on an intention-to-treat basis.

There is little data in the malignant lymphomas concerning growth factor-facilitated dose escalation above the current standard protocols. The general impression emerging from studies in other diseases, however, is that the maximum dose intensification possible with combination chemotherapy will be in the order of 20–40% [25–27]. There are several reasons for these limitations. Firstly, some studies have chosen regimens where standard doses are close to tolerability in organs other than the haematopoietic system. Secondly, neither rHuG-CSF nor rHuGM-CSF has made an impact on platelet recovery, and at more myelosuppressive drug doses, thrombocytopenia becomes progressively more protracted relative to neutropenia (Fig. 1). The major question is whether this level of dose escalation will achieve significant improvement in response rates and survival, and, if so, to what degree? If the improved response rate was 10%, this would require nearly 1000 patients, and if the benefit was 5%, over 3000 patients [28]. Such studies require a massive investment of time, effort and money, and it must be asked whether the large clinical groups or the pharmaceutical industry think this worthwhile. Before embarking on such a study, it would be necessary to identify a drug combination with proven anti-lymphoma activity which could be most readily escalated without intolerable non-haematological toxicity. It could also be argued that such major studies should be delayed until an effective platelet factor is also available. However, it is probably true that there is not a higher priority array of approaches clamouring to be tested in randomised trials.

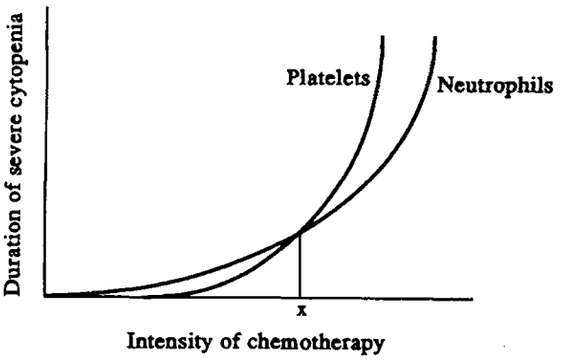


**Fig. 1. Duration of cytopenia and intensity of chemotherapy**

## CONCLUSION

In conclusion, dose escalation with autologous haematopoietic stem cell support may have a role in selected patients with malignant lymphomas, although formal proof is still awaited. Haematopoietic growth factors will largely contribute to this area of treatment by facilitating the mobilisation of peripheral blood stem cells. The value of dose optimisation with standard protocols can probably never be tested, and it thus seems reasonable to use appropriate growth factors when therapy is significantly compromised by myelosuppression. Any impact of currently available growth factors on the escalation of standard regimens without stem cell support is likely to be minor, and consequently any improvement in response will be relatively small. To ascertain such a difference will require very large randomised trials, which will necessitate a major commitment from physicians and the pharmaceutical industry alike.

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**Acknowledgement**—The European School of Oncology gratefully acknowledges an educational grant from Chugai-Rhône-Poulenc, which made the meeting possible.