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Introduction

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In the last five years there has been a significant increase in clinical research into dose escalation of cancer chemotherapy. Peripheral blood stem cell harvesting technology has proved to be an effective and easily adopted method of providing haematological support that does not depend upon a high degree of extra training nor heavy investment of capital. More importantly, the clinical benefits attendant upon its use, particularly reduced bed occupancy and reduced support costs, have made the clinician's task that much easier, both in perception of toxicity and risk to the patient and—very importantly in the current cost-conscious environment—in pursuading managers to allow this area of clinical research to develop.

As in the past, clinical haematological research has been providing many of the leads and indicating the pitfalls and benefits of this sort of approach, encouraging oncologists dealing with solid tumours to exploit the same techniques. Over a decade after studies in solid tumours with dose intensification based upon autologous bone marrow transplantation (ABMT), dose intensification is again being looked at as a strategy for managing other solid cancers. At the beginning of the 1980s small cell lung cancer was perceived as an appropriately chemosensitive tumour for study of the potential benefit of 'consolidation' high-dose chemotherapy supported by ABMT. Despite initial enthusiasm, convincing benefits did not emerge from the small-scale trials of dose intensification and it is quite possible that these outcomes may be repeated disappointingly this time round. Perhaps, however, we have learned some valuable lessons about the shortcomings of dose intensification therapy from our previous experience and above all have adopted possibly better strategies as well as having better tactical weapons!

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In his review of haematological malignancies, Dr Sweetenham has reiterated the evidence for a lack of obvious benefit from dose intensification within the conventional dose range. Consequently growth factors used to accelerate therapy within the conventional range have had a limited and clinically probably inconsequential impact upon disease-free survival and overall survival when assessed in randomised trials. The clinical results have to be interpreted, however, in the light of the impact of the confounding variables of performance status, age, and bone marrow involvement in haematological malignancies—all of which affect the dose delivered, response and survival. There are at last some survival benefits emerging from true dose escalation supported either by ABMT or peripheral blood stem cell transplantation (PBSCT). The mature results of international randomised trials such as the PARMA Study are eagerly awaited.

Ranson and Thatcher argue that in lung cancer studies intensification has been limited to a less than 50% increment of dose. They examine the concept of cross resistance and the importance of multiple-agent chemotherapy in overcoming the problem of somatic mutation-associated resistance. Clinical studies differ in their endpoints and many studies are simply too small to provide clear answers to the questions they set out to address. Important observations on the handling of drugs indicate the importance of pharmacokinetic monitoring which, when performed, indicates enormous inter-individual variation in dose levels from regimens based upon simple surface area calculations alone. They also point to the importance of scheduling effects from the evidence of the action of alkylating agents such as iphosphamide and cyclophosphamide. In general, however, these studies suggest that the failure of rate intensification is basically a failure adequately to destroy enough cancer cells.[1]

The comments from Ranson and Thatcher amplify the commentary of Professor Newland, who reviews the current understanding of platelet physi-

ology and cytokine control thereof. We still have a rather sketchy view at present of appropriate targets and a burgeoning portfolio of cytokines with which to attempt manipulation of this blood element. It appears that more research is required based on a better understanding of cytokine interaction and sequencing.

Mainwaring and Gore emphasise the value of large scale overviews in assessing the impact of different chemotherapies in the management of epithelial ovarian cancer. Drug selection is crucially important and demonstrates the value of cisplatinum and carboplatinum. The impact of true dose escalation requires randomised trials and the most promising case appears to be chemo-sensitive disease in first remission.

In a review of germ cell tumours de Mulder and de Wit illustrate that certain miminum criteria of cisplatinum intensity have to be achieved in respect of dose. However alternating combination chemotherapy or accelerated dose intensity (supported by cytokines) have not shown increased cure rates in poorer prognosis disease. As in other reviews the authors favour the use of true intensification therapy only in poor prognosis disease as a component of initial therapy.

The solid cancer which has created the widest public and professional interest in the last two to three years has been breast cancer. This is in part undoubtedly due to political activity by and on behalf of patients in North America and increasingly in the UK; but undoubtedly is also due in part to the hints of clinical benefit from uncontrolled North American studies of dose intensification in the adjuvant setting as well as advanced disease. From the latter area some very mature data indicate that prolonged disease-free survival is possible following high-dose chemotherapy in clinical situations where this would not be predicted from conventional-dose therapy. It is also increasingly recognised that with accrued experience the dangers inherent in such approaches are gradually diminishing, to low single figures of risk of acute mortality as a complication of high-dose therapy. This in turn is partly due to the adoption of peripheral blood stem cell harvesting to limit the duration of neutropenia and the consequent risk of acute sepsis. However, even within the standard dose ranges, although some of the evidence is conflicting, there is increasing conviction that well established agents like 5-fluorouracil (5-FU) can usefully be reexamined for optimal scheduling despite nearly 40 years of clinical experience in a variety of common cancers. Thus particularly in the UK there is an increasing interest in the use of infusional 5-FU, which may be the most effective way to increase the total dose but also optimise its biochemical target inhibition. The biggest international effort however has been put into improving the cure rate of breast cancer in the 'poor-prognosis' adjuvant setting where the risks of recurrence and death are extremely high. Thus patients with multiple node involvement are being considered for randomised trials of conventional compared against high-dose chemotherapy and the results will be obtained and be assessable over the next five to ten years. PBSC technology however permits further exploration of altered and intensified dosing hitherto not possible from the ABMT technology. Thus provocative results are coming from centres such as the Memorial Sloane-Kettering Institute of multiple high-dose chemotherapy rescued by successive PBSCT infusions. Based on laboratory and theoretical models this may be the best strategy for obtaining cure as opposed to merely producing a high rate of complete remissions. A review of laboratory experiences is a worthwhile exercise for the sceptical clinician. What we know of high-dose chemotherapy and the curability of clinical cancer seems to validate the existing models of dose response and curability in both *in vitro* grafts and xenografts. For the present it is not illogical to explore the potential for multiple high-dose chemotherapy for advanced disease. In the adjuvant setting we must optimise schedules of dose intensification in the attempt to eradicate micro metastatic disease in the high-risk patient.

Despite widespread availability and the relatively simple technology involved, cost is going to be an issue for the foreseeable future. If high-dose chemotherapy begins to show clinical benefit in solid tumours, the cost implications in terms of immediate expenditure for any of the western economies will make it an important healthcare issue. What may seem to be major benefits to the individual physician, and above all to the patient, may seem to be marginal to society at large. We are currently operating in a healthcare system where pressures from central government are to contain and even cap total healthcare spending. These constraints only serve to emphasise the need to define better the potential benefits of such approaches. Greater clarity will come only from enthusiastic support for randomised controlled clinical trials.

Reference

1. RCF Leonard. Small cell lung cancer – current status (Editorial). *Br J Cancer* 1989; **59**: 487–489.