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Comments and Critique

Treatment of Advanced Neuroblastoma

IN THE past 20 years great strides have been made in the treatment of most common childhood cancers. The long-term survival rates of 70–90% in Wilm's tumour and acute lymphocytic leukaemia are examples. An exception is advanced stage neuroblastoma in which disease-free survival remains less than 20% [1]. This poor survival rate has prompted most investigators to use extremely high doses of chemotherapy in an effort to eradicate the tumour. In the present issue, two groups of investigators report both the benefits and toxic effects of such an approach. The two articles record response rates, toxicity and duration of disease control following aggressive, multiagent chemotherapy with vincristine, melphalan, etoposide and carboplatin (OMEC), followed by reinfusion of autologous bone marrow (ABM). In the report by Dr Gordon, *et al.* from Newcastle, the OMEC regimen is given in 1 day. Corbett, *et al.* from London use the same drugs, but they are delivered over 5 days, and somewhat higher doses are used. Both studies report severe toxicity. In addition to the anticipated reversible marrow aplasia, there was severe mucositis, infection, renal and hepatic toxicity, encephalopathy and, in some patients, combined system failure. In both studies, approximately 20% of the patients died of acute treatment-related toxicity. The conclusions reached by the two groups are rather different. Those in Newcastle believe their results to be promising, and record 6 of 11 children (55%) given OMEC to be disease-free at 1 year. The severe toxicity encountered, however, required some modification of the regimen. The authors in London conclude that the 5-day regimen is too toxic to be used on a large scale. Disease-free survival of 2/18 or 11% was less effective for disease control, and not better than melphalan used alone. Although survival of neither group of patients is likely to be stable at this stage, the difference between the two achieves statistical significance at $P < 0.05$. How can one explain this discrepancy? The patients were given different induction regimens, but a similar acute toxicity was noted. Because of the manner in which the pretransplant, supralethal chemotherapy was given, the study with the higher disease-free survival rate actually gave somewhat lower amounts of chemotherapy. It is possible, but unlikely, that a 1-day infusion with a lower dose is more active than a 5-day infusion. However, neither article comments on whether or not the autologous marrows were purged with monoclonal antibodies to free them of neuroblastoma cells before infusion. It is possible that the difference in the recurrence rate was due to contamination of infused marrows.

We certainly agree with both groups of investigators that high-risk neuroblastoma requires aggressive treatment, and to date, the various treatment strategies have not been as successful as any of us would wish. Treatment schedules are usually subdivided into induction and consolidation; at present, both phases are unsatisfactory. Not enough children achieve a stable remission to make them eligible for consolidation (< 50%). Children undergoing both induction and consolidation, with or without marrow rescue, have a long-term survival rate of 15–20%. Thus, 80–85% of such children are treatment failures. We share the frustration of both groups with the lack of success of many regimens, although even this meagre cure rate of high-risk neuroblastoma is a significant advance.

It is possible that, with the chemotherapeutic agents currently available, the limits of what can be achieved with drugs alone have been reached. We need to move from multiagent chemotherapy to multimodal therapy and add other forms of treatment to the total program. Failure is most likely due to residual viable malignant cells which have withstood the effect of multiple drugs, even those with different modes of action. There are several avenues being explored to overcome this resistance. Irradiation can be given externally to the total body, or targeted by radiolabelled metaiodobenzylguanadine (MIBG), or monoclonal antibodies. The cells can be persuaded to mature and become non-malignant ganglion cells with differentiating agents such as retinoic acid. The body's immunity can be stimulated to overcome the residual malignancy by means of gamma-interferon or lymphocyte activated natural killer cells. Unradiolabelled monoclonal antibodies may attack the malignant cells themselves, or render them susceptible to cell-mediated killing. All these methods are currently under investigation in small studies, and some are being incorporated into larger multi-institutional studies. An example is the clinical trial for children with high-risk neuroblastoma being conducted by Children's Cancer Study Group. The double randomization includes a comparison of intensive chemotherapy consolidation with or without bone marrow rescue and maintenance with or without retinoic acid [2].

We wish Corbett, *et al.* had expanded on the statement that melphalan alone is the only regimen with proven efficacy. The reference given for this statement reports consolidation of 12 children with stage III and IV neuroblastoma with high-dose melphalan and ABM [3]. There were 3 survivors. The authors concluded that the median survival was longer than an historical control group receiving conventional therapy, but the survival rate was no better. We doubt if any investigator these days would be content to use a single agent for consolidation. We believe that a multimodal approach is more likely to be successful and, in our current program in Philadelphia, we include both [^{131}I]MIBG and total body irradiation at the time of bone marrow transplant (BMT). Until MIBG has proven efficacy, we would be reluctant to omit the external irradiation. Although it has its undesirable side effects, as does chemotherapy, it is an effective treatment of neuroblastoma, and we believe its inclusion may be responsible for the absence of late relapses encountered in the Philadelphia experience. The longest time to relapse after BMT continues to be at 22 months in more than 60 patients who have now been at risk for up to 12 years.

We would like to add a note of caution here when planning aggressive programs of chemotherapy for children with high risk neuroblastoma. The patient population must be defined carefully if such a regimen runs the risk of incurring fatal toxicity. A protocol that accepts children over the age of 1 year with stage III and IV neuroblastoma, without further definition, could include a certain number—admittedly small—who have an excellent prognosis. Many prognostic factors based on biologic standards have been described. These include elevated serum levels of LDH, ferritin, neuronspecific enolase and *p*-glycoprotein; genetic abnormalities such as *N*-Myc amplification, ploidy, and l–p deletion; and the histologic grade of the primary tumour. We have found that the combination of age, stage, serum ferritin, and histologic grade clearly define a prognostic index with 93% confidence limits [1].

Until survival rates improve, we reluctantly must err on the side of aggressive therapies, so that more children, on balance, are cured, and not focus too much on the side effects of treatment. In Philadelphia we are trying to combine different modalities to increase cell kill, but to some extent reduce the toxicity. For example, we have substituted thiotepa for melphalan, and included granulocyte–monocyte cell-stimulating factor (GM-CSF) in the post-transplant period. Since instituting this regimen, we have had one toxic death in 20 patients and so far have no apparent decrease in efficacy.

It is obvious there is a need for a continuing search for the correct balance of treatments that can destroy the disease and not the patient.

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Learning from Cl-941 about Pharmacokinetically Guided Dose Escalation

OVER THE past 6 years, strategies for phase I trials have been profoundly revised. The revision stems from the original contribution of Collins and co-workers in 1986, who proposed that preclinical pharmacokinetic data should be used to guide phase I studies [1]. This proposal was aimed at correcting some inherent problems that severely limited the conventional approach of such investigations.

Due to the narrow therapeutic index of most anticancer agents, the initial clinical evaluation of a new drug in oncology is traditionally aimed at definition of the maximum tolerated dose (MTD). Unfortunately, the MTD cannot be predicted on the basis of toxic doses in animals [2]. Furthermore, the short-term and long-term toxicity of anticancer agents is potentially so severe that the MTD must be defined in patients instead of healthy volunteers. With regard to safety, the traditional design of phase I trials in oncology required the selection of non-toxic doses for starting human testing (usually 1/10th of the mouse LD_{10} [1, 2]), and the use of empirical dose escalation to minimise the risk of major drug-related morbidity or mortality while approaching the MTD. Inherent in this strategy is an unpredictable length of the escalation process, and the ethical problem that many patients are exposed to ineffective suboptimal doses [1]. Lengthy phase I trials have been, and still are, very frequent [1, 3], adding to the ethical burden of investigators, to the delay of evaluation of new therapies and to the deception of "informed" patients who consent to experimental treatments only because they hope to benefit from them.

The starting point of Collins and colleagues' proposal was the pharmacodynamic hypothesis that equal toxicity corresponded with equal drug concentrations. More specifically, the pharmacodynamic concept meant that the dose-limiting toxicity quantitatively correlated with, and could be predicted by plasma drug concentrations in different species. The practical implication was that investigators could know the end-point of phase I trials from preclinical studies before starting to test in man [1]. With the exception of the antimetabolites, retrospective analyses confirmed that even large discrepancies between the mouse LD_{10} and the human MTD were compensated for when plasma drug exposure, expressed in terms of area under the concentration vs. time curve (AUC), was compared in the two species at these doses [1, 4, 5]. Having shown that pharmacokinetic variation was a major reason for inter-species differences in maximally tolerated doses, Collins *et al.* proposed that investigators set the AUC at the mouse LD_{10} as the target of human testing at which the MTD should correspond, and determine the size of the dose escalation steps by measuring how far the patient AUC at a safe entry dose was from the target AUC [1].

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