Pergamon

European Journal of Cancer Vol. 31A, No. 2, pp. 134–136, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(95)00035-6

"Megatherapy" for Advanced Neuroblastoma—Rationale and Role

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In 1977, the late Professor Tim McElwain suggested that high dose consolidation chemotherapy ("megatherapy") might destroy tumour cells resistant to conventional doses of the combination induction treatment (cyclophosphamide, vincristine and doxorubicin) then in use for children with advanced neuroblastoma and thereby improve their prognosis. He chose single agent melphalan "megatherapy" for three reasons. First, there was already preliminary evidence that high dose melphalan (HDM) was active in another tumour of neural crest origin—malignant melanoma [1]— second, bone marrow suppression and mucosal damage were the only common toxicities of HDM, and could be overcome, and, third, because its short plasma half life (< 2 h) meant that autologous bone marrow, harvested beforehand, could be safely reinfused as soon as 8 h after administration of the drug. Preliminary results of a pilot study indicated that the median survival of patients with advanced neuroblastoma might be extended [2]. Many single arm megatherapy studies, of which HDM has been the most constant "ingredient", have now been carried out by national and international groups in Europe and the United States [3–11] and no obvious difference noted between the outcome of patients "rescued" by allogeneic versus autologous bone marrow or with "purged" compared with "unpurged" autologous bone marrow. However, there has been little critical analysis of the real contribution of this form of treatment and the cost:benefit ratio has been assessed only twice in randomised studies.

The first of these trials, carried out by the European Neuroblastoma Study Group (ENSG) and known as "ENSG1", has been completed and the preliminary results published [12]. Patients with stages III or IV neuroblastoma* received "OPEC" (vincristine, cisplatin, teniposide/etoposide and cyclophosphamide) induction chemotherapy. Surgical removal of the primary tumour was carried out in those who, according to preset criteria, responded sufficiently well to OPEC. 65 patients, carefully stratified by age and stage, were then randomised to receive either a single high dose of melphalan (180mg/m^2) or no further treatment. The final results of ENSG1 showed that HDM improves event free survival for the whole cohort (J. Pritchard *et al.*, unpublished data). For overall survival and for stage IV patients, taken alone, the trends were strongly suggestive of a favourable effect of HDM, although the differences did not achieve formal statistical significance, probably because of the relatively small number of patients randomised in each sub-group. So HDM is "better than nothing" after OPEC and surgery, but is it better than continued administration of conventional dose chemotherapy? This related but distinct question is addressed by the Children's Cancer Study Group Trial (CCG-3391), now in progress in the United States (K. Matthay *et al.*, personal communication). In this study, stage 4 patients receive the same induction treatment and surgery. "Responders" are then randomised either to HDM-containing megatherapy or to continuing intensive but not marrow-ablative induction treatment. The outcome should be known in 1–2 years.

At this point it is worth restating the premise upon which, back in the 1970s, these studies were based. Using a Skipper/Schabel graphical format [13], Figure 1 illustrates a theoretical

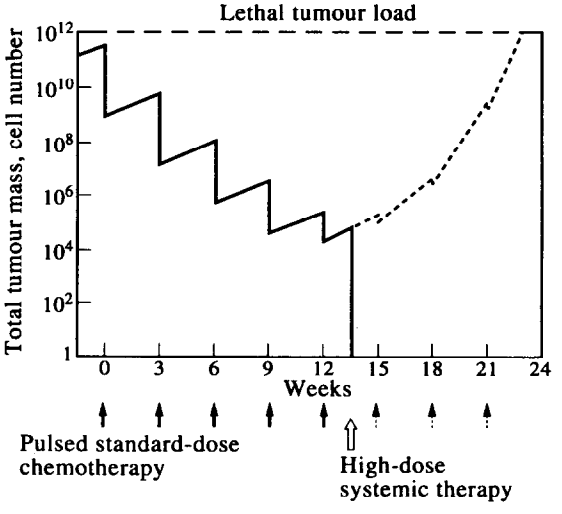

Figure 1. Rationale for "megatherapy" in advanced neuroblastoma. The lethal tumour load in a young child with stage 4 neuroblastoma is probably between 10^{12} and 10^{13} cells and, at diagnosis, the load is often only just below this number. The first pulses of "standard dose" induction chemotherapy cause 2–3 log cell kill (solid line) but, thereafter, drug resistance usually develops and the tumour starts to grow again (broken line) despite more courses of "standard dose" treatment (broken arrows). High dose systemic therapy (open arrow) may overcome drug resistance, and cure the patient.

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* This trial was designed before the introduction of the International Neuroblastoma Staging System (INSS), which uses Arabic numerals.

but plausible scenario for a child with newly-diagnosed stage 4 neuroblastoma. Initially, a majority of tumour cells are sensitive to standard doses of chemotherapy, with 2–3 log depletion of the starting tumour mass with each course. After several months, drug-resistant clones—present *ab initio* or evolving during treatment—persist despite the chemotherapy so that each course yields a "diminishing return". If the drug-resistant cell population proliferates, the therapist loses ground by continuing this treatment because residual disease, albeit "invisibly", starts to grow again. The whole justification for megatherapy is that it might convert "chemoresistance" into "chemosensitivity" simply by dose escalation. Pioneering work in Seattle suggested that this hypothesis translated into clinical benefit in the treatment of acute leukaemia and the era of "marrow transplantation" using multiagent myeloablative regimes, particularly high dose cyclophosphamide and total body irradiation (TBI), was ushered in [14]. However, different tumours behave differently and direct extrapolation to neuroblastoma has to be justified. It is quite possible for instance that, *in vivo*, neuroblastoma resistant to one high dose agent is cross-resistent to multiagent high dose megatherapy regimes. The available evidence suggests that this, in fact, is the case because the outcome for patients with stage 4 disease seems the same regardless of whether HDM is given alone or combined with a variety of other high dose drugs and/or TBI [3–12]. Of particular concern is that the multi-agent regimes are more toxic—often much more toxic—than HDM given alone and some children have died as a consequence. In summary, the cost:benefit ratio is in favour of HDM, following OPEC chemotherapy. More complex megatherapy regimes are not justified, except as small feasibility studies or in randomised trials. Nor is the use of HDM "engraved in stone". In a current ENSG randomised trial—'ENSG5'—standard induction therapy, with 21 day intervals between courses, is compared with an induction regime—"rapid OPEC" [15]—that contains the same drugs at twice the "dose intensity". All "responding" patients have their primary tumour resected then receive HDM with autologous bone marrow support. If the "rapid OPEC" arm has a better outcome, i.e. produces more effective initial "tumour debulking", the contribution of HDM will have to be assessed anew. It is quite possible that the population of tumour cells ablated by the more intensive induction regime is the same as the population of cells ablated by HDM (and/or other agents) after "standard intensity" induction treatment.

What alternative management approaches are there? In this issue of the *European Journal of Cancer* (p. 252) Dr Gaze and his colleagues from Glasgow suggest that the potential of radiotherapy (neuroblastoma is known to be a radiosensitive tumour [16]) has not been fully exploited. They describe a pilot study of a novel megatherapy regime, in which HDM is combined with TBI, local field irradiation of the primary tumour and systemic administration of ^{131}I metaiodobenzylguanidine (^{131}I mIBG) [17].

A refreshing aspect of the Glasgow study is that the design of the experimental regime is based on systematic *in vitro* studies of the effect of radiotherapy, including targeted radiotherapy, on neuroblastoma cell lines and, to reflect the three-dimensional composition of *in vivo* tumours, on tumour spheroids. Too many other megatherapy regimes used in neuroblastoma have been concocted in the naive belief that "more must be better", without supporting scientific evidence. mIBG is structurally similar to guanethidine and is actively taken up by catecholamine-secreting cells and stored in cytoplasmic neurosecretory granules. The molecule remains stable when radioactive iodine isotopes (for example ^{131}I) are substituted for "cold" iodine atoms and can safely be administered intravenously. Successive imaging studies have shown that ^{131}I is successfully "targeted" by mIBG into most neuroblastoma primary and secondary tumours *in vivo*. Moreover, ^{131}I mIBG treatment yields a response rate of around 30–40% in children with chemotherapy-resistant tumours [18, 19] and an even higher response rate in untreated patients [20], making it one of the most active single agents available. Of the 5 "poor prognosis" patients treated by Gaze and associates, 2 were alive at the time of their report, with off-treatment follow-ups of 17 and 18 months, respectively.

The problem with the Glasgow approach is that nasty tumours like neuroblastoma do not necessarily behave "according to the rules"! For instance, drug access to cells in culture or in spheroids is not dependant on a vascular supply, cells derived from cell lines are usually not representative of *in vivo* tumour and, whatever "modelling" may suggest, it is an assumption that such findings extrapolate into clinical practice. Toxicity of complex regimes is another problem, not assessable *in vitro*. The Glasgow regime was accompanied by quite severe haemopoietic and mucosal toxicity. The use of peripheral stem cells and bone marrow growth factors may accelerate haemopoietic recovery but it is possible that radiotherapy delivered in this fashion may damage bone marrow stroma (the "soil" in which the infused precursors must grow) more than chemotherapy-only regimes. Parenteral feeding is used to circumvent the nutritional consequences of combined TBI and HDM but mucositis can be severe and very unpleasant and, at present, there are no "mucosal stem cell CSFs" on the horizon. In the longer term, hypothyroidism, "second tumours" and other serious late effects of radiotherapy are of real concern. Other vectors, especially monoclonal antibodies [21], are available for delivery of ^{131}I *in vivo* to neuroblastoma but, although successful imaging has been achieved, experience with treatment is much less than with ^{131}I mIBG and most of the same theoretical and practical problems apply.

What of the future? Despite a steady flow of pessimistic statements, there is evidence that neuroblastoma is slowly yielding to treatment. The overall cure rate (all stages and all ages) is now around 50% [22, 23] and 10–20% of those patients in the worst prognostic group—those with stage 4 disease, aged $>$ 1 year at diagnosis, can be cured [24]. For those children who do not survive, median survival is now considerably longer than it used to be. Thoughtful approaches, such as that of Dr Gaze and colleagues, based on sound laboratory data and/or on accurate clinical observation, are needed to take things forward. One recent clinical observation is particularly intriguing. Some patients with advanced neuroblastoma resistant to conventional 3 weekly pulsed etoposide-containing chemotherapy, such as OPEC, have had prolonged responses to single agent etoposide given in a completely different schedule—twice-daily oral administration for 21 out of each 28 day cycle. This method of etoposide administration was "borrowed" from the treatment of small cell lung cancer—another tumour derived from the neural crest [25]. If this observation can be confirmed, a randomised trial of these two methods of etoposide delivery will be needed. The possible contribution of cis-retinoic acid, as a potential "maturation" agent, is already under study in Europe and the U.S.A. This author has the feeling that the blockbusting approach, represented by megatherapy, will be out of fashion within a few years. Until then, however, Tim McElwain's strategy prevails: single agent HDM with autologous bone marrow or peripheral blood stem cell support is part of the

standard treatment for > 1 year old children with stage 4 neuroblastoma.

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Acknowledgements—I thank Louise Palmer and Judith Russell for expert help in preparing the manuscript for publication.