

Evolving role of myeloablative chemotherapy in the treatment of childhood brain tumours

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Summary:

Primary brain tumours, a heterogeneous group of cancer that constitute the second most common cancer in childhood, were historically treated with neurosurgical resection and radiation therapy. Chemotherapy has proven to be beneficial for some histological types, which has since led to exploration of the role of high-dose chemotherapy and haematopoietic stem cell rescue. Patients with high-grade glial tumours, primitive neuroectodermal tumours and high-risk medulloblastoma usually fare poorly. The indicators of bad prognosis are metastatic status, extent of resection and age. Children <3 years at diagnosis carry worse prognosis. Rare cancers such as ependymoblastoma, atypical teratoid rhabdoid tumour and choroid plexus carcinoma have a dismal prognosis regardless of the above-mentioned indicators. The use of myeloablative therapy (MAT) has been investigated to improve the rate of long-term DFS, as well as to reduce and delay in the youngest children the use of the craniospinal irradiation associated with unacceptable late effects. We will overview the literature regarding patients with 'good and uncertain indications' to MAT. Ependymoma and brain stem tumours, for which the available data discourage the use of MAT, are excluded. Finally, we will summarize a single Institution experience (Giannina Gaslini Children's Hospital, Genoa) with MAT in the period 1997–2003.

Bone Marrow Transplantation (2005) 35, S31–S34.

doi:10.1038/sj.bmt.1704841

Keywords: brain tumours; childhood; autologous stem cell transplantation

patients with various types of solid tumours. Recognising the chemosensitivity of some types of brain cancers has led to the use of HDCT to increase the steep dose–response curve of some drugs, to cross the blood–brain barrier in a better way and to avoid or at least to reduce radiotherapy (RT) administration to infants and very young children.¹ Various agents have been combined in preparative regimens, based on the known efficacy in brain tumour treatment (such as BCNU), on the demonstrated dose–response effect (carboplatin, cyclophosphamide, melphalan), or because of their ability to penetrate effectively the brain (busulphan, thiotepa and etoposide). Thiotepa, associated with melphalan or busulphan, or carboplatin administered using the Calvert formula plus etoposide are presently the most commonly employed combinations.² In the first studies, two or three agents were often included in the most frequently used myeloablative protocols (ie thiotepa/carboplatin/etoposide) and the effect of each single agent on response was difficult to define. Synergistic toxicity occurred. Few studies report on the efficacy and toxicity of single agents used at high doses. Limiting factors include severe and life-threatening toxicity. Most of the first studies were performed on relapsing patients, while, since the late 1990s, few studies employing up-front myeloablative therapy (MAT) in selected series of patients have been reported.^{3–7} They showed encouraging results and less toxicity when the combination of drugs was conceived to be used as early intensification during induction rather than as consolidation in patients already in CR or VGPR. An other additional advantage of the up-front MAT after short and intensive induction chemotherapy (CT), especially in patients virtually never presenting bone marrow infiltration, is the possibility of collecting an amount of peripheral blood progenitor cells (PBPC) enough for repeated courses of MAT and even as rescue of haematological toxicity after craniospinal irradiation (CSI).

High-dose chemotherapy (HDCT) regimens

HDCT with stem cell rescue was first used as consolidation to front-line therapy, or as salvage treatment in paediatric

'Good indications'

Medulloblastoma (MB) and peripheral neuroectodermal tumours (PNETs). MB is one of the most frequent malignant tumours in the paediatric age, and its peak of incidence is between 5 and 10 years of age. Metastatic

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status and age are the most widely accepted unfavourable prognostic factors, while the prognostic role of gross residual tumour after surgery is controversial. Despite their histological similarity to MB, supratentorial PNETs represent a more heterogeneous group of patients in whom site of origin may also play a role in response to treatment, due to its influence on the resectability. MAT for PNETs has been widely applied and results are often reported along with those of MB making a more precise analysis of its role difficult. Trials performed by the CCG and by the International Society of Pediatric Oncology/German Society of Pediatric Oncology reported an Event free survival (EFS) of $\approx 60\%$ at 5 years for MB (standard risk MB in most cases) after conventional treatment with neurosurgical resection, radiation therapy and standard dose CT.^{8,9} On the contrary, the prognosis is very poor for children with recurrent or refractory to initial therapy MB, or disseminated presentation at diagnosis.^{10,11} The French group reported 20 young children who were treated after relapse with busulphan and thiotepe, followed by radiation therapy. Among the 16 patients with measurable disease at MAT, a 75% response rate was observed, with only one transplant-related death. Overall, the EFS at 31 months was 50%.¹² Dunkel *et al*¹³ reported that seven out of 23 patients (30%) are event-free survivors at a median of 54 months post HDCT with carboplatin, etoposide and thiotepe, with three deaths caused by treatment-related toxicities. Other reports associated patients with supratentorial PNETs and children with MB. The Mason paper,⁴ regarding 62 newly diagnosed brain tumours, report that in responding patients, the 2 year (from MAT) EFS is 45% for MB (11 patients) and 64% for PNETs (10 patients), after consolidation with carboplatin, etoposide and thiotepe association. Strother *et al*⁵ showed a 2-year PFS of 73.7% ($\pm 0.5\%$) for 19 MB and PNET high-risk patients treated with four sequential cycles of cyclophosphamide, cisplatin and vincristine, and stem cell rescue. Response to initial treatment and the absence of bulky disease seem to be correlated with better outcome. Perez-Martinez *et al*¹⁴ recently reported the outcome of seven children younger than 4 years suffering from MB and supratentorial PNETs. As March 2003, four patients (MB) are alive and disease free; one patient has PR (PNET) and two patients (one MB and one PNET) died from disease progression at 12 and 5 months after MAT. The authors assumed that MAT might be useful as consolidation therapy. A recent paper of Broniscer *et al*¹⁵ describes the experience of 17 cases with relapsed noncerebellar PNETs (eight of them with pinealoblastoma, eight in other supratentorial locations and one in the cauda equina) treated with thiotepe, etoposide \pm carboplatin followed, in six cases, by RT. All patients who achieved a radiographic response worse than a CR died (notably, 7/8 pinealoblastoma), while five out of eight supratentorial PNETs remain alive without tumour recurrence (EFS at 5 years, 0 *vs* 62.5%, $P=0.0065$). Surgery at relapse and post MAT RT seem to have a positive impact on 5-year EFS ($P=0.006$ and 0.01, respectively), confirming the role of the multimodal approach to brain tumours. These data are in contrast with those published in 2003 by Gururangan *et al*, who showed a 4-year PFS of 69% in a cohort of 12 patients with pinealoblastoma, including six

children, four of them are long-term survivors after MAT with Cyclophosphamide and melphalan.¹⁶

'Under investigation'

High-grade gliomas. Malignant gliomas include astrocytic malignant tumours (grade III astrocytomas or so-called anaplastic astrocytoma, glioblastoma multiforme) and several mixed tumours (anaplastic oligoastrocytoma and anaplastic gangliogliomas). Tumours containing oligodendroglial components tend to be more chemosensitive also to standard CT (VCR + CCNU + procarbazine association or temozolamide) according to the trials employed in adults where these tumours are a lot more common. Chemosensitivity of anaplastic astrocytoma and glioblastoma is more controversial in adults as in children; a peculiar group of patients in paediatric age is represented by infants harbouring high-grade gliomas. In fact, they seem to have a different biological behaviour and a greater chemosensitivity with complete response after standard CT is documented, and so in this subgroup HDCT can be considered as second-line treatment. Reports on astrocytomas are more common in adults than in children with the largest experiences being those of Biron *et al*¹⁷ and of Durando *et al*,¹⁸ both using high-dose BCNU as preparative regimen. The results are quite disappointing and the role of MAT in relation to the different histological subtypes and to completeness of surgical resection is difficult to assess. Heideman *et al*³ treated 13 children with malignant gliomas with thiotepe and cyclophosphamide plus RT, showing that, despite an objective response rate of 31%, survival of patients with bulky residual disease after surgery is not better than that reported for conventional treatment regimens. A similar response rate was observed in 22 children by Bouffet *et al*,¹⁹ but similarly the conclusion was that for children with high-grade gliomas, MAT is no better than conventional treatments. In countertendency, the CCG group noted that the only five surviving children out of 45 patients with recurrent brain tumour were affected by high-grade gliomas,²⁰ and on this basis ran a pilot phase II study with carmustine, thiotepe, etoposide and involved field RT for children with glioblastoma multiforme. The survival rates at 2 years for the 11 children enrolled was $46 \pm 14\%$, but the study needed to be closed because of the excess of nonfatal grade III or IV pulmonary and neurological toxicity.²¹

Atypical teratoid/rhabdoid tumour (AT/RT). AT/RT is a malignant embryonal tumour. Despite a multimodal approach, prognosis is still very poor with virtually no survivors in the first published series and very few in the most recent reports.²² MB-like CT regimens, even the ones including high doses of drugs do not seem to be effective, as shown by the experience of the Italian cooperative Study of the AIEOP.²³ In the updated series of this group, 29 cases are registered in the period 1995–2003; 11 patients were treated with conventional infant CNS Protocol and 13 with regimens including consolidation with MAT. Five children received no treatment for parental refusal or only palliative therapy. EFS at 5 years is 18.2 and 16.7% ($P=0.61$), respectively. The association of sarcoma-like induction

Table 1 Main characteristics of a series of 46 cases treated with MAT at Giannina Gaslini Children's Research Hospital (1997–2003)

Type of tumour	#	M/F	Infants/> 3 years	#CT+ RT/#CT alone	#A&W
Medulloblastoma	29	20/9	13/16	26/3	22 (75%)
Supratentorial PNETs	6	3/3	4/2	3/3	5 (83%)
Malignant gliomas	4	0/4	2/2	2/2	2 (50%)
Miscellaneous	7	6/1	4/3	3/4	1 (14%)

RT = radiotherapy; CT = chemotherapy; A&W = alive in complete remission.

regimens, followed shortly afterwards by MAT and stem cell rescue, is currently under evaluation; recent case reports have shown prolonged survival (ML Garrè *et al*, personal communication).

Experience at the Giannina Gaslini Children's Hospital

Since July 1997, children with poor prognosis brain tumours have been treated at the Giannina Gaslini Children's hospital with a three-step multimodal protocol. Criteria for enrolment included: relapse after conventional therapy, post surgical residual disease, metastatic spread, unfavourable histology and age <3 years. Phase A (induction) consisted of four cycles of CT (methotrexate + vincristine, hd etoposide, cyclofosamide + vincristine, and carboplatin + vincristine); this sequential intensive schema was at first applied in Milan at Istituto Nazionale dei Tumori for patients with poor-risk MB. Responding children were then treated with two consecutive myeloablative cycles with carboplatin + etoposide and thiopapa + melphalan (Phase B). Radiotherapy (Phase C) was given at haematological recovery to children older than 3 years or in the presence of residual disease. In children >3 years with MB, CSI was delivered at a dose of 24 Gy, while posterior fossa (PF) received 54 Gy and metastatic sites were boosted. Children <3 years received irradiation only if metastasis or residual disease were observed prior to beginning treatment. Volumes and doses were tailored to age at RT, residual disease or metastasis. Children in CR after surgery and at the end of Phases A and B did not receive RT. Between July 1997 and December 2003, a total of 46 cases with malignant brain tumours were treated. Tumour type and main characteristics are shown in Table 1. Best results were obtained in MB and PNETs; in this group, 27/36 cases are alive in CR with a median follow-up of 36 months. In high-risk MB patients above 3 years of age, who represent the largest group treated so far, our experience in 16 cases demonstrates that intensive induction therapy is effective (87.5% of PR + CR). Inclusion of MAT both for infants and for children over 3 years of age has allowed for better control of the disease, and a significant impact on OS and EFS.⁴ The Phase A protocol showed good CD34+ cell mobilising activity, manageable toxicity, with no toxic deaths. All the children, many weighing less than 15–20 kg, performed the PBPC collection adding a peripheral vein access to a monolumen central venous catheter, with no remarkable toxicity, clotting episodes or haemorrhagic problems. In most cases, one or two apheretic procedures sufficed to collect enough CD34+

cells (range 5–56, median $15.2 \times 10^6/\text{kg}$ CD34+) for two consecutive reinfusions and as support to a prolonged myelotoxicity following CSI. Potential problems due to venous access and extracorporeal shift of blood volume were easily manageable.²⁴ A double course of MAT was even feasible, and no treatment-related deaths nor life-threatening toxicities were observed, thus allowing for 'safe', reduced CSI doses in cases with no metastasis.

Discussion

The efficacy of MAT in childhood brain tumours with 'good indications' has been shown in several studies, which also include patients affected by recurrent or resistant MB and some types of PNETs. Encouraging preliminary results report that up-front MAT in these diseases could be taken into consideration in future trials in an attempt to improve EFS and to reduce RT doses in carefully selected, high-risk patients in the context of a multimodal approach in which each component (surgery, CT, RT) should optimise its role and try to improve survival while assuring a 'good quality' of life whenever possible. This latter aim is acquiring particular relevance in modern clinical research, and it is at present mainly addressed to reduce irradiation dose or aggressive surgery along with their consequent bad impact on functional outcome. Referring to 'underinvestigation' type of tumours (ie gliomas, AT/RT) focusing on literature and on our experience, controversial data for high-grade astrocytomas still exist. For AT/RT in the context of new induction treatment, we cannot completely rule out that MAT may play a role in AT/RT. The use of PBPC has dramatically reduced the regimen-related morbidity and mortality, and MAT can be considered a safe and widely applicable treatment. In conclusion, the concepts concerning the role that MAT has in the treatment of brain tumours are continuously evolving owing to a greater multidisciplinary effort and cooperation among the stem cell transplant specialists and neuro-oncologists. Further indications should come from retrospective analyses of multicentric databases (such as the EBMT Solid Tumour Registry) and from prospective single or multiinstitutional controlled studies.

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