Stage 4 neuroblastoma: sequential hemi-body irradiation or high-dose chemotherapy plus autologous haemopoietic stem cell transplantation to consolidate primary treatment

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The aim of the present study was to evaluate the effectiveness of two consecutive nonrandomised treatment programs applied between 1989 and 1999 at the Istituto Nazionale Tumori of Milan in an unselected cohort of 59 children over the age of one with stage 4 neuroblastoma. Both treatment programs consisted of two phases, the induction of the remission phase and the consolidation phase. The induction of the remission phase consisted of intensive chemotherapy, and remained the same throughout the study period. The consolidation phase consisted of sequential hemi-body irradiation (HBI) (10 Gy per session, 6 weeks apart) in the first period (1988–June 1994) and sequential high-dose cyclophosphamide, etoposide, mitoxantrone + L-PAM and autologous haemopoietic stem cell transplantation in the second (July 1994–1999). Intention-to-treat analysis revealed a significantly better outcome for patients treated with the second program, the 5-year event-free survival probability being 0.12 for program 1 and 0.31 for program 2 (P = 0.03). This finding led us to conclude that sequential HBI is useless as consolidation treatment. The high-dose chemotherapy adopted in the second program enabled a proportion of patients to obtain long-term survival but, since the clinical results remain unsatisfactory, new treatment strategies are warranted.

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In the past two decades, the prognosis for patients with stage 4 neuroblastoma over the age of 1 year has progressively changed, with a weak but significant improvement in clinical results (Goldsby and Matthay, 2004). This slight improvement can be related to the greater and greater aggressiveness of the treatment: intensified chemotherapy increases the percentage of clinical remissions, the introduction of megatherapy helps to eradicate resistant clones, and the addition of ‘maintenance’ therapy is expected to control any minimal residual disease (Cheung et al., 1998; Pession et al., 1998; Garaventa et al., 1999; Matthay et al., 1999; Pinkerton et al., 2000). The use of aggressive surgery and radiotherapy to the primary tumour site may also contribute to reducing the risk of local relapse (Kushner et al., 2001; Haas-Kogan et al., 2003; La Quaglia et al., 2004). Nowadays, the majority of clinical trials on advanced neuroblastoma are organised according to the sequence: ‘induction’ of remission with chemotherapy and local treatment at the primary tumour site, ‘consolidation’ with megatherapy, and ‘maintenance’ therapy (Matthay et al., 1999; Berthold and Hero, 2000; De Bernardi et al., 2003). The number of studies focusing on the impact of each treatment modality within this arrangement is still limited, however, and the studies on this issue with a randomised design are rarer still (Ladenstein et al., 1994; Pearson et al., 1994; Matthay et al., 1999; Berthold and Hero, 2000; Pritchard et al., 2005).

In the present study, we describe a mono-institutional experience of two consecutive nonrandomised treatment programs comprising an identical induction phase, followed by two different strategies for the consolidation phase, that is, sequential fractionated hemi-body irradiation (HBI) in the first case and sequential high-dose chemotherapy plus autologous haemopoietic stem cell transplantation in the second. Our aim was to explore the impact of these two strategies on outcome.

PATIENTS AND METHODS

All children over the age of 1 year with previously untreated stage 4 neuroblastoma diagnosed from 1989 to 1999 at the Istituto
Nazionale Tumori of Milan were prospectively enrolled in the institutional treatment programs.

Diagnosis, staging and response to therapy were evaluated according to the International Neuroblastoma Staging System and the International Neuroblastoma Response Criteria (Brodeur et al., 1993). The diagnosis was based on a histological examination or, in some cases, on the documentation of an unequivocal bone marrow infiltration. The initial evaluation included CT or MRI of the primary tumour, 131-I-mIBG scan, TC-99-MDP scan, bilateral bone marrow biopsy and aspirate, serum levels of LDH, neuron-specific enolase and ferritin, and urinary concentrations of vanylmandelic and homovanillic acids. Response to treatment was assessed after each of the two steps in the treatment strategy (induction and consolidation).

During the study period (1989 – 1999), two different, non-randomised treatment programs were adopted (Table 1), both approved by the local Ethical and Scientific Board. The intention was to treat every new child over the age of one admitted to our institution with previously untreated stage 4 neuroblastoma. A stopping rule for toxic deaths was set for both treatment programs. The first program (program-1), applied between January 1989 and June 1994, consisted of an ‘induction of remission’ phase with intensive chemotherapy and a ‘consolidation of remission’ phase. In program-1, this consisted of two consecutive courses at 3-week intervals of cyclophosphamide 7 g sqm–1, etoposide 2 g sqm–1, mitoxantrone 60 mg sqm–1 + melphalan 210 mg sqm–1, followed by autologous peripheral blood stem cell transplantation (Table 1). Stem cells were collected from peripheral blood using G-CSF 10 μg kg–1 day–1 as of day 4 after administering cyclophosphamide up until the day of leukapheresis. If this target was not reached after cyclophosphamide (at least 3 × 10^6 CD34+ cells kg–1), an additional leukapheresis was performed after etoposide, using G-CSF at the same dose as after cyclophosphamide. The aim of program-2 was to evaluate the impact of this consolidation phase on clinical outcome.

In both programs 1 and 2, surgical resection of the primary tumour was on an individual basis and considered as part of the induction of remission phase. In addition, local treatment with radiotherapy was not specified by the treatment plan, and no further treatment was planned after the end of the consolidation phase. Supportive care policies did not change substantially during the study period, with the exception of the use of G-CSF, from 1996 onwards, in cases of febrile neutropenia and documented infection.

In the present study, we describe our mono-institutional experience with the two programs described above. The primary goal of the present study was to assess event-free survival (EFS) and survival (S) probabilities for the two groups of patients enrolled on programs 1 and 2 using an intention-to-treat analysis. Event-free survival was calculated from the first day of treatment up until progression or relapse, or death due to toxicity. Survival was calculated from the first day of treatment until death. EFS and S distributions were estimated using the Kaplan–Meier method, and compared with the log-rank test. To evaluate the homogeneity of the characteristics of the patients enrolled in programs 1 and 2, the frequency distribution of different variables in the two groups was compared using the χ² test for: sex, age, site of primary tumour, LDH level, serum ferritin, serum NSE, AVM/HVA dosage, cumulative % of drug dosages delivered during induction (>120 vs <120% of the initial dose), surgery on the primary tumour site.

RESULTS

All 59 consecutive children over the age of 1 year with stage 4 neuroblastoma at onset observed at the Istituto Nazionale Tumori of Milan during the study period were enrolled. In total, 25 joined program-1 and 34 joined program-2. In all cases, the diagnosis, treatment and follow-up were completed at the Istituto Nazionale Tumori.
The patients’ demographics and clinical characteristics are shown in Table 2. The M/F ratio was 1.3, and the median age at diagnosis was 3 years (range 1–18). The site of primary tumour was the retroperitoneum/adrenal gland in the majority of patients (85%). Skeleton and bone marrow were the most frequent sites of metastases (85 and 72%, respectively), followed by distant lymph nodes (37%), liver (14%), orbitae (14%), central nervous system (8%) and lungs (3%). The distribution of clinical variables at onset, the drug doses given, the number of patients who underwent surgery on the primary tumour site were similar in the two groups.

All patients received at least two cycles of induction therapy and were evaluable for response. The maximal response during induction was as follows: complete remission, 10; very good partial remission, 10; partial remission, 33; no response (stable disease or progression of disease) 6. In all, the percentage of responders was 89%. Six of the patients with partial remission experienced progression of disease during the induction treatment, however, so 47 patients concluded the induction phase and entered the consolidation phase. Two additional patients – one after the first HBI session in program-1, and one after high-dose VP16 in program-2 – had progression of disease during the consolidation phase. Thus, 45 patients completed the entire treatment plan, 18 out of 25 (72%) in program-1 and 27 out of 34 (79%) in program-2. Consolidation treatment determined a further response in two out of 19 (11%) after HBI in program-1 and in 16 out of 27 (59%) after high-dose therapy in program-2 (Table 3). As for the timing of the treatments, 62% of cases concluded the treatment program as scheduled, or with a delay <15 days, while the remaining 38% of cases had an overall delay ≥15 days (range 15–45). The percentage of cases with a delay of the timing of the treatment in program-1 and program-2 were superimposable (data not shown). For both programs, acute toxicity was mainly haematological. There were no toxic deaths or treatment interruptions due to severe adverse events.

Among the patients who concluded the treatment program, 31 relapsed a median 16 months after diagnosis (range 9–66). The relapse pattern was: metastatic spread, 21 (68%); metastatic spread plus local relapse, eight (26%); isolated local relapse, two (6%). None of the patients with nonresponse or progression of disease survived after second-line therapy. In all, 46 out of 59 patients died (22 in program-1 and 24 in program-2). The median follow-up for the entire series at the time of the current analysis (as at June 2004) was 62 months (range 31–164). The 5-year EFS and 5-year S probability for the entire series was 0.18 and 0.25, respectively (Figure 1). Analysing the outcome according to the treatment program adopted revealed a significant difference between the two: the 5-year EFS probability was 0.12 for program-1 and 0.31 for program-2 (P = 0.03); the 5-year S probability was 0.12 for program-1 and 0.35 for program-2 (P = 0.03) (Figure 2).

**DISCUSSION**

Total-body irradiation (TBI) has been widely used in the treatment of advanced NB, mainly as a consolidation strategy, followed by haemopoietic stem cell transplantation (Ladenstein et al, 1994; Matthay et al, 1999). Alternative methods of TBI had also been applied in NB, consisting of cyclic low-dose TBI (D’Angio and Evans, 1983) or sequential HBI in combination with chemotherapy.
been demonstrated in vitro (Fulda et al, 1995) but had never been explored in vivo (Kushner et al, 1990; Pinkerton, 1991; Berthold and Hero, 2000). The consolidation treatment adopted in program-2 led us to support the activity of megatherapy in advanced NB, on the grounds of two arguments. The first is the further response obtained with high-dose therapy after the induction therapy in a consistent number of cases – notably higher than the response obtained with HBI. The second is the 5-year survival probability of patients treated with program-2, which was 0.35 – significantly better than for patients treated with program-1.

In the present study, only a small number of patients had surgery on the primary tumour site so we cannot draw any conclusions concerning the impact of a ‘local’ treatment on the survival probability in this series. Since surgery and radiotherapy on the primary tumour site have been shown to contribute to controlling local relapses in stage 4 NB (Kushner et al, 2001; Haas-Kogan et al, 2003; La Quaglia et al, 2004), it may be that adding a ‘local’ treatment with surgery plus radiotherapy in an extended way to program-2 might further improve the results we obtained.

We are naturally aware that the limited number of patients enrolled over a lengthy study period and the mono-institutional setting could constitute a bias of our study, and that the statistical results should be interpreted with caution as there might be additional unforeseen bias due to the nonrandom design of the treatment programs applied. Furthermore, the possibility that the use of G-CSF could have concurred in the better outcome of program-2 cannot be excluded for certainty. In fact, in the two programs no differences were recorded as to the timing of drug administration schedule and no treatment discontinuation due to acute severe toxicity were recorded in either program. This study included an unselected cohort of patients, the results are described as intention-to-treat, and the survival probability is calculated on the strength of a long follow-up. The use of the same induction treatment throughout the study and the comparable clinical characteristics of the two groups of patients strongly suggest the superiority of the therapeutic results of consolidation treatment with sequential high-dose chemotherapy and autologous stem cell transplantation. Our experience can be added to the limited number of other papers comparing different consolidation strategies after a common induction phase, thus making the results of these strategies fully comparable. These studies evaluated megatherapy vs continuing intensive chemotherapy (Matthy et al, 1999), or maintenance chemotherapy (Berthold et al, 1990; Castel et al, 2001), or no treatment (Pritchard et al, 2005). Combined with the other experiences including megatherapy, they reliably support the conviction that this consolidation treatment modality offers an advantage in terms of survival probability (McCowage et al, 1995; Kushner et al, 2001; Frappaz et al, 2002; Kaneko et al, 2002; Kletzel et al, 2002; De Bernardi et al, 2003).

In spite of all the possible bias, the present study supports the claim that patients with stage 4 NB over the age of 1 year with a tumour responding to initial intensive chemotherapy can benefit from high-dose chemotherapy and haemopoietic stem cell rescue. We are aware that this type of study is not the best way forward and that important clinical questions should nowadays be answered by randomised trials conducted on a multicentre basis with international cooperation. Any chances of improving on the clinical results will obviously come also from new insights on the biology of neuroblastoma and the availability of new active molecules.

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