ABSTRACT

Purpose With a view to improving the prognosis for patients with metastatic medulloblastoma, we tested the efficacy and toxicity of a hyperfractionated accelerated radiotherapy (HART) regimen delivered after intensive sequential chemotherapy.

Patients and Methods Between 1998 and 2007, 33 consecutive patients received postoperative methotrexate (8 g/m²), etoposide (2.4 g/m²), cyclophosphamide (4 g/m²), and carboplatin (0.8 g/m²) in a 2-month schedule, then HART with a maximal dose to the neuraxis of 39 Gy (1.3 Gy/fraction, 2 fractions/d) and a posterior fossa boost up to 60 Gy (1.5 Gy/fraction, 2 fractions/d). Patients with persistent disseminated disease before HART were consolidated with two myeloablative courses and circulating progenitor cell rescue.

Results Patients were classified as having M1 (n = 9), M2 (n = 6), M3 (n = 17), and M4 (n = 1) disease. Seven patients younger than 10 years old who achieved complete response after chemotherapy received a lower dose to the neuraxis (31.2 Gy). Twenty-two of the 32 assessable patients responded to chemotherapy; disease was stable in five patients and progressed in five patients. One septic death occurred before radiotherapy. Eight patients experienced relapse after a median of 12 months. Fourteen of the 33 patients underwent consolidation therapy after HART. With a median 82-month survivor follow-up, the 5-year event-free, progression-free, and overall survival rates were 70%, 72%, and 73%, respectively. No severe clinical complications of HART have emerged so far.

Conclusion HART after intensive postoperative chemotherapy, followed by myeloablative chemotherapy in selected cases, proved feasible in children with metastatic medulloblastoma. The results of our treatment compare favorably with other series treated using conventional therapies.

INTRODUCTION

Medulloblastoma has already seeded through the CSF pathways at diagnosis in up to 35% of patients.1,2 Although 5-year progression-free survival (PFS) is relatively high for patients without metastases, approaching 80%,3,4 for patients with metastases, it is historically approximately 40%.5,6

Modern trials on metastatic tumors focus on improving patients’ prognosis with intensive combined treatments.7 We tested the efficacy and toxicity of a hyperfractionated accelerated radiotherapy (HART) regimen always delivered at the Milan Cancer Institute after intensive sequential chemotherapy had been administered at a handful of institutions. Using an adapted fractionation schedule, we attempted to improve the therapeutic index while preradiation chemotherapy could obtain a minimal amount of tumor left before HART. Response-based postradiation chemotherapy could further improve tumor control. We report our results in 33 consecutive patients.

PATIENTS AND METHODS

Post surgical staging was based on Chang’s system.6 All radiologic examinations were performed soon after surgery with CNS magnetic resonance imaging (MRI) and were centrally reviewed. CSF cytology was examined 2
Chemotherapy

Patients entered an up-front, intensive-dose chemotherapy program, with sequencing non–cross-resistant drugs, at the times shown in Figure 1. They received intravenous (IV) methotrexate 8 g/m² plus vincristine after surgery, then etoposide 2.4 g/m², cyclophosphamide 4 g/m² plus vincristine, carboplatin 800 mg/m² plus vincristine, and, after radiotherapy, vincristine and lomustine maintenance for a year. Granulocytes ≥ 1.0 × 10⁹/L and platelets ≥ 100 × 10⁹/L were required at the scheduled times for drug administration. The maintenance phase of the protocol was amended and intensified after treating the first nine patients because two patients (staged M1 at diagnosis, still with malignant cells in the CSF before radiotherapy) experienced relapse 5 and 11 months after diagnosis. The postradiation phase was replaced with two courses of thiotepa at myeloablative doses (300 mg/m²/d for 3 days) followed by circulating progenitor cell (CPC) administration for all children with persistent liquor seeding at pre-HART restaging, or still with more than one solid location. For children treated before 2002, the second conditioning regimen also included carboplatin (500 mg/m²/d for 2 days) with thiotepa because there were reports of high response rates in relapsing medulloblastoma treated with these two drugs. Peripheral-blood stem-cell collection entailed leukapheresis and cryopreservation after etoposide or cyclophosphamide, followed by subcutaneous granulocyte colony-stimulating factor at 10 μg/kg/d.

Radiotherapy

Once the blood count had recovered from initial chemotherapy (granulocytes ≥ 1 × 10⁹/L and platelets ≥ 75 × 10⁹/L), patients received craniospinal irradiation (CSI) followed by a boost to the posterior fossa and/or any bulky metastases. All patients were irradiated with a 6-MV linear accelerator, with the posterior fossa boost given in 1.5-Gy fractions twice a day to obtain a total dose of 31.2 Gy if patients were younger than 10 years old, if a complete response (CR) was achieved, and 39 Gy to the neuraxis, respectively. For residual lesions in the posterior fossa or metastatic nodules, another boost of 9 Gy could be delivered in six twice-daily 1.5-Gy fractions. An individual computed tomography–based computerized treatment plan was prepared for each child. Computed tomography 5-mm slices were obtained from the orbits, skull base, posterior fossa, and cervical spine, and 8- to 10-mm slices were obtained from the remaining neuraxis. From 1999 onwards, a three-dimensional treatment planning system was adopted for all dosimetric studies. To optimize dose distribution to the neuraxis, treatment plans were prepared, aiming to include at least 95% of the CNS volume in the 95% isodose, and the whole CNS volume had to be included in the 90% isodose.

Patients

The treatment strategy was applied to all newly diagnosed consecutive patients who were older than 3 years at the time of surgery. All involved institutions scientific/ethical committees approved the protocol. All patients’ parents gave their informed consent to the treatment.

Leukapheresis

The procedure is reported elsewhere. Peripheral-blood stem cells were divided into at least two aliquots and cryopreserved.

Evaluation of Disease and Response

In addition to radiologic assessment soon after surgery, CNS MRI was repeated before every other chemotherapy course, before and 5 weeks after completing HART, and, in the patients who underwent myeloablative chemotherapy, upon resolution of myelosuppression after the second high-dose course. CSF cytology was repeated before HART in all patients and, if it was still positive, again after irradiation. Radiologic response was assessed according to the International Society of Pediatric Oncology criteria.

Follow-Up

A year after completing HART, all patients underwent a complete auxologic evaluation and received supportive and substitutional endocrinologic therapy as necessary. They were also offered a complete age-appropriate neuropsychological assessment at various times after their diagnosis and a tailored rehabilitation treatment if needed.

Statistical Methods

Progression-free survival (PFS), event-free survival (EFS) and overall survival (OS) were calculated in years using the Kaplan and Meier method, considering failure and toxicity events as of starting chemotherapy and censoring data for progression and survival at the latest follow-up. Differences in survival between patient groups were evaluated using the log-rank test. χ² tests were used to compare the frequency of patient characteristics. The P value was considered statistically significant at less than .05.

SURGERY

<table>
<thead>
<tr>
<th>HD-MTX (8 g/m²)</th>
<th>HD-VP16 (2.4 g/m²)</th>
<th>HD-CYCLO (4 g/m²)</th>
<th>CBDCA (800 mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>4</td>
<td>7 weeks</td>
</tr>
<tr>
<td>+ G-CSF for CPC harvest</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HART 3-4 weeks after CBDCA

<table>
<thead>
<tr>
<th>If CR pre-HART:</th>
<th>If no CR pre-HART:</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks after end of RT, maintenance CT with:</td>
<td>4 weeks after end of RT, thiotepa (900 mg/m²) in 3 days, for 2 courses (with a 4- to 6-week interval)</td>
</tr>
<tr>
<td>VCR (1.4 mg/m²) every 3 weeks × 18</td>
<td></td>
</tr>
<tr>
<td>CCNU (80 mg/m²) every 9 weeks × 6</td>
<td></td>
</tr>
<tr>
<td>.... 18 patients</td>
<td>.... 14 patients</td>
</tr>
</tbody>
</table>

CPC: circulating progenitor cells

HART doses: CSI 39 Gy if patients ≥ 10 years...25 patients
CSI 31.2 Gy if patients < 10 years...7 patients

Fig 1. Treatment. HD, high dose; MTX, methotrexate; VP16, etoposide; CYCLO, cyclophosphamide; CBDCA, carboplatin; G-CSF, granulocyte colony-stimulating factor; CPC, circulating progenitor cells; HART, hyperfractionated accelerated radiotherapy; CR, complete response; RT, radiotherapy; CT, chemotherapy; VCR, vincristine; CCNU, lomustine.
RESULTS

**Patient Characteristics**

Seven were female and 26 were male; median age was 10 years (range, 3.2 to 34 years). Initial surgery on the primary tumor was complete in 17 patients, subtotal in 15 patients, and biopsy alone in one patient. Eight patients developed signs of posterior fossa syndrome after surgery. Postsurgical staging data are summarized in Table 1. One patient had both CNS deposits and multiple skeletal metastases evaluated by MRI, bone scan, and bone biopsy (M4), with residual tumor in the cerebellum.

**Histologic Diagnosis**

The diagnoses were revised centrally by PC and FG according to the WHO classifications 1993/2000 and were classic medulloblastoma in 26 patients, desmoplastic medulloblastoma in four patients, and large-cell/anaplastic medulloblastoma in three patients.

**Treatment**

**Preradiation chemotherapy.** Twelve patients achieved CR before the radiation phase. Ten patients had radiologic partial response (PR; with residual liquor seeding in four patients), five patients had stable disease (with liquor seeding in four patients and stable meningeal locations in one patient), and five patients had progressive disease. In all, 69% of patients had an objective response after the first phase. Two children with evident disease progression after administering the first two drugs and a girl suffering from *Pseudomonas* sepsis after etoposide were sent for early radiation. One patient had a shunt infection after etoposide and died of brain hemorrhage after shunt removal. One child had a *Pseudomonas* shunt infection after high-dose methotrexate that prevented continuation of the treatment for 46 days: tumor progression was evident, and radiation was prescribed soon after a course of cisplatin plus etoposide, with subsequent CPC mobilization. For children completing the whole phase, preradiation chemotherapy took a median 52 days.

**Radiotherapy.** Thirty-two of 33 patients underwent radiotherapy; six patients younger than 10 years received craniospinal irradiation with HART, for a total dose of 31.2 Gy. One 3.3-year-old received 39 Gy to the spine for huge spinal nodules, 31.2 Gy to the brain, and 59.7 Gy to the posterior fossa. The other 25 irradiated patients received 39 Gy to the neuraxis, 22 patients had a boost to the posterior fossa up to 60 Gy, and eight patients also had a boost to residual disease or bulky metastases. One child with a bone metastasis stopped the posterior fossa boost at 46.5 Gy because of leucopenia. No up-front boost was prescribed for the three remaining children, all younger than 10 years, because they had too many metastatic sites. In all, the radiation treatment lasted from 22 to 42 days (median, 32 days). The interval between surgery and radiation was a median 85 days. HART induced CR in 14 of 20 patients and PR in two patients, whereas three patients still had liquor seeding and one had only a minimal shrinkage of the tumor deposits. Four children with persistent disease after HART reached CR after the first myeloablative chemotherapy course. Figure 2 shows the responses to treatment in the various phases. All patients underwent radiation at the same institution following the local technical guidelines and quality control process. Analysis of the dosimetric data for the series showed that a mean 99.3% ± 0.4% of the whole neuraxis volume was always included in the 95% isodose, with only 10.2% ± 7.6% of said volume receiving 105% of the prescribed dose (mean values ± SD). Considering dose

![Fig 2. Responses to treatment in the various phases. HART, hyperfractionated accelerated radiotherapy; CT, chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. (*) CR after pre-HART CT. (°) CR after HART. ($) CR after myeloablative chemotherapy.](https://example.com/figure2.png)

<table>
<thead>
<tr>
<th>Post-S Stage</th>
<th>Total No. of Patients</th>
<th>Classic T</th>
<th>Desmoplastic T</th>
<th>Anaplastic T</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1NED</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>M1ED</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>M2NED</td>
<td>3</td>
<td>2</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>M2ED</td>
<td>3</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>M3NED</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>M3ED</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>M4ED</td>
<td>1</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: Post-S, post-surgical; NED, no residual primary tumor; ED, residual primary tumor; T, histologic subtype; M1 to M4, stage according to Chang’s staging system.

*Pre-HART CT* 1 early death

12* CR
10 PR (4 CSF+)
5 SD (4 CSF+)
5 PD

**HART**

12* CR
14° CR
2 PR
4 SD (3 CSF+)

**High-dose chemotherapy**

4§ CR

12* + 14° + 4§ = 30 CR
(at end of treatment)
distribution separately for the brain and spine, the 95% isodose encompassed 99.8% ± 0.4% of the brain volume and 93% ± 3.2% of the spine volume, whereas the 105% isodose included 9.6% ± 8.4% and 17.2% ± 5.8% of the brain and spine volumes, respectively (mean values ± SD).

Postirradiation chemotherapy. Sixteen children completed the maintenance phase with vincristine and lomustine, whereas two patients experienced rapid disease progression after radiation, one patient stopped maintenance after 6 months because of acute hydrocephalus requiring shunting, and one patient stopped after 2 months because of bacterial discitis.16

Sufficient CPC (median, $22 \times 10^7$/kg) could be collected in a single leukapheresis after etoposide administration in all but two children, who had one collection after etoposide and one after cyclophosphamide. In all, 14 children received consolidation chemotherapy; 12 had the prescribed myeloablative phase after HART, consisting of two high-dose courses with thiopeta alone, and with thiopeta and carboplatin in three patients, two thiopeta courses in tandem in seven patients, and only one course of thiopeta in two patients. One child with massive disease progression before starting HART was given three myeloablative courses. The child with bone metastases underwent two myeloablative courses before HART.

Treatment Toxicity

Febrile neutropenic episodes occurred in 70% and 25% of patients after etoposide and cyclophosphamide, respectively, with documented bacteremia in 15% of cases in all. Packed RBC and platelet transfusions were administered to 27% and 45% of patients, respectively.

Thirty-one of 32 patients completed HART as planned, but the child with bone metastases had the posterior fossa boost stopped in advance. The median nadir for both thrombocytopenia and leucopenia (platelets $\leq 20 \times 10^9$/L and leukocytes $\leq 1,500$/L) was on the 21st and 20th days of HART, respectively, when it was nearly finished. All 14 patients treated with postirradiation myeloablative courses experienced grade 3 to 4 hematologic toxicity, requiring a median of two packed RBC and platelet transfusions each; they were all fed with enteral or parenteral support for a median of 10 days and given opioids for grade 3 mucositis. Grade 4 infections occurred in two patients during the first myeloablative course (aspecific encephalitis in both cases); they were not given the second course.

Outcome

The median follow-up for survivors was 82 months (range, 7 to 111 months). At 3 and 5 years, PFS was 80% ± 7% and 72% ± 8%, respectively; OS was 77% ± 8% and 73% ± 7%, respectively; and EFS was 77% ± 7% and 70% ± 8%, respectively (mean values ± SE; Fig 3). Eight patients have experienced disease progression so far, a median 12 months (range, 5 to 48 months) after beginning chemotherapy. Relapses were only local in two patients, local and distant in one patient, and only distant in five patients, including the two patients with persistent liquor dissemination after HART; all patients who experienced relapse died of disease a median of 5 months (range, 1 to 23 months) after experiencing relapse. Dividing patients by response to preradiation chemotherapy, the 3-year PFS was 94% ± 9% for patients obtaining CR plus PR and 61% ± 13% for those with stable or progressive disease ($P = .009$). PFS depended neither on the type of metastases (5-year PFS in the M1 group, 78% ± 14% vs 70% ± 10% for the M2 to M4 group), nor on any posturgery residual tumor, total CSI dose and duration (> v < 32 days), time before radiation, or age older or younger than 10 years. One patient had a late adverse event (a left frontal glioblastoma) 60 months after starting chemotherapy.

All four patients with desmoplastic medulloblastoma were in CR at the time of this report with no additional myeloablative treatment, whereas tumor progressed in two of the three patients with anaplastic medulloblastoma after 12 and 13 months, despite their receiving the consolidation treatment too.

Six of the 14 patients treated with myeloablative courses had therapy-induced lesions on MRI, and half of the children had neurologic signs or symptoms judged to be related to radiation-induced changes, as reported elsewhere.17

DISCUSSION

The prognosis for metastatic medulloblastoma is still unsatisfactory. It was established in the 1980s that adding chemotherapy can improve prognosis by comparison with irradiation alone,18–20 but subsequent studies adopting a “sandwich” schedule, like the French Society of Pediatric Oncology21 and Hirntumoren—German Pediatric Brain Tumors Cooperative Group22 studies, or a sandwich plus a maintenance phase, like the Children’s Cancer Group 921 randomized trial,6 failed to improve much on the 40% to 50% PFS for patients with M1 to M3 disease.

More recent studies have reported encouraging results with high-dose chemotherapy and autologous stem-cell transplantation. Strother et al23 enrolled 19 patients with metastases for topotecan treatment followed by CSI and four cycles of high-dose cyclophosphamide with cisplatin and vincristine, then CPC reinfusion. The PFS 2 years after starting the therapy was 73.7% ± 10.5%. This experience was expanded, treating 42 patients with metastatic disease and achieving a 5-year EFS of 66%.7 In a recent trial, 21 young patients with high-risk or disseminated medulloblastoma were enrolled to evaluate their response to an intensified induction chemotherapy regimen and
a single myeloablative chemotherapy cycle with autologous stem-cell rescue, followed by radiotherapy for patients older than 6 years or those younger than 6 years with evidence of residual disease after completing induction chemotherapy. The 3-year EFS and OS rates were 49% and 60%, respectively.\textsuperscript{24}

Our preradiaation included most of the drugs already tested in phase II trials, obtaining a comparable response rate,\textsuperscript{25-27} and also included high-dose methotrexate, which had probably contributed to the good results reported above.\textsuperscript{28} A response at this stage of the treatment meant a significantly better prognosis, as observed by others.\textsuperscript{29} A response to the subsequent HART phase was naturally even more decisive in predicting outcome.

Modified fractionation schedules have attracted interest in pediatric radiotherapy with a view to improving tumor control without increasing toxicity.\textsuperscript{29-32} Data on medulloblastoma cell kinetics are limited. Satouyuki et al\textsuperscript{33} demonstrated a short potential doubling time (mean 51 hours) for medulloblastoma cell lines: if this reflects in vivo tumor behavior, accelerating radiotherapy could help to reduce the impact of repopulation. The benefit of short-lived radiation treatment was emphasized by del Charco et al,\textsuperscript{34} with a statistically significant improvement in local control and PFS when radiotherapy lasted less than 45 days in a series of 53 children with medulloblastoma.

Our hyperfractionated-accelerated schedule, based on the linear quadratic model,\textsuperscript{35} was developed to try to improve the therapeutic results without exacerbating the late sequelae of conventional treatment, using 1.8-Gy daily fractions up to 56 Gy to the neuraxis and 54 Gy to the posterior fossa. With the 1.3 Gy twice/d up to 39 Gy fractionation scheme, CSI took only 15 days, with a theoretical increase in the Extrapolated Response Dose for tumor (ERDT) of 48%. Posterior fossa boosting with 1.5 Gy twice/d would take only another 7 days, with a theoretical increase in the ERDT of 29%. For both volumes and doses, ERDT for late effects were estimated to be the same or slightly less than with conventional radiation treatment. In this series, the potential effect of the duration of radiotherapy suggested by del Charco was accomplished, with HART lasting a median 32 days.\textsuperscript{34}

It is worth bearing in mind that HART obtained objective responses in 80% of patients who still had assessable tumor, including three patients with tumor progression after preradiaation chemotherapy, and that even reduced doses of CSI succeeded in controlling tumor progression in some cases.

The myeloablative phase achieved another four CRs in the five children who still had tumor after HART, but this remission persisted in only one of four children.

Despite the small numbers involved in our study, we confirmed a good prognosis for the desmoplastic variant (100% of cases achieving a lasting remission) and a poor outcome for the anaplastic subtype (with two of three cases of tumor progressing).\textsuperscript{7}

The success of our strategy probably lies in the design as a whole rather than any single element. All patients were accurately staged according to the same guidelines in every treatment phase with central radiologic review. This enabled us to give priority, at each time point, to continuing chemotherapy, shifting to radiation therapy, administering full or reduced doses of radiation, and the choice of intensive consolidation or standard maintenance, depending on the responses obtained. All children were given radiotherapy at the same institution, following the same technical guidelines and quality control processes throughout the study period. The functional and social outcome for our long-term survivors warrants a detailed long-term prospective evaluation, however.\textsuperscript{36}

In conclusion, HART combined with intensive postoperative chemotherapy, and myeloablative chemotherapy in selected cases, proved feasible and successful in treating metastatic medulloblastoma.

\textbf{AUTHOR CONTRIBUTIONS}

Conception and design: Lorenza Gandola, Maura Massimino, Graziella Cefalo, Filippo Sprefico, Roberto Luksh, Franca Fossati-Bellani

Financial support: Franca Fossati-Bellani

Provision of study materials or patients: Lorenza Gandola, Maura Massimino, Graziella Cefalo, Carlo L. Solero, Emilia Pecori, Daria Riva, Paola Collini, Emanuele Pignoli, Felice Giangaspero, Roberto Luksh, Serena Berretta, Geraldina Poggi, Veronica Biaisonsi, Andrea Ferrari, Bianca Pollo, Claudio Favre, Iacopo Sardi, Monica Terenziani

Collection and assembly of data: Lorenza Gandola, Maura Massimino, Filippo Sprefico, Emilia Pecori, Paola Collini, Felice Giangaspero, Roberto Luksh, Veronica Biaisonsi

Data analysis and interpretation: Lorenza Gandola, Maura Massimino, Filippo Sprefico, Paola Collini, Emanuele Pignoli, Felice Giangaspero

Manuscript writing: Lorenza Gandola, Maura Massimino, Filippo Sprefico, Paola Collini, Emanuele Pignoli, Roberto Luksh

Final approval of manuscript: Lorenza Gandola, Maura Massimino, Graziella Cefalo, Carlo L. Solero, Filippo Sprefico, Emilia Pecori, Daria Riva, Paola Collini, Emanuele Pignoli, Felice Giangaspero, Roberto Luksh, Serena Berretta, Geraldina Poggi, Veronica Biaisonsi, Andrea Ferrari, Bianca Pollo, Claudio Favre, Iacopo Sardi, Monica Terenziani, Franca Fossati-Bellani

The author(s) indicated no potential conflicts of interest.

\textbf{REFERENCES}


HART for Metastatic Medulloblastoma


