

Outcome of Children with High-Risk Medulloblastoma Treated with Pre-Irradiation Chemotherapy

Wael H. EL-SAWY, M.D.

The Department of Clinical Oncology, Faculty of Medicine, Zagazig University.

ABSTRACT

Purpose: Our aim was to determine whether: pre-irradiation chemotherapy is active and feasible in children with medulloblastoma.

Patients and methods: Twenty-one patients with high-risk medulloblastoma were given preirradiation chemotherapy as initial postoperative treatment at Radiation Oncology Unit from June 1997 through December 1999, patients were treated within 2 to 6 weeks after initial surgery with Cisplatin 100 mg/m² I.V. infusion over 6 hours day 1 with hydration and diuresis, Vincristine 1.5 mg/m² I.V. push days 1 and 8 (maximum 2 mg), Procarbazine 100 mg/m² PO, days 1 to 14 and Prednisone 40 mg/m² PO, days 1 to 14. Cycles of chemotherapy were given 28 days apart. In the absence of progressive disease, all patients received 3 cycles of chemotherapy, standard craniospinal irradiation followed by 3 cycles of the same chemotherapy regimen given before irradiation.

Results: Among 21 assessable patients, Seventeen with (M0) disease, four had CR, seven had PR and six had SD. Among four patients with (M1) disease at diagnosis, one had CR and three had PR after completion of three cycles of pre-irradiation chemotherapy. After craniospinal irradiation, out of ten patients with PR to pre-irradiation chemotherapy, five achieved CR and out of six patients with SD, three achieved PR and the other three remain SD. at the end of three cycles of post-radiation chemotherapy, there were fourteen patients with CR, five with PR and two with SD. The 3-years PFS was 66.7±10%. The median follow-up time for all survivors was 32 months (range, 20 to 44). Myelosuppression was the predominant toxic effect with preirradiation chemotherapy.

Conclusion: Our preliminary results of neoadjuvant chemotherapy in-patients with high-risk medulloblastoma are encouraging and this modality of treatment can be applied safely with acceptable toxicity.

Key Words: *Brain tumors - Medulloblastoma - Preirradiation chemotherapy.*

INTRODUCTION

Medulloblastoma is the most common malignant brain tumor in children [9,13]. Although

surgery and craniospinal irradiation have been the mainstay of treatment, overall survival (OS) rates of less than 50% to 60% have encouraged the use of adjuvant and neoadjuvant chemotherapy. The impact of chemotherapy in improvement of survival has been documented largely in-patients with advanced disease at diagnosis [5,24]. The study of patterns of failure has played an important role in improving the outcome in-patients with medulloblastoma. The earlier use of surgery alone resulted in virtually no cures and high rates of local failure [16]. The addition of posterior fossa radiotherapy following surgical resection improved the local control in the posterior fossa, but the outcome was still poor because of disease recurrence elsewhere in the neuraxis [16,20]. Clinical features associated with a high risk of treatment failure and death include young age, incomplete surgical resection and metastatic disease in the cerebrospinal fluid, spine, or brain at diagnosis [5,24]. In-patients with high-risk tumors, disease free survival is less than 40-50% with surgery and craniospinal irradiation (CSI) [5,24]. Patients older than 3 years of age with gross total resection of the primary and no evidence of metastatic disease have a lower risk for treatment failure and may obtain long-term survival rates of 60-70% [3,11]. Many investigators suggested the administration of chemotherapy following surgery and prior to radiotherapy in medulloblastoma, as the delivery of chemotherapy to the tumor might be maximal between surgery and radiotherapy resulting in higher activity and low toxicity of chemotherapy. This may be explained by disruption of the blood brain barrier and unchanged vascularization of the tumor due to radiation therapy [1,7,8,14,15,17,18,19]. Based

on the previous data, we conducted a prospective trial in June 1997 in an attempt to evaluate the role of neoadjuvant chemotherapy prior to craniospinal irradiation in children with medulloblastoma. Our aim was to determine whether: pre-irradiation chemotherapy is active and feasible in children with medulloblastoma and to address some issues raised about utilizing pre-irradiation chemotherapy such as:

Does delay in starting craniospinal irradiation allow progression during chemotherapy?

Does pre-irradiation chemotherapy diminish tolerance to craniospinal irradiation?

Does pre-irradiation chemotherapy change the patterns of failure?

Can patients who progress during chemotherapy be salvaged by subsequent craniospinal irradiation?

PATIENTS AND METHODS

Patient eligibility and prestudy evaluation:

From June 1997 through December 1999, 21 patients between 3 and 16 years of age with newly diagnosed high-risk medulloblastoma were entered onto this investigational protocol. All patients had contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) brain studies preoperatively and postoperatively. After histopathologic confirmation of medulloblastoma, patients underwent complete neuraxis staging using spinal imaging with CT myelography or gadolinium-enhanced MRI and cytologic examination of cerebrospinal fluid. The patients were staged according to the staging system described by Chang [2]. High-risk medulloblastoma was defined according to the International Society of Pediatric Oncology (SIOP) criteria: less than complete tumor resection, presence of brain stem invasion or tumor extension beyond the fourth ventricle (Chang T3b or T4), or neuraxis metastatic disease (Chang M2 to M3) at diagnosis [1]. All patients were subjected to medical history and clinical examination including neurological examination. Complete blood picture, electrolytes, blood urea, creatinine and liver function and baseline audiogram were obtained before study entry. Before chemotherapy, isotopic bone scan and bone marrow aspiration were performed to exclude extraneural metastases. All patients or their legal guardians provided in-

formed consent stating that they were aware of the investigational nature of this study.

Preirradiation chemotherapy:

Within 2 to 6 weeks (median 3) of initial surgery, patients began pre-irradiation chemotherapy with Cisplatin 100 mg/m² I.V. infusion over 6 hours day 1 with hydration and diuresis, Vincristine 1.5 mg/m² I.V. push days 1 and 8 (maximum 2 mg), Procarbazine 100 mg/m² PO, days 1 to 14 and Prednisone 40 mg/m² PO, days 1 to 14. Cycles of chemotherapy were given 28 days apart.

Patients with prolonged myelosuppression that resulted in ≥ 28 -day interval between cycles of chemotherapy had doses of the 4 drugs reduced by 25% in all subsequent cycles. In the absence of progressive disease, all patients received 3 cycles of chemotherapy before irradiation; imaging evaluation were performed after the 2nd and 3rd cycles or sooner if clinically indicated.

Criteria of response:

Response was determined by comparing the product of the largest two cross-sectional diameters of the tumor on CT or MRI scan before and after chemotherapy. A complete response (CR) was defined as disappearance of all tumor for a duration of ≥ 4 weeks. A partial response (PR) was defined as $\geq 50\%$ decrease in the product of the cross-sectional diameters for a similar duration. Patients with a less than 25% decrease or increase in the product of the diameters were considered to have stable disease (SD). Progressive disease (PD) was defined as an increase of greater than 25% in the product of the cross-sectional diameters or the appearance of any new lesions. Responses in the primary and metastatic sites were evaluated separately.

Radiation therapy:

In absence of progressive (PD) on chemotherapy, patients were to begin craniospinal irradiation 4 weeks after the 3rd cycle of chemotherapy. The cranial portion was treated with 2 parallel-opposed lateral fields for a dose of 36 Gy/20 fractions (180 cGy/fraction). The neuraxis was treated through single direct or 2 direct-gaped fields to the level of the 2nd sacral vertebra. The spinal fields were appropriately matched, the match lines were shifted every 10 Gy to avoid overdosing or underdosing to seg-

ments of the spinal cord. The spinal dose ranged from 30 to 35 Gy/20 to 23 fractions in 4 to 5 weeks. The posterior fossa boost (15-20 Gy) was given through 2 parallel opposed. The total dose to the posterior fossa was 54 Gy.

Postirradiation chemotherapy:

Three weeks after completion of radiation therapy, patients began 3 cycles of the same chemotherapy regimen given before irradiation.

Evaluation of toxicity:

Treatment toxicity was evaluated according to WHO system [26].

Statistical methods:

Overall survival (OS) was measured from the date of diagnosis to death or the last date of contact. Progression-free survival (PFS) was measured from the date of diagnosis to the date of progression of the disease or the last date of contact. Distributions of PFS and OS were estimated using the method reported by Kaplan and Meier [12]. Standard errors for Kaplan-Meier estimates were calculated by the method proposed by Peto et al. [22,23].

RESULTS

Twenty-one eligible patients were entered onto this study: 13 boys and 8 girls aged 5 to 16 years (median, 8.5). Table (1) represent characteristics of the 21 eligible patients. The Chang Staging classification of the patients is listed in table (2).

Outcome after pre-irradiation chemotherapy:

Twenty-one eligible patients were assessable for response, Table (3) lists the overall response to pre-irradiation chemotherapy. Response was determined after the completion of three cycles of chemotherapy. For patients with greater than one assessable site of disease, overall response was determined by the site that showed the least response. At completion of the first three cycles of chemotherapy, most of the 21 assessable patients had demonstrated their best response. Of seventeen with no metastatic disease at diagnosis (M0), four had CR (23.5%), seven had PR (41.2%) and six had SD (35.3%). Among four patients with distant neuraxis disease (M1) at diagnosis, one had CR (25%) and three had PR (75%) after completion of three cycles of pre-irradiation chemotherapy.

Table (1): Clinical characteristics of patients.

Age:	
Range (years)	5-16
Median	8.5
Sex:	
Male	13 (61.9%)
Female	8 (38.1%)
T-Stage:	
T2	4 (19%)
T3A	14 (66.7%)
T3B	3 (14.3%)
M-Stage:	
M0	17 (81%)
M1	4 (19%)
Extent of surgery:	
Biopsy only	7 (33.3%)
Subtotal excision	12 (57.2%)
Gross total excision	2 (9.5%)

Table (2): Chang's staging of 21 patients with medulloblastoma.

	T2	T3A	T3B
M0	4	8	5
M1	-	2	2

Table (3): Response to pre-irradiation chemotherapy.

	CR	PR	SD	PD
T2:				
M0	1/4	2/4	1/4	0/4
M1	0	0	0	0
T3A:				
M0	2/8	3/8	3/8	0/8
M1	1/2	1/2	0/2	0/8
T3B:				
M0	1/5	2/5	2/5	0/5
M1	0/2	2/2	0/2	0/2

Outcome after craniospinal irradiation:

Non of the five patients with CR after pre-irradiation chemotherapy developed local recurrence or distant metastases, while out of ten patients with partial response to pre-irradiation chemotherapy, five achieved complete response after craniospinal irradiation. Among the six patients with SD after pre-irradiation chemotherapy, three achieved PR and the other three remained SD.

Outcome after completion of chemotherapy:

At the end of three cycles of post-radiation chemotherapy, there were fourteen patients with CR, five with PR and two with SD.

Survival:

All the 21 patients are assessable for survival. The median follow-up time for all survivors is 32 months (range, 20 to 44+). Fig. (1) shows the Kaplan-Meier plot of PFS for the entire group of patients. The PFS and OS at 3 years are $66.7\pm 10\%$ and $69.6\pm 10\%$ respectively.

Toxicity:

Myelosuppression was the predominant toxicity observed with pre-irradiation chemotherapy. Only 3 episodes of febrile neutropenia were observed with no documented infection.

No grade III or VI nephrotoxicity, neurotoxicity, or hepatotoxicity were observed. Nausea and emesis were mild and well controlled with antiemetics. All patients had grade III alopecia.

Among 21 patients who received craniospinal irradiation, four had delays of 7 to 14 days (median 10) in the start of such treatment (beyond day 28 from the start of the third cycle of chemotherapy) because of persistent chemotherapy related myelosuppression. No unusual toxicity was observed during irradiation. The most predominant toxicity with post-irradiation chemotherapy was myelosuppression. Grade III neutropenia occurred in $\geq 60\%$ of patients in each cycle.

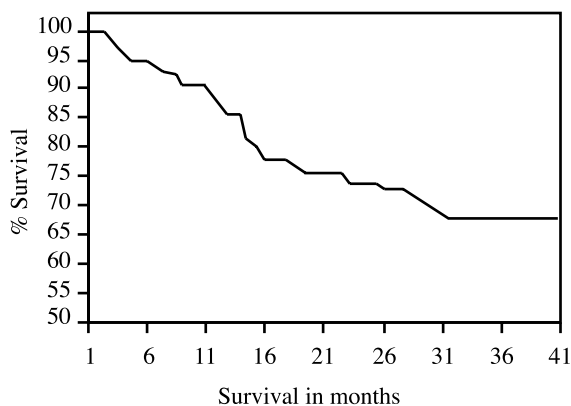


Fig. (1): Progression-free survival of 21 patients with medulloblastoma.

DISCUSSION

Children with incompletely resected medulloblastoma, signs of metastatic disease at diagnosis and those younger than 2-4 years are uniformly identified as "high-risk" cases [8,11,24]. The outcome in patients with high-risk medulloblastoma is less than optimal when treated with resection and craniospinal irradiation only [5,24]. The addition of systemic chemotherapy has improved the outcome in children with residual and/or metastatic disease [5,24]. Studies of pre-irradiation chemotherapy have documented objective disease response and apparent tolerance to radiotherapy [7,11,14,17,19]. The value of pre-irradiation chemotherapy, vs documented efficacy of post-irradiation "adjuvant" chemotherapy, has not been clearly defined [6,7].

The primary rationale for the use of neoadjuvant (pre-irradiation) chemotherapy in infants is to delay the craniospinal irradiation and allow further growth and central nervous system development prior to radiotherapy [4,14,15,17,18,21]. In older children with high-risk disease, the use of neoadjuvant chemotherapy allows the opportunity to test the response of the tumor to the drug therapy [25]. This also allows the chemotherapy to be given without the problem of diminished hematologic tolerance following craniospinal irradiation [14,15,17]. Theoretically, tumor reduction with chemotherapy may facilitate disease control with irradiation. Alternatively, hematologic suppression associated with chemotherapy may delay the initiation of radiotherapy and may cause difficulties in completing craniospinal irradiation [19].

The current study is our first experience with neoadjuvant chemotherapy in newly diagnosed children with high-risk medulloblastoma. Among 21 assessable patients, the overall response rate to three cycles of chemotherapy was 71.4% (15/21 patients). The rate of response associated with current regimen is comparable to other recent pre-irradiation chemotherapy studies in similar groups of newly diagnosed patients [4,7,8,10].

Some issues raised about utilizing pre-irradiation chemotherapy such as: does delay in starting craniospinal irradiation allow progression during chemotherapy? In our patients non-had disease progression during the period of pre-irradiation chemotherapy (12 weeks). In the

French M7 Cooperative study, patients received 8-drugs-in-1-day and high-dose methotrexate prior to and following craniospinal irradiation [7]. Non of the 68 patients were reported to have evidence of disease progression when craniospinal irradiation was delayed for 5 weeks in high-risk patients or 7 weeks in low risk patients, also non of the 15 patients with M0-M1 disease had progressive disease during the 9-week course of pre-irradiation chemotherapy in the study conducted by Mosijczuk et al. [19]. In the study conducted at NCI Cairo, non of the patients developed disease progression during 6 weeks period of pre-irradiation chemotherapy [10]. In contrast with previous report, Harstell et al., using cisplatin or carboplatin and etoposide, \pm cyclophosphamide and vincristine reported that in their older group of patients (≥ 3 years) received 12 weeks of chemotherapy prior to craniospinal irradiation, one-third of the patients had evidence of disease progression by the completion of the chemotherapy [8]. Heideman et al., also reported progression of the disease in 40% of patients (6/15) during the period of pre-irradiation chemotherapy with Carboplatin and Etoposide [9]. Perhaps the most important question raised concerning pre-irradiation chemotherapy: is this delay in craniospinal detrimental to ultimate outcome; i.e., can patients who progress during chemotherapy be salvaged by craniospinal irradiation? In our study, five patients out of ten with PR to pre-irradiation chemotherapy had CR to craniospinal irradiation and three out of six with SD after pre-irradiation chemotherapy had PR after craniospinal irradiation. Harstell et al., however reported that 44% of patients with pre-craniospinal irradiation progression had long-term FFP (free from progression) after craniospinal irradiation [8]. Heideman et al., reported that among six patients with PD during the initial pre-irradiation chemotherapy regimen, secondary disease control was maintained for 12 to 24 months in three before subsequent recurrence; three others have maintained secondary disease control for intervals of 13+ to 60+ months from the time of irradiation [9]. Also, Hussein H.M. and El-Mongy M. in their series reported that 6 patients with stable disease during the 6-weeks period of pre-irradiation chemotherapy, disease control with subsequent craniospinal irradiation was achieved in 5 [10].

While hematopoietic toxicity was the dominant side effect of our pre-irradiation chemo-

therapy regimen, the incidence of grade III and IV hematologic toxicity was similar to that in most other neoadjuvant studies [7,10] and infrequently associated with a delay in the start of craniospinal irradiation.

Conclusion:

The preliminary results of neoadjuvant chemotherapy in-patients with high-risk medulloblastoma are encouraging and this modality of treatment can be applied safely with acceptable toxicity. Studies with large number of patients and long periods of follow-up are required to prove these results.

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