

Medulloblastoma: Conventional Radiation Therapy in Comparison to Chemo Radiation Therapy in The Post-operative Treatment of High-Risk Patients

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ABSTRACT

The aim of this study is to assess treatment results of 48 pediatric high-risk medulloblastoma cases that were treated by surgery, radiotherapy with or without chemotherapy. The impact of adjuvant combination chemotherapy on treatment results will be assessed.

Forty-eight cases of pediatric high-risk medulloblastoma treated from July 2001 to July 2004 were randomized into two groups. The first (group I) included 21 patients who received postoperative cranio-spinal radiation therapy (36Gy+boost 20Gy to the posterior fossa). The second (group II) included 27 cases who received postoperative combination cranio-spinal radiation therapy (with the same dose as the first group) and chemotherapy (vincristine, etoposide, cisplatin). Both groups were compared as regards overall survival (OS), disease free survival (DFS), response rate and treatment toxicity.

In-group I, complete remission (CR) was achieved in 71.4% of the cases; partial remission (PR) in 14.3% of the patients; stationary disease (SD) in 14.3% and none of the cases suffered from progressive disease. The three-year OS was 69.5% and the three-year DFS was 61.3%. In-group II, CR was achieved in 59.3% of the cases; PR in 3.7%; SD in 3.7% and PD in 37.3% of the cases. The three-year OS was 48.4% and the 3-year DFS was 48.9%. Regarding acute treatment toxicity in group I, nine patients (31.5%) developed grade I myelo-suppression and seven cases (24.5%) developed grade II myelo-suppression with three to five days treatment interruption. Whereas in group II, 13 patients (45.5%) developed grade I myelo-suppression and seven cases (24.5%) developed grade II myelo-suppression requiring interruption of treatment for a period ranging from five to seven days with spontaneous recovery. In group I no other acute toxicity was recognized, whereas in group II other toxicities related to chemotherapy were noticed. For example, three patients (11%) developed peripheral neuritis during the course of treatment and two patients (7%) developed renal impairment, which responded to medical treatment. Late treatment toxicity, manifested as reduction in intelligence quotient (IQ), was noticed, which makes conventional treatment of medulloblastoma unsatisfactory. In group I; 13 patients (62%) suffered a reduction of 8-20% in IQ in comparison to their normal

siblings, whereas in Group II; 13 patients (48%) developed a reduction in IQ ranging from 12-21%.

Conclusion: The current treatment of medulloblastoma has a detrimental effect on long-term survivors. Whereas acute toxicity is considered mild and tolerable, late toxicity regarding diminution in IQ makes current treatment unsatisfactory because of the long-term mental disability of the cured patients. We believe that, the poorer outcome in the chemo-radiation group was due to the treatment interruption during radiation therapy caused by myelosuppression since the incidence of myelosuppression was higher in the chemo-radiation group and the recovery time was longer.

Key Words: Medulloblastoma - Pediatric - Chemotherapy - Radiotherapy.

INTRODUCTION

Medulloblastoma accounts for approximately 20% of all primary pediatric CNS tumors, 40% of all tumors arising from the cerebellum and it is the most common malignant brain tumor of childhood. The peak age of incidence is between 3 and 4 years; and boys are affected two times as common as girls [1]. Medulloblastomas often grow invading the surrounding CNS structures. Wide spread seeding of the sub-arachnoid space may occur. The reported frequency of CNS spread outside the area of the primary tumor at diagnosis is 11% to 43% and such spread eventually occurs in as many as 93% of patients [2,3].

Multimodality treatment regimens have substantially improved survival in this disease, however the tumor is incurable in about a third of patients. Current treatment has not improved long-term survival to a satisfactory degree. Several pathways have been involved in the patho-

genesis of medulloblastomas such as N-myc, C-myc and epidermal growth factor receptor (EGFR) genes amplification. The knowledge of these pathways has been used to develop new ways of treating children with medulloblastoma [4].

The use of adjuvant chemotherapy in cases of medulloblastoma is justified by several criteria, which are partially related to the tumor and partially related to the patient. These include the rapid rate of growth and high mitotic index of medulloblastoma cells, chemo-responsiveness of the tumor cells to a variety of agents and tendency of the disease to metastasize systemically or via the cerebrospinal fluid. Moreover, the distorted blood brain barrier due to the disease and surgical intervention allows the passage of chemotherapy offering a therapeutic option. Chemotherapy overcomes the treatment failure caused by under dosage at field junctions and the hazardous late effects of radiation on the skull, spine and central nervous system development, which could be reduced by adding chemotherapy. Moreover, the drugs used for medulloblastoma cases are lipophilic, readily cross the blood brain barrier and have a radiosensitizing effect [5,6]. On reviewing the literature, small-scale studies and trials revealed an improved disease free survival (DFS) in patients treated by combined modalities and poor survival results with conventional treatment (surgery and cranio-spinal irradiation).

PATIENTS AND METHODS

The present study is a prospective analysis of the treatment results of 48 cases of pediatric high-risk medulloblastoma attending the pediatric unit of Kasr-El-Aini center of Radiation Oncology and Nuclear Medicine (NEMROCK) from July 2001 to July 2004. The patients were followed-up for 3 years.

Eligibility criteria are a minimum age of 3 years and a maximum age of 18 years, normal blood count, normal liver and kidney function tests at the start of treatment, absence of

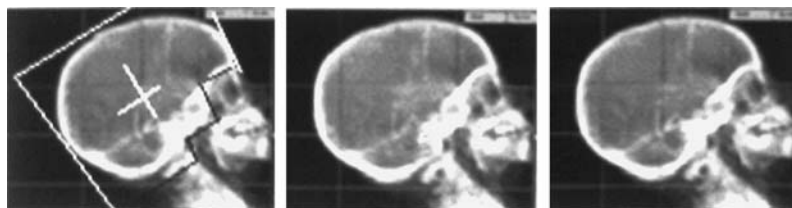
metastases, Karnofsky performance status not less than 60% and a diagnosis confirmed by surgical biopsy or excision. High-risk patients are those who have one or more of the following criteria:

Positive CSF
T3 and T4 lesions
Ependymal or glial differentiation
<4 years of age

All cases had a radiological assessment by postoperative cranio-spinal MRI and chest X-ray. Laboratory assessment of the patients included cerebrospinal fluid cytology, complete blood picture, liver and kidney profiles. Clinical assessment of the patients included the onset, duration and the main presenting symptoms of the disease. Finally neurological assessment of the patients was performed and evidence of consanguinity was recorded.

In order to evaluate the role of chemotherapy in high-risk medulloblastoma, patients eligible for the study were randomized either to receive post-operative cranio-spinal irradiation (group I) or combined post-operative chemo and radiotherapy (group II). Both groups were compared as regards response rate, treatment results, overall survival (OS), disease free survival (DFS), and treatment toxicity. Group I included 21 patients (43.7%) and group II included 27 patients (56.2%).

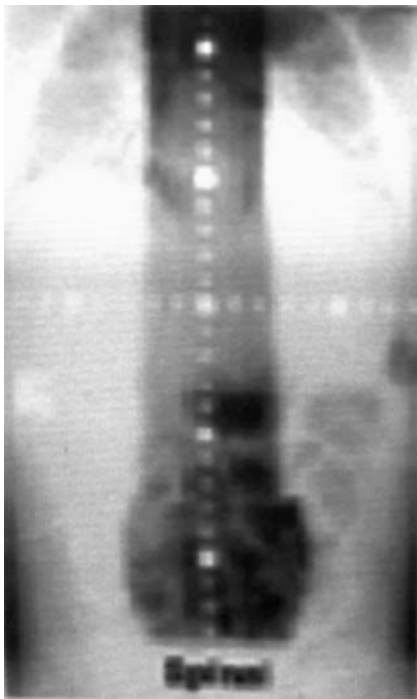
Radiation therapy was given by cobalt machine at SSD 80cm with orbit fixation at a dose of 3600 cGY to the whole cranium and a boost of 2000 cGY to the posterior fossa. Spinal radiation was given at a dose of 3600 cGY by two fields; the first field from C2 to L₁/L₂ and the second field from L₁/L₂ to S₂/S₃. Spinal radiation was given at a dose of 150 cGy per fraction, 5 fractions per week for 4-5 weeks with monitoring of the patient by complete blood picture (CBC) twice weekly [5-7]. WHO grading criteria were used for recording toxicity.



(A) Whole brain field.



(B) Posterior fossa field.



(C) Spinal field.

As regards chemotherapy, vincristine was given at a dose of $1.4\text{mg}/\text{m}^2$ weekly during spinal radiation therapy. After cranio-spinal radiation therapy, patients received 4 cycles of etoposide $100\text{mg}/\text{m}^2$ D₁ to D₃ and cisplatinum $75\text{mg}/\text{m}^2$ D₁. Chemotherapy cycles were given every 21 days and had to be preceded by a normal complete blood picture (CBC), serum creatinine and creatinine clearance [8-10]. WHO grading criteria were used for recording toxicity.

All cases were followed-up monthly by neurological examination and monitored for treatment toxicity as well as every 3 months by cranio-spinal MRI, chest X-ray and CSF cytology.

Statistical Methods:

Chi-square/Fisher exact tests compared independent proportions. Kaplan-Meier-estimated overall and disease free survival rates and log rank test compared groups. *p*-value is significant at 0.05 levels [11].

RESULTS

In the present study, the mean age of patients in group I was 6.95 years, while in group II it was 6.92 years. The mean duration of symptoms was 4.04 months in group I, whereas in group II it was 2.92 months. In group I, there were 15 males representing 71.4% and six females representing 28.6% of cases. Whereas in group II, there were 17 males representing 63% and 10 females representing 37% of the cases.

In group I, the most common presenting symptom was symptoms of increased intracranial tension (\uparrow ICT); 19 cases (90.5%) followed by Ataxia; 15 cases (71.4%), neurological deficits; 12 cases (57.1%), and squint; 8 cases (38.1%). In group II, the most common presenting symptom was also increased intracranial tension; 25 cases (92.6%), followed by neurological deficits; 19 cases (70.4%), ataxia; 15 cases (55.6%), and finally squint; 14 cases (51.9%).

In group I; an incisional biopsy was done in 8 cases (38.1%), total excision of the tumor was done in 12 cases (57.1%) and a stereotactic biopsy was done in 1 case (4.8%). A shunt was inserted in 11 cases (52.4%) and CSF cytology was positive in only four cases (19%). In group II; an incisional biopsy was done in 15 cases (55.6%), total excision was done in 11 cases (40.7%) and a stereo-tactic biopsy was done in 1 case (3.7%). A shunt was inserted in 15 cases (55.6%) and CSF cytology was positive in only six cases (22.2%).

In group I, the pathology revealed a desmoplastic medulloblastoma in 9 cases (42.9%) and a classic medulloblastoma in 12 cases (57.1%), whereas in group II, a desmoplastic medulloblastoma was diagnosed in 9 cases (33.3%) and a classic medulloblastoma in 18 cases (66.7%).

Regarding treatment response in group I: CR (complete remission; defined as complete disappearance of the tumor) occurred in 15

cases (71.4%), PR (partial response; defined as 75% reduction in the size of the tumor) occurred in 3 cases (14.3%), SD (stationary disease; defined as 25% reduction in the size of the tumor) occurred in three cases (14.3%), whereas PD (progressive disease) was not observed. In group II: CR occurred in 16 cases (59.3%), PR occurred in 1 case (3.7%), SD in one case (3.7%) and PD in nine cases (37.3%). The difference in the incidence of disease progression between the two groups was statistically significant by Fisher exact test ($p=0.004$) (Table 1).

As regards survival, the overall survival for both groups was 57.4%, the three-year survival for group I was 69.5% and 48.9% for group II. The difference was statistically non-significant ($p=0.09$) (Fig. 1). The three-year disease free survival was 63.3% for group I and 48.9% for group II (Fig. 2). The difference was statistically not significant.

The three-year survival for patients who underwent incisional biopsy was 69.63%, whereas for those performing complete surgical excision, it was 58.1% with a non-significant statistical difference ($p=0.50$) (Fig. 3).

In group I; 14 cases were alive and free (66%), 2 cases died with disease (9.3%) and 5 cases were alive with disease (23.8%). In group II; 11 cases died with disease (40.7%) and 16 cases were alive and free (59.2%). The difference between the two groups was statistically non-significant ($p=0.99$) (Table 2).

On analyzing the pattern of failure in group I, one patient developed a spinal lepto-meningeal relapse and three cases revealed local failure. In group II, spinal relapse occurred in 4 cases and local failure occurred in 5 cases.

Regarding acute treatment toxicity in group I; nine patients (31.5%) developed grade I myelosuppression and 7 cases (24.5%) developed grade II myelosuppression with three to five days treatment interruption. In group II; 13 patients (45.5%) developed grade I myelosuppression and 7 cases (24.5%) developed grade II myelosuppression requiring interruption of treatment for a period ranging from five to seven days with spontaneous recovery. In group I no other acute toxicity was recognized, whereas in group II other toxicities related to chemotherapy were noticed. For example, three pa-

tients (11%) developed grade II peripheral neuropathy (mild paraesthesia and loss of deep tendon reflex) during the course of treatment and 2 patients (7%) developed grade I-II renal impairment (nephrotoxicity caused by cisplatinum), which responded to medical treatment (grade I, creatinine <1.5 times the normal limit; grade II, creatinine 1.5-3 times the normal limit). Grade III alopecia developed in all patients but hair growth was noticed six weeks after ending radio and chemotherapy. In comparison, late treatment toxicity was noticed regarding reduction in IQ (Intelligence Quotient) which makes conventional treatment of medulloblastoma unsatisfactory. In group I, 13 patients (62%) suffered a reduction in the range of 8-20% in IQ in comparison to their normal siblings. Similarly, 13 patients (48%) in group II developed a reduction in IQ ranging from 12-21%. Consequently, the conventional treatment of medulloblastoma is considered unsatisfactory.

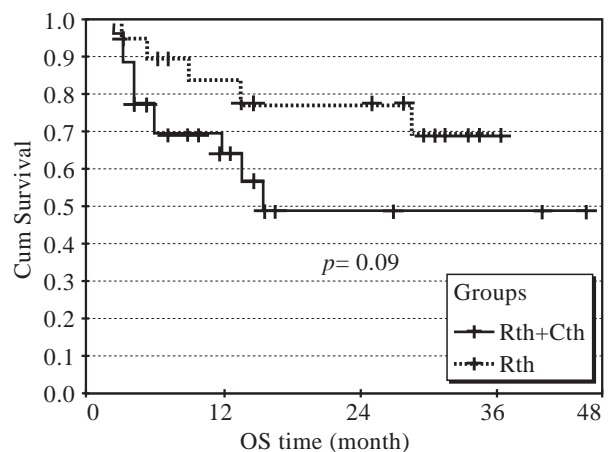


Fig. (1): Overall survival according to adjuvant therapy.

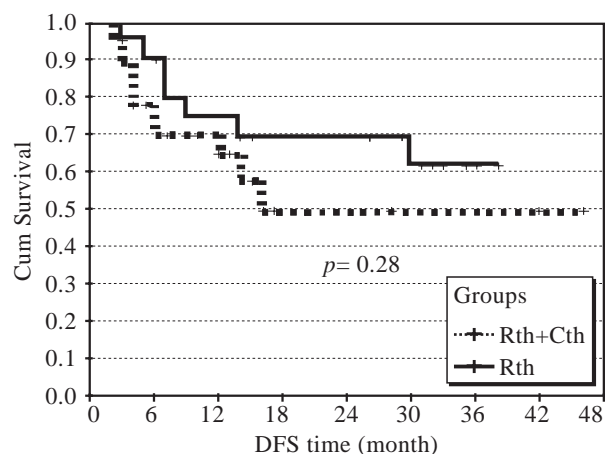


Fig. (2): Disease free survival according to adjuvant therapy.

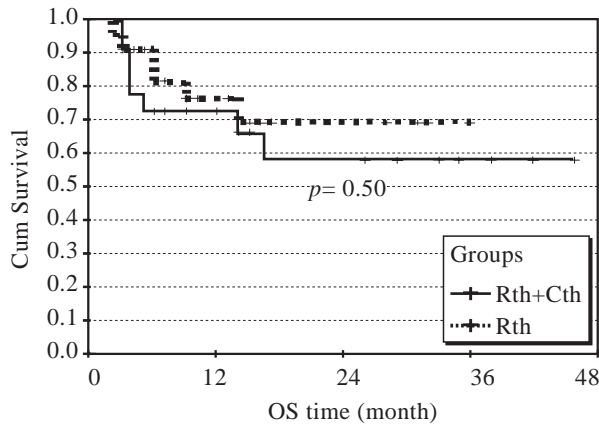


Fig. (3): Overall survival according to the type of surgical excision.

Table (1): Treatment response.

Response	Radiation group	Radio/chemo group
CR	71.4%	59.3%
PR	14.3%	3.7%
SD	14.3%	3.7%
PD	—	37.3%

CR: Complete remission, PR: Partial remission, SD: Stationary disease, PD: Progressive disease.

Table (2): Treatment results as regards survival and treatment failure

Status	Group I	Percentage	Group II	Percentage
Alive and free	14	66%	16	59.2%
Died with disease	2	9.3%	11	40.7%
Alive and with disease	5	23.8%	—	—

DISCUSSION

The present study is a prospective analysis of the results of treatment of 48 pediatric high-risk medulloblastoma cases.

In the present study, the mean age of patients was 6.9 years. This coincides with the work of Paulino, [12] where the mean age was 7.2 years and Modha et al. [13] where the mean age was 7.8±4.2 years.

Our data show that the most common presenting symptom was increased intracranial tension (↑ICT) in 91.7% of the cases followed by neurological deficit in 64.6%, ataxia in 62.5%

and squint in 45.8% of the patients. These observations regarding symptomatology resemble the work of Prados and Wara [14] where increased intracranial tension was the most common presenting symptom followed by ataxia and neurological deficit. In the present study, total excision of the tumor was performed in 47.9% of cases, excision biopsy in 47.9%, stereotactic biopsy in 4.2% and a shunt was inserted in 52% of the cases. This coincides with the work of Khafaga et al. [15] where 61% of the cases underwent excision biopsies, complete excision of the tumor was performed in 30.8%, and stereotactic biopsies in 4%, of the patients. In addition, a shunt was introduced in 66.4% of the cases. Our current study does not resemble the work of Modha et al. (13) where complete tumor excision was done in 75% of the cases, subtotal excision in 25% of the cases and ventriculo-peritoneal shunts in 47% of the cases.

In our study, the 3-year OS for patients receiving cranio-spinal radiation therapy alone was 69.5% and the 3-year DFS was 63.3%. On the other hand, the 3-year OS and the 3-year DFS for patients receiving cranio-spinal radiation therapy and chemotherapy were 48.9% and 48.9% respectively. These results are less than those obtained by La et al. [16] who reported a three-year survival and a three-year DFS for the radiotherapy treated group of 64.9% and 74% respectively. Moreover, for the chemoradiotherapy treated group, a three-year survival and a three-year DFS of 54%, and 91% respectively were obtained. The present results also resemble the results of Packer et al. [17] where the three-year OS and the three-year DFS for the radiotherapy treated group were 65.1%, and 57.3% respectively; whereas for the combined chemo radiotherapy group, the survival rates were 56% and 61% respectively.

In this study, the three-year survival for patients who performed surgical biopsy was 69.63% and it was 58.1% for those performing total excision of the tumor. These results are more or less similar to the results of Khafaga et al. [15] where the three-year survival for patients performing surgical biopsy was 79.1% and for those performing total excision was 63.2% with a statistically non-significant difference. Our results are consistent with those of Modha et al. [13] and Kocsis and Sjekely [18] who found no significant difference in survival

figures between patients performing total resection and those performing surgical biopsy only.

In the current study, the three-year survival and the three-year DFS for patients receiving cranio-spinal radiotherapy were 69.5% and 63.3% respectively. Fukunaga et al. [19] obtained slightly better survival figures (72.3% OS and 67.1% DFS). This was achieved by using lesser radiotherapy volumes in the form of stereotactic radiation therapy boost to the posterior fossa lesion instead of radiation to the whole posterior fossa. The advantage of this treatment modality was that, it induces less reduction in I.Q. and verbal skills. However, 14/27 of the cases studied exhibited local failure and 11 cases developed a spinal lepto-meningeal failure.

Our data showed that, the 3-year survival and the 3-year DFS for patients receiving combined chemo-radiotherapy was 48.9% and 48.9%, respectively. In comparison, Grill et al. [20] achieved a 3-year survival of 61.75% and a three-year DFS of 56.3% using combined chemotherapy and low dose radiotherapy (2400 cGy). Children who received the lower doses had less drop in verbal comprehension scores. Their full scale IQ (FSIQ) was around 76.9 whereas children who received higher doses had an (FSIQ) of 63.7 or less.

In our study, 66% of cases are alive and free of disease, 23.8% are alive with disease, and 9.3% of cases died in the radiation therapy group. Whereas in the combined chemo-radiation therapy group, 59.2% of cases are alive and free 40.7% of the cases died. This is more or less similar to the work of Pezzota and Cardero di Monteremolo [21] where 55.2% of the cases were alive with disease and 55.8% of the cases died in the chemo radiotherapy group. The present work also resembles the work of Calaminus et al. [22], where 56.7% of the cases were alive and free, 32.4% of the cases died, and 10.8% of the cases were alive with disease in the chemo radiotherapy group.

On analyzing the pattern of failure in group I, one patient developed a spinal lepto-meningeal relapse and three failed locally. In group II, spinal lepto-meningeal relapse occurred in four cases whereas local failure occurred in five cases. These results were different than the results of Sun et al. [23] who performed a study on 35 patients with high-risk medulloblastoma.

They obtained failure to treatment in 10 cases; four of them suffered from a local failure and six developed a spinal lepto-meningeal failure.

Acute toxicity of our current treatment is considered mild and tolerable, whereas late toxicity regarding diminution in IQ makes current treatment unsatisfactory because of the long-term mental disability of long-term survivors. Our results are similar to the results of Walter et al. [24] who reported an average loss of 4 to 6 IQ points per year and did not reach a plateau with time. Dennis et al. [25] reported that 90% of the surviving children had impaired intelligence. Mulhern et al. [26] added that the younger the age, the more critical the impairment of intelligence. Children younger than 9 years suffer the most. Silverman et al. [27] noticed that, irradiated children had an IQ 12 to 17 points below the non-irradiated siblings. Moreover, Kioffer et al. [28] found in their study on pediatric medulloblastoma patients treated with variable doses of cranio-spinal irradiation that, neuropsychological deficits in patients treated with lower doses had less affection in verbal and non-verbal skills and less reduction in IQ. However, these results were not statistically significant in comparison to the other patients treated with higher doses.

In conclusion, the current treatment of medulloblastoma has a detrimental effect on long-term survivors. Acute toxicity of our current treatment is considered mild and tolerable. Whereas, late toxicity regarding diminution in IQ and the poor survival figures make current treatment for medulloblastoma unsatisfactory because of the long-term mental disability of the cured patients and the poor survival outcome in high-risk cases. Thus, refinements in treatment are recommended and should be focused on improving the quality of life and raising the survival figures. We believe that further improvement can be achieved. This entails identifying the groups of children who would benefit from lower doses of radiation without affecting cure rate. In addition to making our radiation conformal to minimize the dose delivered to normal tissues.

Moreover, we believe that the poorer outcome in the chemo-radiation group was due to the treatment interruption during radiation therapy caused by myelosuppression. This is because the incidence of myelosuppression was

higher in the chemo-radiation group and the recovery time was longer.

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