Concomitant Weekly Vincristine and Radiation Followed by Adjuvant Vincristine and Carboplatin in the Treatment of High Risk Medulloblastoma: Ain Shams University Hospital and Sohag Cancer Center Study

MAMDOUH M. SALAMA, M.D.*; EHAB M. GHORAB, M.D.**; ASHARAF G. AL-ABYAD, M.D.* and KHALED M. AL-BAHY, M.D.*
The Departments of Neurosurgery* and Radiation Oncology & Nuclear Medicine**, Ain Shams University.

ABSTRACT

**Purpose:** To evaluate survival, progression free survival (PFS) and toxicity of children with newly diagnosed high risk medulloblastoma who were treated with weekly vincristine concurrently during irradiation followed by adjuvant carboplatin and vincristine.

**Patients and Methods:** High risk medulloblastoma patients with postoperative gross residual disease that was >1.5cm² and/or metastatic disease (M+) were planned to receive craniospinal irradiation (CSI) 36 Gy followed by boost to the posterior fossa for a total of 55.8 Gy. Concomitantly during radiation, patients received weekly vincristine 1.5mg/m². Six weeks after completion of radiation therapy, patients were scheduled on a regimen of weekly vincristine (1.5mg/m²) and carboplatin (150mg/m²) for 4 weeks, 3 weeks rest then another cycle for a total of 48 weeks.

**Results:** The study included seventeen high risk medulloblastoma patients presented to Ain Shams University hospitals and Sohag Cancer Center between November 2001 and March 2005. Their median age was 8.4 years (range from 5 to 14 years), they were 12 males and 5 females. The overall survival at three year was 70.6% and the 3-year PFS was 58.8%. The 3-year overall survival for M+ patients was 50% Vs. 81.8% for M0 patients (p=0.04). The 3-year PFS was 50% for M+ patients Vs. 63.6% for M0 patients (p=0.15). The treatment was well tolerated. During CSI, 3 patients only (17.6%) developed grade 3 neutropenia. During adjuvant chemotherapy, the complications were more frequent and of deeper degree. Grade 3 and 4 neutropenia were observed in 5 patients (29%). One patient (6%) developed grade 3 peripheral neuropathy.

**Conclusion:** Our results show that the present chemotherapy and radiotherapeutic approach is able to improve overall survival and PFS in high risk patients with gross residual disease but not in patients with metastatic disease (M+) that may require more intensive therapy.

Key Words: Medulloblastoma - Radiation - Vincristine - Carboplatin.

INTRODUCTION

Medulloblastoma (MB) is a highly malignant embryonal tumor arising in the cerebellum, and accounting for approximately 20%-25% of pediatric central nervous system neoplasms [1,2]. For decades, the standard therapy for MB has been maximal surgical resection followed by craniospinal irradiation (CSI) to a dose of 35 to 36 Gy with a boost to the posterior fossa, thus giving a total of 55-56 Gy with 5 year progression free survival (PFS) and overall survival of 50% to 65% [3,4]. Current clinical trials and standard management define high risk patients as those children younger than 3 years, with overt metastatic disease (M+) based on CSF cytology or neuroimaging, or those who have more than 1.5cm² residual on early post-operative imaging [5]. For high risk patients, especially those with M+, the 5 year PFS and survival with radiation only was 0% to 30% [6,7]. A small but significant survival benefit was demonstrated for the use of chemotherapy for high risk patients [8,9]. The International Society of Pediatric Oncology (SIOP-1) performed a randomized study of CCNU and vincristine chemotherapy after radiation versus radiation alone in patients with MB. The improvement in disease free survival was noted.
only in subgroups of patients with poor risk factors, including brain stem involvement and metastatic patients (M+) [8]. This was confirmed with subsequent Children Cancer Group (CCG-942) study [9].

Chemotherapy for MB has been evaluated in both the adjuvant (post-irradiation) and neoadjuvant (pre-irradiation) setting. A recently completed PNET-3 study, in which 179 MB patients randomly assigned to be treated with radiation alone or 4 cycles of chemotherapy (vincristine, etopside, carboplatin and cyclophosphamide) followed by radiation. The benefit of neoadjuvant chemotherapy versus radiation therapy was demonstrated only in M0/M1 patients [3]. Several clinical trials proved that PFS and overall survival were in favor of adjuvant compared to neoadjuvant chemotherapy. Progressive disease rate of 20%-30% have occurred during various neoadjuvant regimens. Neoadjuvant chemotherapy was accompanied by increased myelosuppression causing a higher rate of interruption and extended overall treatment time. Current studies indicate that radiotherapy should start ideally within 4 weeks of surgery and definitely not more than 6 weeks after surgery. The authors concluded that adjuvant chemotherapy would seem to be more effective [10-17].

Platinum drugs and vincristine are of the more commonly utilized drugs for children with MB. There appears to be a dose response effect for carboplatin, with response rates of 32% using 560mg/m² every 4 weeks and 43% for 175mg/m² weekly [18]. Vincristine has been widely used both during irradiation and in combination chemotherapy given before or after irradiation with proven effect [9-17].

Based on the above mentioned data, we designed our study to evaluate the regimen of weekly vincristine concurrently during irradiation followed by adjuvant carboplatin and vincristine in high risk MB patients. The primary end point was survival and PFS and the secondary end point was pattern of failure and toxicity.

PATIENTS AND METHODS

This prospective single arm trial was conducted on 17 patients who were at least 3 years old, with histologically proven MB. Initial evaluation included: History, and physical examination, complete blood count, serum chemistries and chest X-ray. Before study entry, postoperative magnetic resonance imaging (MRI) of the entire brain and spine, performed with and without gadolinium enhancement was required. The spinal axis had to be visualized in at least two planes. CSF cytologic examination was obtained at time of surgery or postoperatively by lumber puncture. The extent of surgical resection was indicated by the neurosurgeons' report in the protocol of operation and postoperative computer tomography of the brain that should be performed 24 hours after tumor resection. Tumor staging was determined according to Chang classification [19]. Other eligibility criteria included, adequate hematologic status (leukocyte count >4000/uL, absolute neutrophil count >1500/uL, platelets >100,000/uL and hemoglobin >10mg%), adequate kidney function (creatinine <1.5mg/dL), adequate liver functions (bilirubin <2mg/dL, and transaminase levels < three times the upper normal limit). Exclusion criteria included no evidence of extraneural distant metastasis (M4), no prior malignancy, no prior radiotherapy or chemotherapy to the head and neck region and no concurrent serious medical illness. Eligible patients were assigned to receive weekly vincristine concomitant with irradiation followed by carboplatin and vincristine for 48 weeks. Parents of each patient gave written informed consent before entering the study.

Treatment plan:

Radiation therapy was administered with Cobalt-60 machine or 4-6 MV linear accelerator. All patients were treated in prone position in a head immobilization device. Radiation therapy requires the systemic inclusion of the entire subarachenoid space (full neuraxis irradiation, CSI) followed by boost to posterior fossa. For CSI administration, the patients were treated with two parallel opposed lateral fields including the cranium and upper cervical spinal canal, matching a posterior spinal field. The cranial fields must be planned carefully to include the entire intracranial subarachnoid space including cribiform palate and infratemporal regions. The lower border of cranial fields was set at the C3-4 junction. The upper border of the spinal field matched the lower border of cranial field. The lower border of the spinal field is set to encompass the lowest level of the thecal sac as determined by MRI, typically at or below S2. The width of the spinal field should be
sufficient to dosimetrically encompass the full width of the spinal canal. A spade configuration is necessary to allow adequate lateral coverage of the sacral nerve roots at the lower sacral margin. For larger children, two matched fields (upper and lower fields) were used. Gap junctions were used between the whole cranium and the spinal field and between spinal fields whenever two spinal fields were needed. It is important to feather all junctional zones, shifting the anatomic junction site by at least 5mm every 8-9 Gy, effectively once a week. For the posterior fossa volume, the upper border was set 1cm higher than the midpoint between the foramen magnum and the cortex. The anterior border was the posterior clinoid. To cover the inferior and posterior borders, field edge margins were set beyond the clavarium, with a lower border typically at the lower border of C1. Radiotherapy was given in daily fractions, 1.8 Gy per fraction, 1 fraction per day, 5 days per week. Doses of 36 Gy were given over 20 fractions over a period of 4 weeks followed by a boost to the posterior fossa to 55.8 Gy. For CSI, the dose to the head was specified at the midplane of the central axis, and for the spinal component, to the anterior spinal cord on the central axis. A 10 Gy boost was administered locally in case of spinal metastasis.

The chemotherapy consisted of two drugs, vincristine and carboplatin. During radiotherapy, weekly vincristine was given at a dose of 1.5mg/m² (maximum 2mg). Six weeks after completion of radiation therapy, patients were started on a regimen of weekly vincristine (1.5mg/m²) and carboplatin (150mg/m²) for 4 weeks, 3 weeks rest then another cycle for a total of 48 weeks. All patients underwent complete blood picture and blood chemistry before each cycle of chemotherapy.

Contrast enhanced MRI of the brain and spine were performed 6 weeks after radiotherapy and before initiation of adjuvant chemotherapy and then every 3 months (after every 2 cycles of chemotherapy) for 2 years then annually. At time of clinical abnormality suggestive of disease relapse or progression, patients were to have MRI of the entire neuraxis and CSF cytology sampled.

**Evaluation of response:**

Response criteria were evaluated from radiological brain imaging (including computerized tomography and gadolinium enhanced magnetic resonance imaging) performed one month after completion of radiation therapy and at the end of chemotherapy together with clinical responses by assessing the patient performance status and steroid dependence after treatment [20]. The responses were then graded into four categories:

- Complete response (CR): Disappearance of all enhancing tumor on consecutive brain imaging scans, not receiving corticosteroids, and neurologically stable or improved.
- Partial response (PR): >50% reduction in size of enhancing tumor on consecutive brain scan, corticosteroid dosage stable or reduced, and neurologically stable or improved.
- Progressive disease (PD): >25% increase in the size of enhancing tumor or any new tumor on brain scans, or neurologically worse, and corticosteroid dosage stable or increased.
- Stable disease (SD): All other situations.

**Survival and progression free survival:**

Survival was measured from the date of entry into the trial until death from any cause or last follow-up. PFS was measured from the date of entry into the trial until date of first evidence of disease progression or death from disease. The method of Kaplan-Meier was used to estimate survival and PFS [21]. The log-rank statistical test was applied for the comparisons of the functions. The difference was statistically significant if p-value <0.05.

**Assessment of normal tissue toxicity:**

Toxicity was evaluated according to National Cancer institute (NCI) criteria [22].

**RESULTS**

The study included seventeen patients with histologically proven MB presented to Ain Shams University hospitals and Sohag Cancer Center between November 2001 and March 2005. The characteristics of the treated patients are detailed in Table (1). The median age was 8.4 years (range from 5 to 14 years), 12 were males and 5 were females. Tumor extension was classified according to the Chang classification [19]. Twelve patients (71%) presented with T3 stage and 6 patients (35%) were found to have metastatic disease (M+) at time of diagnosis. Four patients underwent biopsy only...
and 13 patients had partial surgical resection. Shunt surgery was carried out in 12 patients (71%).

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Bone metastasis developed in one of the two patients who have neuraxis dissemination only. All the patients who developed neuraxis dissemination originally had metastatic disease “M+” (3 out of 6 patients with metastatic disease). All but two of the patients who had complete clinical and radiological response to treatment remain disease free through the study while all patients who had less than complete response recurred or progressed.

Survival and progression free survival:

The median follow up duration was 32 months (range from 8-43 months). The overall survival at three years was 70.6% (95% confidence interval 65.7%-75.8%) (Fig-1) and the 3-year PFS was 58.8% (95% confidence interval 53.6%-64.9%) (Fig-2). The median survival was 32.35 months (95% confidence interval 27.54-37.15) and the median time to disease progression was 29.76 months (95% confidence interval 23.97-35.55). The 3-year overall survival for M+ patients was 50% (95% confidence interval 43%-57%) vs. 81.8% (95% confidence interval 74.8%-88.2%) for M0 patients (Fig. 3). The difference was statistically significant (p=0.04). The 3-year PFS was 50% (95% confidence interval 43%-57%) for M+ patients vs. 63.6% (95% confidence interval 55.3%-71.6%) for M0 patients (Fig. 4). The difference was not statistically significant (p=0.15).

Toxicity:

A- Radiotherapy:

The median duration for radiotherapy course was 46 days (average 42-55 days). The most frequent side effect of radiotherapy observed in all patients was loss of hair (alopecia) in areas of irradiation. Grade 1/2 Myelosuppression, expressed by decreased number of leukocytes was observed in 13 patients (76%). Three patients (17.6%) developed grade 3 neutropenia that required treatment interruption and symptomatic treatment. No grade 4 myelosuppression had been recorded. All the patients had variable degree of dyspepsia (nausea, vomiting and sickness) especially towards the end of CSI course that required treatment interruption in only 3 patients (17.6%). No grade 2 or greater late radiation toxicity was encountered. There was no evidence of radiographic or symptomatic radiation necrosis.

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<th>Table (1): Baseline demographic features and tumor characteristics for 17 high risk MB patients.</th>
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<td>No. of patients</td>
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<td>M3</td>
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<tr>
<td>Extent of surgical resection:</td>
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<tr>
<td>Biopsy</td>
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<td>Partial resection (50%-90% resection)</td>
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Response:

All patients had bidimensionally measurable disease on MRI at study entry. Twelve patients (71%) achieved complete response. Complete remission was achieved in 9 out of 11 patients (81.8%) with M0 and in 3 of 6 patients (50%) with M+. Partial response or stable course of disease was observed in 4 patients (23%). The disease progressed during adjuvant chemotherapy in only one patient that necessitated only best supportive care.

<table>
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<th>Table (2): Response criteria after chemoradiation treatment for 17 high risk MB patients.</th>
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<td>Complete response</td>
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<td>M0 (11 patients)</td>
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<td>M+ (6 patients)</td>
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<td>Partial response</td>
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<td>Stable disease</td>
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<td>Progressive disease</td>
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Recurrence or progression of MB after treatment was observed in 7 patients (41%): 4 patients (23.5%) were diagnosed to have local recurrence of the tumor, 2 patients (12%) had neuraxis dissemination, and one patient (6%) had both local recurrence and neuraxis dissemination. Bone metastasis developed in one of the two patients who have neuraxis dissemination only. All the patients who developed neuraxis dissemination originally had metastatic disease “M+” (3 out of 6 patients with metastatic disease). All but two of the patients who had complete clinical and radiological response to treatment remain disease free through the study while all patients who had less than complete response recurred or progressed.
B- **Chemotherapy:**

Fourteen patients (82.4%) completed the planned course of chemotherapy. Three patients didn’t receive the planned chemotherapy course because of disease progression. Grade 3 and 4 neutropenia that required hospital admission and treatment with colony stimulating factors and broad spectrum antibiotics were observed in 5 patients (29%). No grade 3 or 4 anemia or thrombocytopenia was recorded. Mild degree of peripheral neuropathy (grade 1 or 2) was observed in all patients that were relieved by 50% reduction of vincristine dose till recovery. One patient (6%) developed grade 3 peripheral neuropathy that required treatment interruption. All patients experienced mild degree (grade 1/2) of nausea and vomiting during chemotherapy that didn’t interfere with chemotherapy administration. No ototoxicity or renal impairment was observed.

**DISCUSSION**

In our study, complete clinical and radiological response which based mainly on tumor size was observed in 12 of patients (71%). Complete remission was achieved in 9 out of 11 patients (81.8%) with M0 and in 3 of 6 patients (50%) with M+. All complete responders but two remained disease free throughout the study while all patients who had less than complete response recurred or progressed. Recurrence or progression of MB after treatment was observed in 7 patients (41%). All the patients who developed neuraxis dissemination originally had metastatic disease “M+”. Kortmann et al., 2000 (German HIT “91”) randomized 137 patients to receive either postoperative chemotherapy (ifosfamide, etopside, high dose methotrexate, cisplatin and cytarabine for 22 weeks) prior to radiation therapy (72 patients) or immediate
postoperative radiation therapy concomitant with vincristine followed by 8 cycles of maintenance chemotherapy (cisplatin, vincristine and CCNU) (65 patients). Maintenance chemotherapy would seem to be more effective in this study. In the group of patients who received immediate postoperative radiation and maintenance chemotherapy, 22 patients had gross residual tumor, and 14 patients had metastatic disease (M2-3). Complete remission was achieved in 17/22 patients (77.2%) with gross residual disease. What was surprisingly high and unexplainable is that, 85.7% of patients with metastatic disease (12/14 patients) had complete response (18). Rutkauskiené and Labanauskas, 2005 performed a randomized trial comparing radiation therapy alone versus concomitant chemoradiation followed by vincristine, CCNU and cisplatin in high risk MB patients. Complete radiological response was higher in chemoradiation group compared with radiation only group (100% Vs. 33.3%). All patients treated with radiation alone relapsed within 2 years after diagnosis [23]. These results were based mainly on changes in tumor size. Contrast enhancement on CT or MRI, while not a true representation of tumor size as it demonstrates the region of blood brain barrier disruption, is accepted as a surrogate for tumor size. However as the size of region of enhancement is altered by surgery, radiotherapy and by the use of steroids, this is why most authors didn't rely on tumor response as a valuable measure for assessment of treatment strategy in brain tumors [10-17].

Although usually five years rates are proposed for the analysis of survival data, three year survival rates were used in our study because of short time of follow-up. In our study the 3-year PFS was 58.8% and 3-year overall survival was 70.6%. The 3-year overall survival for M+ patients was 50% Vs. 81.8% for M0 patients. The difference was statistically significant (p=0.04). The 3-year PFS was 50% for M+ patients Vs. 63.6% for M0 patients. The difference was not statistically significant (p=0.15) mostly because of small number of patients. Reviewing the literature confirmed the impact of neuraxis dissemination at diagnosis on early tumor progression and relapse [9,14,15, 23-25]. The Children’s Cancer Group conducted a randomized phase III study (CCG 942) which compared radiotherapy alone to radiotherapy followed by adjuvant CCNU, vincristine and prednisone. The benefit of chemotherapy was significant only for patients with high M-stage and T3-T4 disease. The 5 year PFS for these poor risk patients was 46% if chemotherapy was given versus 0% without chemotherapy. Five- year event free survival of 40% was observed for patients with M1 disease as compared to 59% for patients with M0 disease [9]. In a multi-institutional single arm trial for MB patients treated postoperatively with CSI concomitant with vincristine followed by 6 cycles of cisplatin, vincristine and CCNU. This regimen resulted in 5 year PFS rate of 90% for patients with localized disease and 67% in 15 patients with metastatic disease [24,25]. In CCG trial (CCG 921) comparing the 8 drugs (vincristine, methylprednisone, CCNU, hydroxyurea, procarbazine, cisplatin, cyclophosphamide and cytarabine) in 1 day chemotherapy given before irradiation with CCNU, vincristine, and prednisone (VCP) given after irradiation in MB patients showed clear survival advantage for VCP given adjuvant to radiation over 8 in 1 day therapy given before radiation. In that study 5-year estimate of PFS was 63% in adjuvant group. Five-year estimates of PFS for patients with M0, M1 and M2 tumors were 70%, 57% and 40% respectively. In that study, the presence of a positive CSF cytology alone, M1 stage, was not a statistically significant factor in PFS compared with M0 [14]. In Kortmann et al., 2000 (German HIT “91”) trial, the 3-year PFS was 66%. No difference in PFS between those with and without residual local disease (72% Vs. 68% respectively). Patients with M2/3 disease had 3-year PFS of 30% [15]. In Rutkauskiene and Labanauskas, 2005 trial, 2-year PFS and overall survival were 88.9% and 71% respectively in chemoradiation group [23].

In our study we use CSI dose of 36Gy. Reduction of CSI dose in conjunction with adjuvant multi agent chemotherapy resulted in lower PFS rates in high risk patients. Prados et al., 1996 treated 24 high risk patients with MB with one cycle CCNU based chemotherapy prior to radiation and 6 cycles of same chemotherapy after irradiation. Seventeen patients received CSI dose <30Gy. The 3-year PFS was 33% [26]. Another group of investigators reduced the CSI dose in high risk patients to 24Gy and used a CCNU based chemotherapy regimen prior to and following the completion of radiotherapy.
The 5 year PFS rate was only 20% in the 15 patients with M+ disease [10]. In the French M7 study [12], the dose of cranial irradiation was reduced to 27Gy with a dose of 35Gy to the spine. Chemotherapy consisted of 8 in 1 regimen with methotrexate. The 7 year PFS rate for 22 patients with metastatic MB was 43% with improved survival in those patients who received a higher dose to the supratentorial brain. Six of seven relapses in the supratentorial brain occurred in patients who received less than 30Gy to this area. From these findings, it can be inferred that the craniospinal dose should not be reduced in high risk patients; however, more aggressive treatment of the neuraxis may be reasonable strategy for improving PFS in high risk patients [16].

Vincristine and platinum drugs are of the more commonly utilized drugs for children with MB. Weekly carboplatin is known to be an active agent in the treatment of recurrent and advanced MB and was selected instead of cisplatin because of a desire to avoid ototoxicity which is a particular problem for children with MB who require radiotherapy to whole cranium including middle and inner ear [3]. Fourteen patients (82.4%) completed the planned course of chemotherapy. Three patients didn’t receive the planned chemotherapy course because of disease progression and not due to treatment toxicity. During adjuvant chemotherapy, the complications were more frequent and of deeper degree compared with that occurred during irradiation. The most frequent complication was myelosuppression. This is mainly due to the use of myelosuppressive agent, carboplatin, in addition to exhausted bone marow by previous CSI. Three patients (17.6%) developed grade 3 neutropenia during radiation. Five patients (29%) developed grade 3 and 4 neutropenia and one patient (6%) developed grade 3 peripheral neuropathy. Cortmann et al., 2000 reported the incidence of grade 3 and 4 neutropenia in 47.3% of patients in adjuvant arm and 67.8% in neo-adjuvant arm [15]. No ototoxicity was observed in our study. Ototoxicity a known complication of cisplatin was observed in 32% of cases in Packer et al., trial that utilized adjuvant cisplatin, vincristine and CCNU as an adjuvant treatment of MB [25]. One patient (6%), in our study, developed grade 3 peripheral neuropathy. Similarly, Prados et al., reported only one case of grade 3 neuropathy in their trial [26].

**Conclusion:** Our results showed that the present chemotherapy and radiotherapeutic approach is able to improve overall survival and PFS in high risk patients withgross residual disease but not in patients with metastatic disease (M+) that require more intensive therapy. On going international studies for high risk patients are exploring chemotherapy dose intensification as well as radiosensitization. The feasibility of administering several courses of high dose chemotherapy with peripheral blood stem cell support after irradiation recently was demonstrated in limited institutional trial [27]. The COG is currently evaluating the use of carboplatin as a radiosensitizer administered during radiation to patient with high risk medulloblastoma. In addition, modern conformal techniques that deliver the full dose to the primary target region, reducing the radiation dose to the cochlea and hypothalamic-pituitary axis, to date appear to provide local disease control comparable to that achieved with full posterior fossa irradiation [28-30].

**REFERENCES**


Concomitant Weekly Vincristine & Radiation Followed


