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ORIGINAL ARTICLE

Multicenter experience of adult medulloblastoma: A study of Anatolian Society of Medical Oncology (ASMO)

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Summary

Purpose: *Medulloblastoma (MB) is rarely seen in adults. For adjuvant therapy in adults the same therapy protocols used in pediatric cases are used. The present study retrospectively evaluated the data of MB patients who were treated in different Oncology Centers in Turkey.*

Methods: *The data of 60 adult patients with MB from 8 Oncology Centers diagnosed between 2005 and 2012 were retrospectively analyzed.*

Results: *The median patient age was 28.8 years (range 16-54). The administered chemotherapy included procarbazine+lomustin+vincristine (group A, N=31) and cyclophosphamide/ifosfamide+vincristine+cisplatin (group B, N=13). Median chemotherapy courses were 4 (range 1-8). Median progression free survival (PFS) was 76 months and median overall survival (OS) has not been reached in both groups. In young female patients and in those who received adjuvant chemotherapy, median PFS and OS were longer but without statistical significance. Mean PFS and OS were 65.9 months and 101.2 months in group A and 113.6 months and 141.6 months in group B, respectively.*

Conclusion: *Improved survival results were obtained in women, in patients aged below 25 years, in those who underwent gross total excision (GTE) and in those who received adjuvant therapy with cyclophosphamide/ifosphamide.*

Key words: *adjuvant, adult, chemotherapy, medulloblastoma*

Introduction

MB is a primitive neuroectodermal tumor of the central nervous system (CNS). It is the most commonly encountered tumor in the childhood (15-25%) and is very rare (1%) in adults [1,2]. In pediatric patients, total tumor excision is followed by the combination of craniospinal irradiation (CSI) and adjuvant chemotherapy [3]. As it is a rarely seen malignancy in the adulthood, there is a limited number of retrospective and prospective studies for adjuvant therapy. Furthermore, the benefit of adjuvant therapy after surgery and CSI is not clear [4-7]. In the adults, the same therapy protocols used in pediatric cases are used for adjuvant therapy. In previous studies, several combinations including lomustine, cisplatin, vincristine, procarbazine, etoposide, and cyclophos-

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phamide have been used [5-11].

The present study retrospectively evaluated the data of adult MB patients who were treated in different Medical Oncology Centers in Turkey.

Methods

The data of 60 patients diagnosed with MB between 2005 and 2012 in 8 Oncology Centers were retrospectively analyzed. Patients who had another malignancy were excluded. Patient demographic characteristics, pathological characteristics of tumors, metastatic sites, types of treatment (surgery, radiotherapy (RT) and chemotherapy), treatment schedules, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and survival data were evaluated using the medical records of the patients. Patients lacking this information were excluded.

Statistics

Demographic and clinical data were analyzed using median, range or counts and frequencies as appropriate. PFS was calculated from the date of diagnosis to the date of first progression or relapse. OS was calculated from the date of diagnosis to death from any cause or the date of last contact. Statistical analyses were performed using the Student's t-test and Pearson's x^2 test for parametric and Mann–Whitney U test for non-parametric analysis. Patient survival was estimated by using the Kaplan-Meier method and compared with log rank test. Results were considered significant when two-sided p values were <0.05. For statistical analysis, SPSS for Windows, version 15.0 software (SPSS Inc., Chicago, Ill, USA) was used.

Results

Patient characteristics

Thirty six patients (60%) were male and 24 (40%) female. Median age was 28.8 years (range 16-54). GTE in 42 (70%) patients and subtotal excision (STE) in 18 patients (30%) were performed. Postoperative RT was delivered to 56 (93.3%) patients; 24 (40%) patients received RT alone and 27 (45%) received RT in combination with vincristine, 4 (6.7%) received RT in combination with cisplatin and one (1.6%) patient received RT in combination with temozolomide. Forty four (73.3%) patients were treated with adjuvant chemotherapy. Thirty one (51.6%) patients received procarbazine+lomustin+vincristine (PCV, group A) and 13 (21.7%) received cyclophosphamide/ifosfamide+vincristine+cisplatin (group B). Median chemotherapy cycles were 4 (range 1-8) (Table 1).

Recurrence or metastasis were detected in 10 (16.6%) patients. Salvage surgery was performed in 5 (8.3%) patients. Reirradiation was applied in 10 (16.6%) patients; 7 (11.7%) of them received gamma/cyberknife stereotactic surgery (SRS). The most common sites of recurrence/metastasis were the CNS, lung and bone. The patient characteristics are summarized in Table 1.

Table 1. Patient characteristics

Characteristics	*N (%)*
Males	36 (60)
Females	24 (40)
Gross total excision	42 (70)
Subtotal excision	18 (30)
RT	56 (93.3)
RT alone	24 (40)
RT+ vinciristine	27 (45)
RT+cisplatin	4 (6.7)
RT+temozolomide	1 (1.6)
Adjuvant chemotherapy	44 (73.3)
PCV (group A)	31 (51.6)
Cyclophosphamide / ifosfamide+vincristine+cisplatin (group B)	13 (21.7)
Chemotherapy cycles, median (range)	4 (1-8)
Recurrence or metastasis	10 (16.6)
Secondary surgery	5 (8.3)
Reirradiation	10 (16.6)
Gamma/cyberknife	7 (11.7)
Median age, years (range)	28.8 (16-54)
≤25	31 (51.9)
>25	29 (48.3)

RT: radiotherapy, PCV: procarbazine+CCNU+vincristine

Survival analysis

Median PFS was 76 months (range 32.9-119) and median OS has not been reached for all patients. When assessment was done by gender, mean PFS was 91±15.7 months in males and 112±15.5 months in females, while mean OS was 105±12.2 months in males and 116±14.3 months in females, but median values could not be reached (p=0.4, p=0.6). When the patients were examined by age, median PFS and OS were 76 months (range 29.6-122.8) and 111 months (range 83.5-139.7) in 31 patients aged below 25 years and 75 months (range 28.7-121.5) and 108 months (range 81.5-134.5) in 29 patients aged above 25 years (p=0.4, p=0.7), respectively. Although there was no significant difference between the group that received adjuvant chemotherapy and the group that did not, the group that received chemotherapy showed higher mean PFS and OS (PFS 104 months vs 85 months, p=0.7; OS 112 months vs

100 months, p=0.7). Among 44 patients who received adjuvant chemotherapy, mean PFS and OS were 65.9±17.2 months and 101.2±16.8 months in group A and 113.6±20.2 months and 141.6±12.5 months in group B, but the difference was not statistically different (p=0.13, p=0.12). Median PFS and OS could not be reached.

Table 2. Patient survival

	Median (months)	*p value*
All patients		
PFS	76	
OS	NR	
Male PFS	91 (mean)	0.4
Female PFS	112	
Male OS	105	0.6
Female OS	116	
Age ≤25 PFS	76	0.4
Age >25 PFS	75	
Age ≤25 OS	111	0.7
Age >25 OS	108	
Chemotherapy PFS		
Yes	104	0.7
No	85	
Chemotherapy OS		
Yes	112	0.7
No	100	
Chemotherapy		
Group A PFS	65.9	0.13
Group B PFS	113.6	
Group A OS	101.2	0.12
Group B OS	141.6	
Surgery		
GTE PFS	76	0.4
STE PFS	38	
GTE OS	NR	0.09
STE OS	68	
RT PFS		
Yes	96	0.8
No	40	
RT OS		
Yes	NR	0.9
No	44	
Radiotherapy		
RT alone PFS	75	
RT+vincristine PFS	96	0.9
RT+cisplatin PFS	53	
RT+temozolomide PFS	64	
RT alone OS	81	
RT+vincristine OS	128	0.8
RT+cisplatin OS	64	
RT+temozolomide OS	64	
Reoperation PFS		
Yes	68	0.05
No	NR	
Reoperation OS		
Yes	76	0.04
No	NR	
Re-Radiotherapy PFS		
Yes	37	0.1
No	NR	
Re-Radiotherapy OS		
Yes	87	0.3
No	NR	
Gamma/cyberknife PFS		
Yes	75	0.04
No	NR	
Gamma/cyberknife OS	81	
Yes	NR	0.05
No		

PFS: progression-free survival, OS: overall survival, GTE: gross total excision, STE: subtotal excision, RT: radiotherapy, NR: not reached

In patients who underwent GTE, median PFS was 76 months (range 41.6-110.3) but median OS could not be reached. In patients who underwent STE, median PFS was 38 months (range 18.9-57) and OS 68 months (range 34.4-101.5) but without statistical significance (p=0.4, p=0.09). In patients who received RT and those who did not, median PFS and OS were longer in the former group but without statistical significance (p=0.8, p=0.9). In patients who received RT alone, median PFS was 75 months (range 40.5-120.3) and OS 81 months (range 66.7-130.4); in the group treated with RT+vincristine, PFS was 96 months (range 60.5-136.1) and OS 128 months (range 70.2-150.1); in the group treated with RT+cisplatin, PFS was 53 months (range 30.5-78.2) and OS 64 months (range 20.1-82.4).

After disease progression, the median PFS was 68 months (range 6.2-129.7) and OS 76 months (range 20.4-131.5) in patients who underwent repeat surgery but for those who did not have surgery, the median values could not be reached, the difference being statistically significant (p=0.05, p=0.04). When the group that underwent gamma/cyberknife stereotactic surgery (SRS) was compared with the group without SRS, the former had median PFS of 75 months (range 26-123.9) and OS of 81 months (range 31-130.9), but in the latter median values could not be reached (p=0.04, p=0.05) (Table 2).

Discussion

There is no standard of care in the adult MB patients. Due to small number of patients and a limited number of prospective studies, the use of adjuvant chemotherapy is unclear [5,7,12]. In some previous studies, high-risk patients showed decreased risk for recurrence and death with adjuvant chemotherapy [7,13]. However, no difference

in PFS and OS was found between low-risk and high-risk patients. A number of authors reported that adjuvant chemotherapy could produce better outcomes in low-risk patients [7,13,14]. In a prospective study that investigated patients with non-metastatic MB, no statistically significant differences in PFS and OS were detected in patients treated with adjuvant chemotherapy compared to those who did not [5]. In this study, prolonged PFS and OS were detected in patients treated with adjuvant chemotherapy compared to those who did not, but this lacked statistical significance.

Adjuvant therapy protocols are not solid. In the studies performed several drugs were used, either alone or in combination, including lomustine, cisplatin, vincristine, procarbazine, etoposide, cyclophosphamide, with 5-year PFS and OS ranging between 60 and 80% ±10, respectively [5-11,15]. Due to small number of patients, no robust comparison can be done across chemotherapy groups. In the study performed by Greenberg et al., the patients were given two different chemotherapy protocols. A group treated with cyclophosphamide+vincristine alternating with cisplatin+etoposide showed longer median PFS and OS compared to a group treated with cyclophosphamide+lomustine+vincristine (p=0.4, p=0.05, respectively) [12]. The present retrospective study was able to include a sufficient number of patients. When we examined our patients by the adjuvant chemotherapy protocols that they received, PFS and OS were longer in the group treated with cyclophosphamide/ifosphamide (group B) compared to the group treated with PCV (group A).

In MB, surgery and CSI are the cornerstone of the treatment [20,21]. In surgery, GTE or STE may be performed. While two different studies showed that GTE was associated with good prognosis, others did not show this positive correlation [18-20]. In our analysis, despite the lack of statistical significance, the group who underwent GTE showed longer survival. Although postoperative CSI is the standard of care, there is no standard for a concomitant therapy with RT. In some studies performed in pediatric patients, concomitant use of RT and chemotherapy gave better survival outcomes [21-23]. In a study, it was demonstrated that weekly vincristine therapy given concomitantly with RT increased the complete response rate in metastatic patients [21]. In another study, the patients who received RT concomitantly with another therapy had higher radiological complete response rates compared to those who received RT alone [22]. In a study performed by Mamdouh et al. in a high-risk patient group, concomitant use of vincristine and RT increased PFS and OS [23]. In our study, the patient who concomitantly received RT and vincristine showed the longest median PFS and OS (96 months and 128 months).

In the present study, female patients showed longer OS compared to male patients but this difference was not statistically significant. In some studies, it was found that female gender was positively correlated with survival [14,24,25]. In a study performed in children, it was found that female hormones had a protective effect against tumor recurrence and increased the sensitivity to therapy [26].

Even rare, extraneural involvement occurs in the bone, bone marrow, lymph nodes, liver and lung and it is generally associated with the end-stage of disease. Most common relapsing site is the CNS in both adults and children. However, late relapse is more common in adults. In adults, mean time to relapse is 26 months and 29% occur within at least 5 years [5].

In a study that investigated the correlations between age and survival in adult patients, a poorer prognosis was found in the patients aged above 19 years [18]. Similarly, another study showed longer PFS in patients aged below 25 years [27]. In our study, median PFS and OS were longer in patients aged below 25 years but no statistically significant difference was found.

There is no randomized study for salvage surgery in case of recurrence. In the guidelines used in clinical practice, chemotherapy after maximally safe re-resection and/or RT after the resection is recommended [28]. Good responses were reported to be obtained with SRS or reirradiation plus re-resection after the recurrence [29,30].

Conclusion

In the present study, salvage therapy after disease progression was not analyzed due to the small number of cases. Limitations of this study include its retrospective design and risk classification of the patients. However, better survival results were obtained in women, in patients aged below 25 years, in those who underwent GTE and in those who received adjuvant therapy with cyclophosphamide/ifosphamide.

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