Retrospective analysis of patients with relapsed/refractory medulloblastoma after autologous stem cell transplantation

Ramazan Acar¹, İsmail Ertürk¹, Halil Kızılöz², Sezgin Okçelik², Birol Yıldız¹, Musa Barış Aykan¹, Gül Sema Yıldızan Keskin¹, Erdim Sertoğlu³, Bilgin Bahadır Başgöz³, Nuri Karadurmuş¹

¹University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Medical Oncology, Ankara, Turkey
²Nevşehir State Hospital, Clinic of Urology, Nevşehir, Turkey
³University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Biochemistry, Ankara, Turkey
⁴University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Internal Medicine, Ankara, Turkey

ABSTRACT

Aims: Medulloblastoma is very rare and accounts for only 1% of intracranial tumors in adults. There are limited treatment options for adult medulloblastoma patients who have relapsed or refractory disease. We aimed to show real-life data on health outcomes in adult patients with recurrent or refractory medulloblastoma patients who received autologous hematopoietic stem cell transplantation (AHSCT).

Methods: We analyzed the data of 15 patients who underwent AHSCT after ifosfamide, carboplatin, and etoposide (ICE) as high-dose chemotherapy (HDCT) regimen for relapsed or refractory medulloblastoma from 2010 to 2020. Overall response rate (ORR), overall survival (OS) and progression-free survival (PFS) of the patients were evaluated.

Results: Fifteen patients were observed in this study. The mean age of the study group was 27.9±8.1 years and 53.3% of the patients were female (n=8). ORR was 100%. The median OS and PFS were 24 months [95% confidence interval (CI): 11.4-36.5] and 13 months (95% CI: 10.2-15.8), respectively. One-year OS and PFS rates were 77% and 55.2%, respectively. Five-year OS rate was 82.5%.

Conclusions: AHSCT with ICE as HDCT regimen is a safe and effective treatment option for relapsed or refractory adult medulloblastoma patients with an acceptable ORR, OS and PFS time.

Introduction

Medulloblastoma is the most common central nervous system embryonal tumor of childhood, constituting 25% of all intracranial neoplasms (1). In contrast, adult medulloblastoma is very rare and accounts for only 1% of intracranial tumors (2). Current conventional management of adult medulloblastoma involves maximum safe resection followed by craniospinal radiation with or without concurrent adjuvant chemotherapy depending on the clinical risk classification (3). Clinical risk stratification included age, the extent of resection, metastatic status, and tumor biology (4). Metastatic patients might undergo chemotherapy. Besides, autologous hematopoietic stem cell transplantation (AHSCT) should be selected (5). In the literature, a limited number of patients underwent high-dose chemotherapy (HDCT) and AHSCT due to relapsed or refractory medulloblastoma even after surgical debulking and radiotherapy (6,7). According to the literature, data about AHSCT in adult medulloblastoma patients appear to be small case series. Similar treatment methods are used in Turkey. The only center which use AHSCT in solid organ tumor in Turkey is the Gülhane Training and Research Hospital Medical Oncology Department. The other oncology departments in Turkey are sending their
medulloblastoma patients to our center for treating with AHSC]. Therefore, the results reflect the data of Turkey.

We aimed to demonstrate the real-life data about relapsed or refractory medulloblastoma patients who received HDCT and AHSC] and to increase the awareness of this rare treatment choice.

**Methods**

**Study Design and Patients**

The study was carried out by investigating the patients with relapsed and refractory adult medulloblastoma, who had received HDCT and AHSC] in University of Health Sciences Turkey, Gülhane Training and Research Hospital between January 2010 and March 2020 in diagnosis, follow-up, treatment, complications outcomes. The study is a single-center, retrospective study.

A retrospective case control study was carried out with 15 cases that were previously diagnosed and treated or currently on a treatment for medulloblastoma, and they were evaluated in terms of demographic characteristics, cancer specific features including history, stage of the cancer, previous or ongoing treatment and previous surgery or radiotherapy.

The patients received ifosfamide at a total dose of 12 gr/m² divided six days on days -8 to -3, carboplatin at a total dosage of 1,200 mg/m² divided six days on days -8 to -3 and etoposide at a total dosage 1,200 mg/m² divided six days on days -8 to -3 ifosfamide, carboplatin, and etoposide (ICE) as HDCT (8). After chemotherapy, the patients rested on days -2 and -1. Autologous stem cells were reinfused on day 0. We infused at least 3 million (3x10⁶) CD34+ stem cells. After infusions, all patients were followed in our Stem Cell Infusion Center. All patient rooms were single, isolated with a special ventilation system. During the stem cell transplant process, patients’ relatives were forbidden to visit and bring food from outside for protecting them from infections.

The primary endpoint of this study was to assess the progression-free survival (PFS) outcome and overall survival (OS) periods. Secondary endpoints were to identify prognostic clinical factors for disease progression after AHSC], and to define the safety and the toxicity profile of the HDCT and AHSC].

**Data Collection**

Medical records of the patients, who were admitted to the Department of Medical Oncology at the University of Health Sciences Turkey, Gülhane Training and Research Hospital and eventually diagnosed with medulloblastoma, were investigated whether they previously or currently had received AHSC]. Medical records of suitable cases were enrolled in a SPSS data-sheet by the registered staff of Department of Oncology at the University of Health Sciences Turkey.

**Statistical Analysis**

Patients’ demographics, clinical and biochemical features, and clinical and radiologic outcomes were recorded on an SPSS v.17 (SPSS Inc., Chicago, IL USA) data sheet considering the patients’ confidentiality. Data were accessible only by the authorized institutional staff and caregivers. The Student’s t-test was utilized for evaluating normal distribution of data. Demographic indices provided the mean values with the standard deviation or the median values as appropriate. Frequencies were noted in numbers with percentiles. Survival analysis was conducted utilizing the Kaplan-Meier tables and survival plots provided.

**Results**

**Patient and Disease Characteristics**

We determined that 50 patients were followed up with the diagnosis of medulloblastoma between January 2010 and March 2020. Fifteen of the patients (30%) received HDCT and AHSC]. The mean age of the study group was 27.9±8.1 years and 53.3% of the patients were female (n=8). All patients were stage 4 at the time of diagnosis. Tumor histology revealed classic type medulloblastoma in 12 (80%) patients and three (20%) patients showed desmoplastic/nodular type medulloblastoma at diagnosis. Large anaplastic type and extensive nodular types were not observed. Bone was the most seen metastatic site [4 (26.7%)] among the patients included in the study. Lymphoid nodes and lungs were the other most common metastatic sites, respectively. Three patients (20%) of them had more than two metastatic sites. Numbers of lines before AHSC] treatment were more than three in all cases. Six (40%) of the patients were treated with AHSC] as the third line therapy. Nine (60%) of them were treated with AHSC] as the fourth line therapy (Table 1). Eleven patients had complete response (73.3%), two patients had partial response (13.3%) and two patients had stable disease (13.3%). Progression was not observed at the first controls. Overall response rate (ORR) was 100%. Later in long term follow-up period, we detected progression. All cases received radiotherapy as the first line therapy after surgery. They underwent different combination therapies for the second, third and fourth lines (Table 1).

**Treatment Administration and Survival Outcome**

All cases underwent AHSC] following various degrees of salvage chemotherapy both before and after surgery due to relapsed or refractory disease. As HDCT, all patients received ICE regimen. The mean and median follow-up times
following AHSCT were 15.1±18.4 months and seven months, respectively. The median OS and PFS were as follows; 24 months [95% confidence interval (CI): 11.4-36.5] and 13 months (95% CI: 10.2-15.8), respectively (Figure 1, 2, Table 2). OS and PFS at the 12th month were 77% and 55.2%, respectively. Five-year OS was 82.5%.

Toxicity of AHSCT

The numbers of side effects related to AHSCT are demonstrated in Table 3. Leukopenia, anemia, thrombocytopenia, neurotoxicity, febrile neutropenia, diarrhea and vomiting/nausea were found 100%, 100%, 100%, 46.6%, 100%, 66.6%, and 100%, respectively. Majority of the patients received erythrocyte, thrombocyte transfusions and granulocyte colony stimulating factors several times after 12 or 16 days following the AHSCT. Eleven patients (73.3%) had grade 4 thrombocytopenia. No bleeding was observed in any patients. Grade 2 and 3 febrile neutropenia were observed among all patients. A broad-spectrum antibacterial therapy was administered in all patients, including 3rd generation

| Table 1. The demographic and disease-related characteristics of the patients |
|---------------------------------|-----------------|-----------------|-----------------|
| Features                        | n (%)           | Mean ± SD       | Median          |
| Age (years)                     | 15 (100)        | 27.9±8.1        | 27 (18-43)      |
| Gender                          |                 |                 |                 |
| Male                            | 7 (46.7)        |                 |                 |
| Female                          | 8 (53.3)        |                 |                 |
| Histopathology                  |                 |                 |                 |
| Classic type                    | 12 (80)         |                 |                 |
| Desmoplastic/nodular type       | 3 (20)          |                 |                 |
| Large/anaplastic type           | 0 (0)           |                 |                 |
| Extensive nodular type          | 0 (0)           |                 |                 |
| Stage at the time of diagnosis  |                 |                 |                 |
| 4                               | 15 (100)        |                 |                 |
| Site of metastases              |                 |                 |                 |
| No metastases                   | 0 (0)           |                 |                 |
| Liver                           | 2 (13.3)        |                 |                 |
| Lymph node                      | 3 (20)          |                 |                 |
| Lung                            | 3 (20)          |                 |                 |
| Bone                            | 4 (26.7)        |                 |                 |
| More than 1 sites               | 3 (20)          |                 |                 |
| The response of the patients after AHSCT |                 |                 |                 |
| Stable response                 | 2 (13.3)        |                 |                 |
| Partial response                | 2 (13.3)        |                 |                 |
| Complete response               | 11 (73.4)       |                 |                 |
| Progressive disease             | 0 (0)           |                 |                 |
| The treatments lines patients received before AHSCT |                 |                 |                 |
| Treatments                      |                 |                 |                 |
| Radiotherapy                    |                 |                 |                 |
| Vincristine+Procarbazine+Mustard|                 |                 |                 |
| Cisplatin+Etoposide+Cyclophosphamide | 8 (53.3)  | 1 (6.7)        |                 |
| Cisplatin+Lomustine+Vincristine | 1 (6.7)         |                 |                 |
| Ifosfamide+Carboplatin+Etoposide|                 |                 |                 |
| HDCT (ICE) + AHSCT              |                 |                 |                 |

AHSCT: Autologous hematopoietic stem cell transplantation, HDCT: High dose chemotherapy, ICE: Ifosfamide, Carboplatin, Etoposide, SD: Standard deviation
cephalosporins, teicoplanin, anti-pseudomonal azlo-ureido penicillin, carbapenems, linezolid and macrolides for empirical purpose. Blood and urine cultures were taken. No bacteria or fungal infections were seen. There was no life-threatening toxicity. One patient had reversible grade 3 renal toxicity. No death was observed relating to the treatment. There was no death in the first 100 days. Six (40%) patients died due to the disease progression at the follow-up period.

**Discussion**

Medulloblastoma treatment is based on clinical risk stratification (3). Current therapy combines surgery, chemotherapy, radiotherapy, and HDCT with AHSCT (9). In this study, we analyzed the efficacy and safety of HDCT with ICE regimen and AHSCT treatment in patients with relapsed or refractory adult medulloblastoma, who underwent at least three lines of therapy before. All patients underwent surgery. Before AHSCT, all patients had radiotherapy as the first-line therapy. As a second-line therapy, they received combination chemotherapies such as Vincristine plus Procarbazine plus Mustard, Cisplatin plus Etoposide plus Cyclophosphamide, Cisplatin plus Lomustine plus Vincristine or Ifosfamide plus Carboplatin plus Etoposide (10,11). Medulloblastoma is a high risk for most of our patients that received AHSCT as the third-line therapy. According to the packer staging criteria, which included age, the extent of resection, metastatic status, and tumor biology, all patients in our study were high-risk and additionally as far as we know, medulloblastomas are chemosensitive tumors (12,13). There were several retrospective studies about AHSCT in medulloblastoma (6,7). Most of them consisted of pediatric patients. Various HDCT regimens were applied before AHSCT. Moreover, all patients were stage four at diagnosis. All the patients received ICE regimen as HDCT in our study.

Histologically, medulloblastoma is an embryonal neuroepithelial tumor originating from the cerebellum and dorsal brain stem. Classic, desmoplastic/nodular, large cell/anaplastic, and extensive nodularity are the subgroups of medulloblastoma. The most common histologic variant is classic medulloblastoma in both children and adults (70-80%), and the least common is

| n (%) | Median | Mean ± SD |
|-------|--------|-----------|
| OS    | 24 months (95% CI: 11.4-36.5) |
| PFS   | 13 months (95% CI: 10.2-15.8) |

| Follow-up time | OS | PFS |
|---------------|----|-----|
| 12 months     | 77 | 55.2|
| 5 years       | 82.5| |
| The duration of follow-up time | 7 (3-71) | 15.1±18.4 |

OS: Overall survival, PFS: Progression-free survival, AHSCT: Autologous hematopoietic stem cell transplantation, SD: Standard deviation, CI: Confidence interval
medulloblastoma with extensive nodularity (3%) (14,15). We observed classic type medulloblastoma in 12 (80%) patients and desmoplastic/nodular type medulloblastoma in three (20%) patients at diagnosis.

The five-year survival rate for both children and adult medulloblastoma is intermediate and about 70%. SHH subtype predicts poor prognosis. SHH, WNT, and group 4 are detected 60%, 15%, and 25% of adult patients, respectively (16). Five-year survival rate is 80% in adults who have WNT subtype. In our study SHH, WNT and group 4 were detected as 80% (n=12), 6.7% (n=1) and 13.3% (n=2), respectively and 5-year survival was 82.5%. This was similar to the literature.

Some studies showed ORRs in the range of 83-100% (5-7). Okada et al. (8) observed ORR in 83% patients who underwent ICE regimen as HDCT. Zia et al. (6) observed ORR in 100% of patients who underwent carboplatin, etoposide, and cyclophosphamide. Both of these studies had six children patients. We observed ORR as 100% in 15 patients. Later progression developed in eight patients. Six of them died in the follow-up (40%, n=6). Nine patients are still alive. Six of the alive patients have complete remission. Three patients are still receiving treatment.

Zia et al. (6) showed an average of 13.5 months of PFS and an average of 21.5 months of OS after AHSCT. Additionally, Zia et al. (6) reported the median 26.8 months of OS for the medulloblastoma patients receiving AHSCT (6). In our study, we observed OS and PFS at the 12th month as 77% and 55.2%, respectively. The OS rate for five years was 82.5%. These results were similar to previous literature.

Okada et al. (8) reported that the rate of grade 4 neutropenia and thrombocytopenia were observed to be 100%. The toxicities were recovered within 26 days. Safety analysis of this report showed the feasibility of the ICE regimen as HDCT and AHSCT in patients with heavily pretreated medulloblastoma. In our study, all toxicities were observed.

Although this study had a small sample size of medulloblastoma patients with further line AHSCT and long follow-up, there are some limitations to report. It was a retrospective study, and the patient population was relatively heterogeneous. The patient sample size was small. Medulloblastoma patients in this study underwent AHSCT for metastatic medulloblastoma at an experienced high-volume referral center. We believe that these patients need multidisciplinary expertise and hence should be treated at centers of stem cell transplantation with excellence. The strengths of the study include AHSCT in further lines and relatively more patients in a rare disease. The results cannot be applied to other countries with different cancer epidemiology and practice.

Table 3. Toxicities during autologous hematopoietic stem cell transplantation treatment

| Toxicity               | n (%)         |
|------------------------|---------------|
| Leukopenia             |               |
| Grade 4                | 15 (100)      |
| Anemia                 |               |
| No                     | 0 (0)         |
| Grade 1                | 1 (6.7)       |
| Grade 2                | 10 (66.7)     |
| Grade 3                | 4 (26.6)      |
| Thrombocytopenia       |               |
| No                     | 0 (0)         |
| Grade 1                | 0 (0)         |
| Grade 2                | 1 (6.7)       |
| Grade 3                | 3 (20)        |
| Grade 4                | 11 (73.3)     |
| Neurotoxicity          |               |
| No                     | 8 (53.3)      |
| Grade 1                | 3 (20)        |
| Grade 2                | 4 (26.7)      |
| Febrile neutropenia    |               |
| No                     | 0 (0)         |
| Grade 1                | 0 (0)         |
| Grade 2                | 14 (93.3)     |
| Grade 3                | 1 (6.7)       |
| Vomiting/nausea        |               |
| No                     | 0 (0)         |
| Grade 1                | 1 (6.7)       |
| Grade 2                | 2 (13.3)      |
| Grade 3                | 9 (60)        |
| Grade 4                | 3 (20)        |
| Diarrhea               |               |
| No                     | 5 (33.3)      |
| Grade 1                | 2 (13.3)      |
| Grade 2                | 7 (46.7)      |
| Grade 3                | 1 (6.7)       |
| The final status of the patients |         |
| Exitus                 | 6 (40)        |
| Alive                  | 9 (60)        |

AHSCT: Autologous hematopoietic stem cell transplantation

Conclusion

In conclusion, AHSCT with ICE regimen remains one of the best determined systemic treatment options for progressive adult medulloblastoma patients. Also, the treatment was associated with good efficacy and tolerability.

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Ethics

Ethics Committee Approval: The ethics committee of University of Health Sciences Turkey, Gülhane Training and Research Hospital approved the study with 2020-112 ethical committee number on March 10, 2020.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.S., B.B.B., Design: E.S., B.B.B., Data Collection or Processing: R.A., İ.E., Analysis or Interpretation: B.Y., M.B.A., G.S.Y.K., Literature Search: E.S., N.K., H.K., S.O., Writing: E.S., B.B.B.

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