ABSTRACT

Background and Objectives: Medulloblastoma are a highly malignant tumor of the central nervous system, very frequent in the childhood, but remains rare in adulthood. This study aims to analyze the frequency, clinical and therapeutic aspects of adults medulloblastomas.

Methods: We retrospectively analyzed the data from the record of adult’s patients treated for medulloblastoma between January 2000 and December 2015 in in the Radiation oncology department of the Ibn Rochd University Hospital Center.

Results: The average age was 27.96 years (Range: 20-53 years). The sex ratio M/F was 4 with a clear male predominance. The most common symptom was intracranial hypertension, which was present in 22 patients, followed by headaches and cerebellar syndrome which were present in 9 patients. The tumor was mostly located in the cerebellar hemispheres with an average size of 5.75 cm. One patient had pulmonary metastasis at the time of diagnosis.

Twenty-four patients had a surgical resection. Complete resection was performed in 13 patients. Thus, twenty-one patients have received craniospinal irradiation with a dose of 36 Gy followed by a boost in the posterior fossa with a total dose of 54-56 Gy. Twelve patients have received Chemotherapy. Six patients are still alive. Survival rates were 50% at 3 years, 35% at 5 years, and 30% at 10 years.

Conclusion: Medulloblastoma is a devastating disease with a bad prognosis. The clinical presentation is variable and the management is multidisciplinary. Radiotherapy treatment with or without Chemotherapy play an important role in the control of the disease and recurrences avoidance. Our study illustrates the importance of treatment by radiation.

Keywords: Adults medulloblastoma, craniospinal irradiation, radiotherapy.

Submitted: July 14, 2022
Published: October 23, 2022
ISSN: 2593-8339
DOI: 10.24018/ejmed.2022.4.5.1418

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I. INTRODUCTION

Medulloblastoma is a highly malignant tumor of the central nervous system (grade IV on the WHO classification), very frequent in the childhood, it can occur at any age, and was diagnosed 25 to 40% during adulthood [1]. Although, medulloblastoma remains rare representing less than 1% of cerebral tumors [2]. Standard treatment is based on a multimodal association including a maximal resection surgery, craniospinal irradiation (CSI), and cytotoxic chemotherapy. This is valid for both standard and high-risk patients. In order to provide more accurate risk-adapted treatment and developing targeted therapies, a better understanding of the disease appears to be a relevant challenge with the aim of decreasing side effects in low-risk patients and improve efficiency in high-risk patients. In this work, we analyze our own experience with the management of adult’s medulloblastoma in the Radiation oncology department of the Ibn Rochd UHC, with an overview of the actual medulloblastoma molecular classification that leads to a multidisciplinary approach and therapeutic strategies to optimize medulloblastoma care.

II. PATIENTS AND METHODS

In our retrospective study, we have analyzed the data of 25 adult patients who were 20 years or older that were suffering from a medulloblastoma newly diagnosed. They have been treated between January 2000 and December 2015 in in the Radiation oncology department of the Ibn Rochd UHC.

III. RESULTS

The average age was 27.96 years (Range: 20-53 years). The sex ratio M/F was 4 with a clear male predominance.

The most common symptom was intracranial hypertension, which was present in 22 patients, followed by headaches and cerebellar syndrome which were present in 9 patients.

Sixteen patients had a pre-operative cerebral CT (Fig. 1), fifteen had a pre-operative Cerebral MRI and seven patients had of them. The tumor was mostly located in the cerebellar hemispheres for ten patients, with a tumor size that was varying from 3.5 to 6.1 cm with an average size of 5.75 cm (Fig. 2).

In order to define the tumor seeding, three patients had a medullar MRI and three had a lumbar punction, that revealed for One of the patients blastoid cells in the spinal fluid, suggesting a spinal metastasis at the time of diagnosis, meanwhile only One patient had pulmonary metastasis revealed by respiratory symptoms. Twenty-four patients had a surgical resection. Thirteen patients had a Gross total resection (GTR) and three patients had a subtotal resection (STR). Based on the quality of surgery and the spinal and distant extend of the disease, the risk stratification has been established. Thereby, seventeen patients were defined as high risk and eight as a standard risk. All our patients had grade IV medulloblastoma, the classic subtype was the most frequent histological subtype confirmed for fourteen of our patients.

Radiotherapy treatment with or without Chemotherapy play an important role in the control of the disease and recurrences avoidance. Thus, twenty-one patients have received craniospinal irradiation with a dose of 36 Gy followed by a boost in the posterior fossa with a total dose of 54-56 Gy (Fig. 3).

Fig. 1. Axial view of a cerebral CT scan showing a tumor of the vermis.

Fig. 2. Coronal view of a cerebral MRI (T2) showing a tumor of the posterior fossa with a mass effect and hydrocephalus.

Fig. 3. Sagittal view of previsional cible volume and dose distribution (Centre Mohammed VI pour le traitement des Cancers- CHU de Casablanca): Global PTV: Cranial + spinal; Isodose 95% of 36 Gy; PTV of the posterior fossa; Isodose 95% of 54 Gy.

All patients were placed on ventral decubitus position and immobilized with a thermoplastic radiotherapy head mask. The clinical target volume (CTV) included Cranio spinal irradiation (CSI) plus a local (posterior fossa/tumor bed) boost for nineteen patients, while two patients had only cranio spinal irradiation without the posterior fossa boost. Low
grade. Hematologic side effects were noticed for six patients, four patients had neutropenia and two had thrombocytopenia, while two patients had cutaneous toxicity.

Twelve patients have received Chemotherapy that was adjuvant for five of them, using 8 courses of the PACKER protocol with a good tolerance, only three patients had secondary effects: two had digestive symptoms as nausea and vomiting and one patient had a bone marrow aplasia.

Six patients are still alive. Survival rates were 50% at 3 years, 35% at 5 years, and 30% at 10 years.

IV. DISCUSSION

Medulloblastoma (MB) is the most frequent primary malignant brain tumor (WHO grade IV) in children, but it is very rare in adults, and often, survival rates and prognostic factors for adult MB are difficult to assess [3].

Dr. Rorke proposed in 1983 a classification system that included medulloblastomas with other histologically similar primary CNS neoplasms composed of undifferentiated neuroepithelial cells, these lesions were called “primitive neuroectodermal tumors” (PNET) [4]. Overtime, many guidelines for the classification of CNS tumors were published. As the interest for medulloblastomas has grown and evolved, they were reviewed as a distinct subtype of embryonal tumors and four separate histological subsets were admitted (classic, desmoplastic, extensive nodularity, and large cell) [5].

Then in the late 2000s, the emergence of DNA and RNA sequencing data led to understand that medulloblastomas could be classified into multiple distinct subgroups, each one with a unique molecular genetic signature [6], [7].

Histology differs somehow between adults and children. More adult medulloblastomas are desmoplastic (25–40%) [8], [9], and 30% in the present series were desmoplastic. In a series of children’s medulloblastomas, 15% were desmoplastic [10]. In our study and based on the 2016 WHO classification, the classic subtype was the most frequent histological subtype confirmed for 56% of our patients.

In order to define a new way to rank medulloblastomas based on histopathological and molecular characteristics, the newly published 2021 WHO classification determines new subsets below the 4 principal molecular groups: 4 subgroups of SHH and 8 subgroups of non-WNT/non-SHH medulloblastomas [11].

Some of these subgroups are associated with clinicopathological and genetic features that provide clinical utility, having either diagnostic, prognostic, or predictive value. Even the 4 morphologic types have now been united into one section that qualifies them as morphologic patterns of an inclusive tumor type [12].

Risk stratification has to be determined so that we can decide for adjuvant treatments [13]. Many tools are used, especially Chang staging tool that has been used for decades, it’s based on tumor dimension and disease spread [14]. Reference [15] proposed a risk stratification system that has the particularity of being appropriate for both adults and children. high risk (HR) MB is defined as age less than 3 years, or 9.5 cm² of residual tumor after resection, or presence of any metastasis (M+). In our study, 68% of patients were defined as high risk and 32% as a standard risk.

For all medulloblastomas, treatment is multimodal, and the first step consists of maximal safe resection surgery. Recently published, a retrospective study that included more than 700 patients in pediatric population, evaluated the clinical importance of extent of resection. The extent of the resection has no impact on the overall survival. Nevertheless, there was a progression-free survival (PFS) benefit of gross total resection over subtotal resection [16]. In a population-based study including 454 patients from Surveillance, Epidemiology, and End Results (SEER), [17] demonstrated that gross total resection is a favorable prognostic factor.

Nonetheless, actual guidelines propose that maximum safe resection is the principal purpose of initial surgery in both adult and pediatric MB patients [13].

Craniospinal irradiation (CSI) is the master piece of medulloblastoma treatment, in fact, Postoperative CranioSpinal Irradiation (CSI) with chemotherapy is the standard adjuvant treatment of resected medulloblastoma. Radiotherapy (RT) should be performed within 30 days after surgery [18]. The timing of radiotherapy has been studied in two previous trials that confronted immediate RT following surgery vs delayed RT 4–6 weeks after surgery. Both of them concluded that delayed RTH has reduced the repercussions [19]. Radiation therapy is based on Craniospinal irradiation (CSI) in addition to a local (posterior fossa/tumor bed) boost, this technique was first described by [20] in a study that showed a survival rate at 3 years of over 60 %. Since the entire cerebrospinal fluid (CSF) space is at risk of disease dissemination, the entire arachnoid space is defined as the clinical target volume (CTV). The cranial CTV should include the cribriform plate, the most inferior parts of the temporal lobes, the whole pituitary fossa and the extension of CSF within the dural sheath of cranial nerves [21]. The Spinal CTV should include the entire subarachnoidal space till the lower limit of the thecal sac to encompass the extensions along the nerve roots laterally. The inferior limit is best determined on the latest spinal MRI [22]. This usually comes down to the bottom of S1 vertebra as an obvious CSF space but there is often elongation which is less obvious extending down to the bottom of S2 or even further inferiorly [21]. For the Planning target volume (PTV) margin, most institutions add a 3–5 mm margin to the cranial CTV and a 5–8 mm margin to the spinal CTV [23].

Commonly the dose depends on the risk stratification: For standard-risk patients, a dose of 23.4 Gy in 13 fractions is prescribed for the craniospinal irradiation, followed by a tumor bed boost to complete the dose of 54–55.8 Gy. The CSI irradiation for high-risk patients have to reach 36–39.6 Gy in 20–22 fractions, followed by a tumor bed boost to 54–55.8 Gy [24]. Several trials are aiming to rise treatment efficacy and to reduce treatment toxicity as The EORTC 1634-BTG/NOA-23 trial for post-pubertal patients with standard risk medulloblastoma that is experiencing “reduced radiotherapy dose”. SHH-subgroup patients will also be randomized between the SMO inhibitor sonidegib in addition to standard radio-chemotherapy vs. standard radio-chemotherapy alone [25]. Advanced photon techniques like volumetric arc therapy (VMAT) or tomotherapy allow a better protection of the organs at risk with a higher coverage of the target volume [26]. Due to the many benefits of the proton beam therapy, it is being used more and more.
especially for pediatric patients [27], by using this technique, the risk of late toxic effects can be decreased while the tumor control is similar compared to photon techniques [28].

A prospective study published in 2012 by [29] followed seventy adult patients with non-metastatic medulloblastoma treated with postoperative radiotherapy, 49 of these patients received maintenance chemotherapy, lomustine, vincristine, and cisplatin after radiation according to a pediatric protocol [29], [30]. This trial came to the conclusion that some adults’ patients are eligible for chemotherapy treatment until secondary effects aren’t tolerated. However, both groups (treated with or without chemotherapy) didn’t show any betterment of the prognostic [29].

Clinical trials challenged many other protocols, including the “Packer protocol”, which is started 6 weeks after the end of radiotherapy sessions, by giving the vincristine weekly with eight cycles of lomustine, vincristine, and cisplatin [31].

V. CONCLUSION

Medulloblastoma remains a devastating disease with a bad prognosis, Knowledge of molecular biology, oncogene amplification and the multiple pathways involved in the development of MB has enabled treatment strategy to be adapted to the aggressiveness of the lesion, providing promising targets for treatment.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

REFERENCES