New perspectives in the treatment of adult medulloblastoma in the era of molecular oncology

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Abstract

Medulloblastoma is the most common central nervous system tumor in children, while it is extremely rare in adults. Multimodal treatment involving surgery, radiotherapy and chemotherapy can improve the prognosis of this disease, and recent advances in molecular biology have allowed the identification of molecular subgroups (WNT, SHH, Groups 3 and 4), each of which have different cytogenetic, mutational and gene expression signatures, demographics, histology and prognosis.

The present review focuses on the state of the art for adult medulloblastoma treatment and on novel molecular advances and their future implications in the treatment of this disease.

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Keywords: Medulloblastoma; Adults; Treatment; SHH; WNT

1. Introduction

Medulloblastoma, a malignant, invasive, embryonal tumor of the cerebellum with a preferential manifestation in children and a marked tendency to cerebros-spinal fluid (CSF) metastatization [1], is found in 15–30% of all childhood primary tumors of the central nervous system (CNS). About 70% of the cases occur in patients under 15 years of age, the incidence peak being 3–6 years [2]. In adults, medulloblastoma is much less frequent, accounting for less than 3% of primary CNS tumors. A recent US registry analysis from the Surveillance, Epidemiology, and End-Results (SEER) database [3] found that the incidence of medulloblastoma was 1.5 cases per million in the general population, children being ten times more likely to develop the disease than adults (6.0 vs. 0.6 cases per million). Males are 1.58 times more likely than females to be diagnosed with medulloblastoma during childhood, but this difference is not maintained in adulthood [3].

2. Histopathology and biology

The exact cellular origin of medulloblastoma is a matter of debate. It has been suggested that the disease might arise from two distinct embryonal cell groups: cells from the ventricular zone (VZ), which differentiate into Purkinje cells, basket cells, and other glial and neuronal cells of the cerebellum, and cells from the external germinal layer (EGL) that produces cerebellar granule cells. These cell groups are related to different molecular subtypes of medulloblastoma: it widely known that VZ cells give origin to the wingless (WNT) subtype, while sonic hedgehog (SHH) medulloblastomas derive from EGL cells [4].

The latest 2007 WHO classification [1] of CNS describes five histopathological subtypes of medulloblastoma: classic (80% of all medulloblastomas in children, 70% in adults), desmoplastic (15% in children, 30–40% in adults), anaplastic (10–20%), large-cells (2–4%), and extensive nodularity (3%). Differences between children and adults have been found for histological subgroups, which are of prognostic significance: desmoplastic and nodular subtypes are associated with a better prognosis in children <5 years of age whereas anaplastic and large-cells are associated with poor prognosis in all age patients [5]. Medulloblastoma, typically having a median localization in children, is more commonly lateral in adults [6].

3. Clinical and radiological presentation

Because medulloblastoma arises in the posterior fossa, a frequent complication is hydrocephalus due to the compression of ventricle IV, with a consequent increase in intracranial pressure. Common symptoms are vertigo, vomiting, ataxia and headache. Patients with a tumor localized in the mid-cerebellum may have symptoms (nystagmus,
Table 1 Chang’s staging system.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor less than 3 cm in diameter and limited to the classic midline position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres.</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor greater than 3 cm and invading one adjacent structure or partially filling fourth ventricle.</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumor further invading two adjacent structures or completely filling the fourth ventricle with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing marked internal hydrocephalus.</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor arising from floor of fourth ventricle and filling fourth ventricle.</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor spread through aqueduct of Sylvius to involve third ventricle, midbrain, or down into upper cervical cord.</td>
</tr>
<tr>
<td>M0</td>
<td>No gross subarachnoid or hematogenous metastasis.</td>
</tr>
<tr>
<td>M1</td>
<td>Microscopic tumor cells found in CSF.</td>
</tr>
<tr>
<td>M2</td>
<td>Gross nodular seeding in cerebellum, cerebral subarachnoid space, or in third or fourth ventricles.</td>
</tr>
<tr>
<td>M3</td>
<td>Gross nodular seeding in spinal subarachnoid space.</td>
</tr>
<tr>
<td>M4</td>
<td>Extraneuraxial metastasis.</td>
</tr>
</tbody>
</table>

Diplopia, hearing loss, seventh cranial palsies) that are related to compression of the cranial nerves. If the medulloblastoma spreads to the spine, peripheral neurological deficits may be present.

At MRI, medulloblastoma typically appears within the posterior fossa in the form of tumor masses, which are usually iso- to hypointense on T1-weighted (T1-W) images. The T2 signal varies, ranging from hyperintense to hypointense. Contrast enhancement, usually present, can vary in degree and extent. Other typical features are increased signals on diffusion-weighted images (DWI) and a decreased apparent diffusion coefficient (ADC), which may help in differentiating from other posterior fossa tumors, such as pilocytic astrocytoma and ependymoma [7].

4. Staging

Correct staging, crucial for a reliable risk stratification of patients, influences the therapeutic approach. Metastatic spread has higher incidence in children than adults (13% vs. 8%) [8,9] and typically follows CSF and leptomeningeal dissemination along the spinal cord. The cerebellum and brain are the most common sites of metastases in conjunction with spinal diffusion. Atypical metastatic sites are bones, which are the most common extra-CNS sites (80%) for both children and adults, followed by the lung (in adults) and liver (children). The time interval between diagnosis of the primary and detection of metastases is usually shorter in children than adults (20 months vs. 36 months) [6]. Patients are usually divided into average and high-risk groups, according to Chang’s classification and based on findings at [10] (Table 1). Staging examinations of fundamental importance are brain/spinal contrast enhanced MRI, performed both before and after (48 h) surgery, and CSF cytology, performed after MRI. If CSF is positive, this investigation should be repeated 20 days after surgery in order to rule out any false positive findings.

Patients are considered average risk when they present neither metastases nor residual disease after surgery (residual disease being defined as >1.5 cm²), and have favorable histology (i.e. other than large cells/anaplastic histology). High-risk patients have metastases, and/or residual disease >1.5 cm² and/or large cells/anaplastic histology.

Although the above-mentioned prognostic factors are widely accepted and used in clinical practice, the impact of metastases and residual disease on outcome is a matter of debate due to contradictory results obtained in different trials. Chan et al. [11] reported a 5-year progression free survival (PFS) rate of 47% and 59% in patients with and without metastatic dissemination, respectively. Brandes et al. reported a 5-year PFS of 61% vs. 78% in metastatic and non-metastatic patients, respectively [12]. Similar data were also found previously by Carrie et al. [9]. The prognostic value of M1 disease is an open question: it is not clear whether CSF dissemination has an outcome similar to that of M0 or metastatic disease. At present, M1 disease is considered high-risk and should be treated accordingly.

Data on residual disease are also contradictory. Chan et al. [11] found a 5-year PFS rate of 86% for patients without residual tumor, against 27% for patients with residual tumor. On the other hand, Brandes et al. found that residual disease had no significant impact [12].

5. Molecular subgroups

One of the most important advances in the knowledge of medulloblastoma is the discovery of molecular patterns allowing the division of medulloblastomas into distinct molecular subgroups with different cytogenetic, mutational and gene expression signatures, as well as different demographics, histology and prognosis. A number of studies have been performed to improve on the identification of a variable number of subgroups [13–16]. There are two well characterized subgroups of medulloblastoma with peculiar pathways: WNT and SHH. The remaining groups have been labeled as non-WNT/SHH, and their numbers vary in different studies. A recent consensus [17] established that medulloblastoma can be divided into four main molecular subgroups: WNT, SHH, group 3 and group 4.

5.1. WNT

The least common medulloblastomas, WNT account for 10% of all medulloblastomas (15% in adults) [18]. Typically they occur in children over three years of age, are rarely found in adults with medulloblastoma, are equally distributed between males and females, have a classic histology, and are rarely metastatic; their prognosis is best in children, with 5-year survival rates of >95%, whereas in adults the
5-year survival rate is 80%. This subgroup is characterized by enhanced WNT-beta catenin pathway activation. Catenin beta 1 gene mutation (CTNNB1) is the most common genetic alteration in this subgroup (present in 90% of the cases). The mutation and abnormal activation of Ctnnb1 leads to an enhanced activation of MYC and MYCN oncogenes, with a subsequent increase in cellular proliferation [19]. Other frequently altered genes are DDX3X (50%), SMARCA4 (26%), MLL2 (12%) and TP53 (12%). Genetic signatures of the subgroup are typically loss of chromosome 6q and 17p [20]. Given its better prognosis, this subgroup of patients is considered for de-escalated therapeutic protocols in order to minimize any long-term adverse events.

5.2. SHH

The SHH subgroup, consisting of 30% of all patients with medulloblastoma, mainly comprises adults (60%) [18], and infants, this form being rarer in children aged ≥3 years. The prognosis is intermediate for both age groups, the 5-year survival rate being in the region of 70%. Almost every histological subtype is present in this group, but desmoplastic and nodular forms are almost exclusive to the SHH subgroup. Metastatization is uncommon, its distribution being equivalent in both sexes. The most commonly found genetic mutations are PTCH1 (28%) or suppression of the fused homologue (SUFU). Other frequently mutated genes are: TP53 (13%), MLL2 (13%), MYCN (8%), LDB1 (7%), GLI2 (5%). Deletions of chromosomes 9q, 10q, 6q and CDK6 amplification are also frequent [21].

SHH, a transmembrane protein, activates another transmembrane protein, the smoothened regulator (Smo). This event activates two transcription factors, GlI1 and GlI2, and arrests the transcription repressor Gli3. These factors induce cell proliferation via the overexpression of MYCN oncogene and cyclins Ccnd1 and 2. Within this pathway Ptc1 acts as a Smo inhibitor. Mutations of this protein, the most frequent molecular alterations in this subgroup, lead to the constitutional activation of SHH pathway [22].

A recent study [23] demonstrated that the presence of TP53 mutations in SHH medulloblastoma allows a further prognostic stratification, this mutation being associated with a poorer survival. TP53 can also be mutated in WNT tumors, but in this subgroup it does not seem to be of prognostic significance. This subgroup, probably the most widely studied, has the greatest dramatic clinical implications; since SHH pathway inhibitors (specifically Smo inhibitors) have been proven to be effective, they are currently being evaluated in phase III trials (NCT01708174).

5.3. Group 3

This group, which has the worst prognosis with 5-year survival rates of 40 to 50% [21], makes up 25% of the diagnoses, the condition occurring in children and infants, with a predominance in males (2:1). It has rarely been described in adults (<2%) [24]. The tendency to metastatization is high (45%), and the most commonly found genetic alteration is proto-oncogene MYC mutation/amplification (16.7%). This group is characterized by an elevated genomic instability with frequent chromosome 1p gains, 10q and 5q loss and the presence of isochromosome 17 [21].

5.4. Group 4

Group 4 is the largest subgroup of all, accounting for 35% of all medulloblastomas [21]. The condition occurs in adults (20–25% of all adult medulloblastomas) and children (35%), the latter having better prognosis than adults. Overall, the prognosis is intermediate, with an overall survival rate of 75%. Metastases occur in 35–40% of cases. Almost all cases have classic or large-cells histology. The incidence in males is three times higher than in female. MYCN and CDK6 amplifications are the most commonly found genetic alterations in this group [21].

6. Other molecular alterations

Alterations of different proteins and pathways, described in medulloblastoma and currently being evaluated as potential therapeutic targets, can occur in any of the above molecular subgroups.

6.1. Notch

The notch pathway seems to be involved in medulloblastoma proliferation: during embryonal development, Notch2 signaling induces proliferation of GCP (precursors of the cerebellar granule cell, one of the cells in which medulloblastoma originates), via the up-regulation of the Hes1 transcription factor. Furthermore, Notch2 activation induces BMP suppression and an increase in Atoh1/Math1 expression [22]. However, the results of a phase I/II study evaluating the efficacy of the gamma-secretase/notch pathway inhibitor RO4929097 on various tumors, including recurrent childhood medulloblastoma (NCT01088763) are not yet available.

6.2. BMP

Bmp family is a group of negative regulator proteins that act, during cerebellum development, as inhibitors of SHH-induced GCP proliferation. Involved in this process are Bmp2 and Bmp4, which also plays a role in inducing the differentiation of GCPs [25,26].

In preclinical models it has been found that BMPs inhibit medulloblastoma proliferation [26], thus suggesting that molecules functioning as BMP agonists might be effective in the treatment of medulloblastoma [27].
6.3. Epigenetic alterations

Epigenetic alterations, mostly involving histone modifiers, have been widely described in medulloblastomas, and are under evaluation as a potential therapeutic target. Truncating mutations of histone methyltransferases MLL2 and MLL3 have been found in WNT, group3 and 4 medulloblastomas [28–30], whereas mutations of histone demethylases KDM6A and ZMYM have been identified in Group 3 and 4 [30,31]. Overexpression of H3K27me3 methyltransferase and (polycomb repressive complex 2 (PCR2 complex) component enhancer of zeste homolog 2 (EZH2) has been found in some medulloblastomas [32]. At present, different agents targeting these proteins have been developed and are currently under evaluation for medulloblastoma, in particular: histone deacetylase vorinostat, valproic acid and romidepsin and inhibitors of EZH2 (NCT01076530, NCT00867178, NCT01861990, NCT00053963, NCT01897571).

7. Treatment

7.1. Neurosurgery

As the extent of resection (total or near total), the first therapeutic approach, is of prognostic significance, the most radical possible excision should be undertaken [33] by experienced surgeons for optimal outcome with a standard risk of complications. In the presence of hydrocephalus, it might be necessary to relieve intracranial pressure with ventriculoperitoneal shunt or third ventriculostomy before proceeding with the surgical tumor resection. Ventriculostomy is often undertaken prior to resection in order to spare the patient ventriculoperitoneal shunt placement [34].

Surgical resection can be complicated by hemorrhage, meningitis, cervical instability and posterior fossa syndrome (swallowing difficulties, mutism, truncal ataxia and emotional instability.

7.2. Radiotherapy

Since surgery alone is associated with a high incidence of recurrence [35,36], complementary therapy is needed if medulloblastoma is to be treated with a curative intent. The cornerstone of medulloblastoma treatment is post-operative radiotherapy, for both patients with average and those with high-risk disease.

Radiotherapy should start within the fifth postoperative week, as it has been demonstrated that delay is associated with worse local control and an impaired prognosis [37]. Furthermore, time to completion of RT has been demonstrated to be important in terms of prognosis, as delays and interruptions may have a negative impact on event free survival (EFS) [38].

The dose-response relationship is well established. Berry et al. [39] described a disease free survival (DFS) of 77% at 10 years when radiation doses to the posterior fossa exceeded 52 Gy. Hubbard et al. [35] described a 91% 5-year disease control rate with doses of >54 Gy, against 33% for doses of <54 Gy.

7.2.1. Average risk

Radiotherapy is burdened by important toxicities, especially in young children, whose neurological and intellectual development can be compromised by it. Efforts have therefore been made to reduce irradiation dose whenever possible in pediatric patients. Packer et al. [40] reported positive results their trial in which children with non-metastatic medulloblastoma (no metastases or positive CSF) were treated with postoperative, reduced-dose craniospinal radiation therapy (23.4 Gy in13 fractions) plus a boost to the posterior fossa (31.8 Gy in 17 fractions) with concomitant vincristine and adjuvant lomustine, vincristine, and cisplatin. In this study, the PFS rate was 86% at 3 years and 79% at 5 years, these percentages being comparable to those obtained with full-dose radiotherapy [40]. In a study by Packer et al. [41], 421 patients with non-metastatic medulloblastoma (no metastases or positive CSF and residual disease <1.5 cm²) were treated with reduced craniospinal irradiation (23.4 Gy/13 fractions) with a posterior fossa boost of 32.4 Gy/17 fractions and the same chemotherapy as in the previous study by Packer et al. EFS at 5 years was 81% and OS, 86%. Adverse events, in particular hematologic toxicity and infections, were more predominant in the cyclophosphamide regimen. Following these results, this approach has become widely used in various institutions for the treatment of average risk children, with a preference for the lomustine based scheme, due to the better tolerance and its efficacy, which is similar to that achieved with the cyclophosphamide regimen [40].

Adult patients with average risk medulloblastoma are usually treated with post-operative radiation therapy only, as the use of chemotherapy in this subset of patients is still controversial and the hematological toxicity greater; data available on this aspect are reported in small retrospective studies [42] and one prospective trial [43].

7.2.2. High risk

Standard radiotherapy for high-risk patients is craniospinal irradiation (36 Gy/20 fractions with posterior fossa boost of 19.8 Gy/11 fractions), patients with spinal metastatic dissemination requiring higher spinal irradiation doses (39.6 Gy/22 fractions).

Chemotherapy is part of the treatment for high-risk patients but, to date, there is no consensus on regimens, doses, and timing of the chemotherapy in either pediatric or adult settings. In children, different schedules have been used in clinical trials and, at present, no one is considered standard. In adult patients, the preferred chemotherapeutic regimens are cisplatin or carboplatin and etoposide with or without
cyclophosphamide, widely used on the basis of the results of the prospective study by Brandes et al. [12]. The exact timing of chemotherapy in adults (before or after radiotherapy) is still matter of debate.

New radiotherapy techniques are under evaluation in order to reduce side effects from the treatment. Intensity modulated radiotherapy (IMRT) [44] and helical tomotherapy [45] have been evaluated, but only in a small series of patients for which results were disappointing. Tomotherapy does seem to be favorable in terms of target volume coverage, dose homogeneity, and reduction of dose to non-target tissues, but concerns have been raised regarding longer radiation beam-on times that could lead to higher whole-body isodoses due to intra-fraction motion. Increased whole-body doses could increase the risk of radiation-induced tumors, especially in children. Proton therapy allows the delivery of high therapeutic dose within the target area, with lower non-target tissues irradiation than for standard and three-dimensional conformational therapy [46,47]. Normal-tissue dose sparing has been achieved with IMRT and proton treatment of the posterior fossa and spinal column. For example, in the study by St. Clair et al., the dose to 90% of the cochlea was reduced from 101.2% of the prescribed dose with conventional X-rays to 2.4% with protons. Similarly, the dose to 50% of the heart volume was reduced from 72.2% with conventional X-rays to 0.5% with protons [46]. In their study, Merchant et al. [47] created models to compare the effects of proton therapy vs. photon therapy in medulloblastoma and other brain tumors. These models showed that proton therapy could lead to a reduction in hearing impairment (less cochlear dose distribution) and slower cognitive and IQ decline over time. Also, reduced doses to the hypothalamic–pituitary axis may decrease the incidence of hypopituitarism.

7.3. Chemotherapy

7.3.1. Average risk

The role of chemotherapy in the treatment of medulloblastoma has long been debated, both in the pediatric and the adult setting. In average-risk children, the use of chemotherapy was established after the results of trials that showed it prolonged EFS and OS. The PNET-3 [38] trial compared pre-radiation chemotherapy (alternating vincristine-etoposide-carboplatin and vincristine-etoposide-cyclophosphamide) followed by radiotherapy with radiotherapy alone in children with non-metastatic disease (M1 patients were allowed), and found that EFS was significantly improved by chemotherapy and RT (78.5% at 3 years and 74.2% at 5 years compared with 64.8% at 3 years and 59.8% at 5 years), whereas no statistically significant difference was found between the two regimens for OS. At multivariate analysis it was found that chemotherapy \( (P = 0.0248) \) and time to complete RT \( (P = 0.01) \) affected EFS. In the German HIT91 trial [48], patients were randomized to receive neoadjuvant chemotherapy before radiotherapy (investigational arm) with ifosfamide, etoposide, intravenous high-dose methotrexate, cisplatin, and cytarabine given in two cycles. In the standard arm, patients received immediate postoperative radiotherapy, with concomitant vincristine followed by eight cycles of maintenance chemotherapy consisting of cisplatin, lomustine, and vincristine. Relapse free survival was better in the post-RT group (78% vs. 65%), as was OS, with a 10-year OS rate of 91% vs. 62% in M0 patients and 70% vs. 34% in M1 patients. Following these results and those from the trial by Packer et al. [41], which showed that a RT dose reduction was feasible with concomitant vincristine and adjuvant chemotherapy (lomustine, cisplatin, vincristine), cytotoxic therapy became a standard practice in the treatment of children with medulloblastoma on a type 1 level of evidence. At present, the mainstay for patients older than 3 years and younger than 18 years of age is reduced dose RT (23.4 Gy/13 fractions) with posterior fossa boost of 32.4 Gy/17 fractions and concomitant vincristine administration with subsequent adjuvant chemotherapy (lomustine, cisplatin, vincristine), up to 8 cycles.

The role of chemotherapy in adults with average risk disease is still matter of debate. Given the rarity of the disease in the adult population, data on treatment derive mostly from retrospective, small series, and randomized studies are complicated to perform (Table 2). In the one available prospective study [43], in which patients were treated with radiotherapy (only if they were average risk) and with pre and post radiotherapy chemotherapy (if they were high risk), patients with average risk disease treated with RT alone had a 5-year PFS of 76%, compared with 61% of high risk patients treated with additional chemotherapy. Updated data after a follow up of 7.6 years showed no difference between the PPS and OS of average risk patients treated with RT only (54.8 Gy in 30 fractions) and high-risk patients treated with chemotherapy and RT (5 years PFS 80% vs. 69%; 5 years OS 80% vs. 73%). Results from a large retrospective analysis by Padovani et al. [42], showed that there was no difference between patients with average risk medulloblastoma treated with radiotherapy alone and that of those treated with radiotherapy in association with adjuvant chemotherapy \((P = 0.7)\); in this retrospective study, the Authors collected data from 253 adult patients in order to analyze prognostic factors, and found, in the group of standard risk patients \((n = 123)\), no significant difference between the 56% of patients treated with axial doses of \( \geq 34\) Gy and that of patients treated with craniospinal doses <34 Gy in combination with chemotherapy (46%) \((P = 0.7)\). However, chemotherapeutic regimens were not homogeneous, as data were collected during a prolonged period from different centers. For average risk patients only fourth ventricular floor involvement \((P = 0.035)\) and posterior fossa radiation dose <50 Gy 8 \((P = 0.004)\) were significantly associated with a worse prognosis at a multivariate analysis.

Current treatment for adult patients with average risk medulloblastoma, craniospinal irradiation (36 Gy in 20 fractions + posterior fossa boost \(- 18/19.8\) Gy in 10–11 fractions), is followed by a 5-year PFS of \(>75\%\). Adjuvant
chemotherapy could be evaluated in higher risk histology (large cells/anaplastic).

7.3.2. High risk

In general, it is accepted that the addition of chemotherapy to radiotherapy in high-risk patients improves the outcome. Nevertheless, data available are insufficient and questions remain open, especially regarding timing, dose and schedule of chemotherapy. The majority of trials undertaken demonstrate that the prognosis is dismal for this subgroup of patients. As described below, most of the trials showed that metastatic patients had a PFS of 20–40% and a 5-years survival rate of 20–30%.

The CCSG trial [49] found that patients with metastatic disease had a 5-year EFS of 46% when treated with chemotherapy and radiotherapy, compared with zero for patients treated with chemotherapy alone. The study randomized 233 patients with medulloblastoma to receive RT alone or RT followed by adjuvant chemotherapy with CCNU, vincristine and prednisone. The EFS of non-metastatic patients was unchanged (EFS 51% for RT alone and 61% for RT and chemotherapy, \( P = 0.27 \)), whereas patients with metastasis benefited from this chemotherapeutic regimen. In the HIT91 [48] study, 137 patients were randomized to receive pre-RT chemotherapy (ifosfamide, etoposide, high-dose methotrexate, cisplatin and cytarabine for 2 cycles) or concomitant vincristine and maintenance post-RT chemotherapy with cisplatin, CCNU and vincristine for 8 cycles. In patients with metastatic disease, maintenance chemotherapy was followed by a 5-year PFS rate of 30% and an OS of 30%.

In their series, Chan et al. [11] reported a 5-year PFS rate of 45% with chemotherapy and radiotherapy. Prados et al. [50] treated 27 medulloblastoma patients (24 of which with high-risk disease) with chemotherapy plus radiotherapy. One cycle of chemotherapy was given prior to, and for 6 cycles following, radiotherapy. Chemotherapy consisted of procarbazine, 6-thioguanine, dibromodulcitol, CCNU and vincristine. Hydroxyurea was given concomitant with RT. Fifteen patients had M1 or higher stage; these patients had a 5-year PFS and OS of 20% and 40%, respectively.

Brandes et al. [43] achieved a PFS rate at 5 years of 45% in the group of adult patients with high-risk disease treated with cisplatin, etoposide, cyclophosphamide before and after radiotherapy. Updated results [12] showed that this group of patients had 5-year PFS rate of 69% and 5-year OS rate of 75%, similar to those patients with average risk disease treated with radiotherapy alone. Whether to treat adult patients with pre-RT or post-RT chemotherapy is still a matter of debate. In general, chemotherapy administered before cranio-spinal irradiation (CSI) is better tolerated, because after radiotherapy the incidence of hematological and neurological toxicity is higher. In the study by Friedrich et al. [51], in which adult patients were treated according to the HIT 2000 protocol (CCNU, vincristine and cisplatin for 8 cycles after radiotherapy), the incidence of grade \( \geq 3 \) hematotoxicity was 58% and grade 2–3 neurotoxicity was 69%. Half the patients enrolled managed to receive all the 8 cycles and most of the patients experienced delays and required dose reductions. Another aspect is that in the studies that compared pre-RT with post-RT chemotherapy [48,52], the outcome of the patients who received CT before RT was not inferior to that obtained in patients treated with post-RT chemotherapy. Furthermore, in the study by Brandes et al. [12] no patients treated with pre-RT chemotherapy had disease progression during chemotherapy.

Adult patients have been frequently treated with cisplatin, etoposide and cyclophosphamide or with cisplatinor carboplatin plus etoposide [12].
7.4. Recurrent disease

At present there is no standard treatment for recurrent disease. Depending on the site and the extent of relapse, different therapeutic options can be considered.

7.4.1. Surgery

Re-section is recommended if the patient is a suitable candidate for surgery and in the presence of local, resectable relapses [53,54]. No data from randomized trials comparing re-section with other therapeutic approaches data are available. Nevertheless, data in literature have shown a prolongation of survival in patients re-rected for recurrence [55].

7.4.2. Radiotherapy

Radiotherapy, in particular stereotactic radiotherapy or radiosurgery, might be a therapeutic option in cases of recurrence with single, small lesions. Results from a small series of patients showed a control rate of 89% with these techniques, with survival rates of 65% at 1 year, 25% at 3 years and 17% at 5 years. The risks of re-irradiation have been described in literature, various authors reporting high rates of cumulative toxicity, in particular radionecrosis [56,57].

7.4.3. Systemic treatments

Systemic treatments are considered in cases of multifocal relapse. There is limited data regarding the different agents and schemes used, as few clinical trials have been performed in order to test the efficacy and superiority of one treatment over another; data available generally derive from case reports and single institution experiences. In general, patients can be treated with platinum-etoposide containing regimens if the time to recurrence is long enough (>6 months) from first treatment. In literature there are reports of the activity of regimens such as CVP (cisplatin-cyclophosphamide-etoposide) or MOPP (methotrexate, procarbazine, vincristine, prednisone) [58], temozolomide and bevacizumab [59] or temozolomide alone [60].

Another approach is high-dose chemotherapy (HDCT) with stem cells transplantation. Most of the data in literature [61–65] derive from single case reports and small series and show prolongation of survival. Only one trial included a comparison group and reported an OS of 3.47 years with HDCT against 2 years following conventional chemotherapy [66]. Out of 66 patients reported in these publications, 7 died of toxicity. Therefore, this therapeutic option should be limited to a small group of selected patients and performed only in centers with expertise in the management of medulloblastoma and HDCT.

Novel biological agents are under evaluation for the treatment of recurrent medulloblastoma. The most developed and promising agents are inhibitors of the hedgehog pathways, in particular Smo inhibitors, such as vismodegib and LDE225 (sonidegib). Vismodegib, which was active in one patient with bone metastases from medulloblastoma [67] and showed a degree of activity in patients of the SHH subgroup in a phase I trial [68], is currently under evaluation in a phase II trial in adult patients (NCT00939484). LDE225 demonstrated efficacy in patients with solid tumors in a phase I trial [69] and is currently under evaluation in a phase II (NCT01125800) and a phase III trial (NCT01708174), in which the hedgehog pathway is being explored using a 5-gene signature assay; a strong association between activation of this pathway and tumor response has been observed in patients with medulloblastoma. Therefore, the ongoing phase III trial is testing LDE225 on patients with the activated hedgehog pathway only. As it is known that these agents are effective in patients harboring Smo mutations (about 10% of all medulloblastomas), these agents can be offered to a small subset of patients. It should also be borne in mind that their activity is limited in time, and mechanisms of resistance have already been described. In particular, a mutation of Smo (SMO-D473H) that has no effect on HH signaling and induces loss of interaction between vismodegib and Smo has been identified [70]. Upreregulation of Gli2, was found to be an important alternative mechanism that confers resistance against Smo antagonists [71,72]. IGF1R-Pi3K target genes were overexpressed in NVP-LDE225 – resistant cells, suggesting that an up-regulation of this pathway may contribute to the development of resistance [72].

7.5. Targeting stem cells

It has been suggested that medulloblastoma cells have similar features to neural stem cells. Indeed, many of the pathways present in medulloblastoma, such as WNT, SHH and NOTCH, are also involved in the embryonal development of the neural tissue, and active in neural stem cells [4]. It has also been suggested that only a fraction of medulloblastoma cells have a stem-like phenotype, and it has been demonstrated that some cells can be maintained as neurospheres with the same techniques used to grow non-tumoral stem cells [73,74]. Furthermore, a fraction of medulloblastoma cells express stem-cell marker CD133 [75,76]. Stem cells, which usually have a high rate of proliferation, contribute to tumor growth and are known to be particularly resistant to common therapeutic agents. Targeting stem cells has always been an appealing issue in oncology. Some molecular targeted drugs are under development to target medulloblastoma stem-cell pathways, such as inhibitors of the hedgehog pathway and Notch. Hedgehog inhibitors above show some activity against medulloblastoma; nevertheless, it is unclear whether these drugs also affect medulloblastoma stem cells. In preclinical models, Notch inhibitors induce a marked reduction of CD133 cells in medulloblastoma cell lines [77]. Another proposed therapeutic approach is to target the stem cell niche, the micro-environment composed of supportive cells, extracellular matrix and factors required for the support and growth of stem cells. It is believed that, by disrupting this environment, stem cells will be eliminated. In preclinical models [78], it was found that CD133 medulloblastoma cells were
localized in the proximity of endothelial cells and small vessels. This raises the hypothesis that anti-angiogenic treatment could be beneficial in targeting medulloblastoma stem cells [4].

7.6. Immunotherapy

Immunotherapy is another therapeutic approach that has been considered for the treatment of medulloblastoma. The target antigens that have been identified are cancer testis antigens (CTAs), MAGE and GAGE proteins [79,80]. MAGE-4 expression has been found in 50% of medulloblastomas, MAGE-A in 62% and GAGE in 84% [79]. MAGE antigens, already successfully targeted in other tumor types [81,82], are a promising targets for immunotherapy in patients with medulloblastoma. Other possible immunotherapeutic approaches are vaccinations against EGFRvIII in combination with GM-CSF, which have already been tested in other brain tumors [83], and intrathecal infusion of lymphokine activated killer (LAK) cells. This last therapeutic strategy was tested on 8 patients with the achievement of complete responses in 3 patients for up to 20 months [84]. Unfortunately, these results have not been replicated in the successive studies.

8. Conclusions

Over the past 20 years, the outcome of patients with medulloblastoma has improved, thanks to the use of chemotherapy and improvement in radiotherapy techniques, which have enabled a reduction in the incidence of late iatrogenic sequelae. Major steps forward in the treatment of medulloblastoma are the advances made in molecular sequencing and the classification of the disease into molecular subgroups. The different molecular types of medulloblastoma have their peculiarities in terms of prognosis, clinical presentation and molecular targets. By identifying molecular subgroups of medulloblastoma it will become possible to modify the therapeutic options for specific patients. The current management protocols do not yet consider these molecular groups as a key factor in management, protocols still relying exclusively on clinical features. One of the main questions is how to incorporate molecular biology findings into the decision making process for the treatment of medulloblastoma. Division into molecular subgroups might become a useful tool for the risk stratification the patients, enabling the decision to be made as to whether to offer a more or less aggressive treatment based on the expected prognosis. For example, WNT tumors have an excellent outcome and could be treated less aggressively (reduced RT doses, avoidance of chemotherapy). Furthermore, the identification of specific molecular alterations should lead to the development of targeted agents, such as Smo inhibitors for SHH tumors. It thus seems reasonable to foresee that the integration of standard treatments (chemotherapy and RT) and targeted agents will become a therapeutic option for SHH medulloblastomas.

The ongoing phase II trial (NCT01878617) well exemplifies treatment selection according to molecular stratification: the amount of radiation therapy and type of chemotherapy administered will be determined by the patient’s treatment stratum, based on the tumor’s molecular subgroup assignment and the clinical risk. Patients will be subdivided according to the molecular subgroups will be WNT, SHH and Non-WNT/Non-SHH, and then assigned to a clinical risk group (low, standard, intermediate, or high) based on the assessment of radiological staging, histology and chromosomal abnormalities. Patients with low-risk WNT tumors will undergo reduced dose craniospinal irradiation, while high-risk patients will be treated with standard RT and 4 cycles of cisplatin, vincristine and cyclophosphamide. SHH patients will receive standard treatments followed by maintenance therapy with vismodegib. After undergoing RT and chemotherapy, non-WNT/non-SHH patients with high-risk disease will be given maintenance treatment with pemetrexed and gemcitabine [87].

In conclusion, the discovery of molecular subgroups has generated a numerous hypotheses for tailoring of treatment, and most of the tailored treatments suggested are already under evaluation. The results of ongoing studies are awaited in order to understand whether the adaptation of therapies to the molecular subgroups could lead to an improvement in the outcome of the disease.

Further molecular characterization will allow the identification of novel targeted therapies and will help improve the reliability of risk stratification for patients. It is therefore hoped that a more personalized approach to this disease will be achieved, and patients with a good prognosis will be spared the side effects of intensive treatments, while new and intensified therapeutic approaches could be modeled for high-risk patients in order to improve their survival.

Conflict of interests statement

The authors declare that they have no conflict of interests.

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