Medulloblastoma in childhood: a clinical and biological study

Michiels, E.M.C.

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Introduction
1) Introduction

Cancer is the most common cause of death from disease in children under the age of 15 years. Tumors of the central nervous system (CNS) are the second most frequent type of cancer, after leukemia. They account for about 20% of cancer patients. CNS tumors form a very heterogeneous group, in which the gliomas account for most patients (about 60%), while medulloblastomas come second with approximately 20% of all CNS tumors.

The medulloblastoma was first described by Bailey and Cushing in 1925. It belongs to and is by far the most frequent representative of the group of the embryonal CNS tumors, also called central Primitive Neuroectodermal Tumors (PNET). As will be explained in the chapter of the classification of brain tumors, the terms medulloblastoma and PNET were both used for the same tumor, while some authors also included histologically different tumors in the diagnosis "PNET". As a consequence, medulloblastoma and PNET are often analyzed together in literature. In this review we will concentrate on medulloblastoma as far as possible.

Medulloblastomas preferably arise in the midline of the cerebellum (Figure 1) and they have the propensity to spread via the cerebrospinal fluid to the spinal canal. Despite intensive therapy, including surgical resection, radiotherapy and sometimes chemotherapy, survival rates are still disappointing.

In those patients who survive, serious long-term effects become apparent. Therefore, in the future, it is necessary not only to improve survival for these children, but also to reduce the long-term damage of the therapy.

2) Epidemiology

Several authors studied the incidence of central nervous system tumors and medulloblastoma in children. Schoenberg et al. 2 found in their study of primary intracranial neoplasms of childhood an average annual incidence rate of 2.17 cases/100000 population per year, of which 24.2% were medulloblastoma. This is in agreement with Young et al. 3 who found an incidence rate of central nervous system tumors in children of 23.9 per million per year of which 20% were medulloblastoma.

In the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program from 1973 to 1986, 4, 532 cases of medulloblastoma were analyzed. Age at diagnosis ranged from 0 - 86 years, although 77.4% of the patients was less than 19 years old. Mean age at diagnosis for these cases was 7.3 years, with peaks at 3 and 7 years.
Most studies find a male predilection for central nervous system tumors in general and medulloblastoma in particular, with ratios from 1.2:1 to 2:1 \(^3-7\). In the study of Schoenberg \(^2\) there was no significant difference in incidence between boys and girls.

Therapeutic irradiation to the head seems to be an established risk factor for the development of brain tumors \(^8-12\). Use of diagnostic X-rays in utero and the development of brain tumors is described, but the reduced use of radiography in obstetrics and the lower radiation doses used in modern techniques make this a hypothetical problem nowadays \(^11\). Analysis of other factors such as exposure to electrical current, paternal agriculture-related exposures or paint exposure did not reveal consistent results and need further investigation. Some authors \(^13\) found that maternal consumption of sodium nitrite in cured meats increases the risk of brain tumors in their offspring, whereas the ingestion of vitamins A, C, E and folate protects against this effect \(^14\). Others however did not demonstrate an effect of nitrite \(^15\). Interestingly, the decline in incidence of medulloblastoma that is seen since the mid 1980s by some authors \(^16\) could be due to the introduction of multivitamin suppletion during pregnancy.

3) Familial predisposition and inherited disorders

There are only a few reports of medulloblastoma occurring in siblings \(^17,18\) suggesting a hereditary origin of these tumors. Some hereditary disorders such as neurofibromatosis, tuberous sclerosis, the Li-Fraumeni syndrome, the Turcot syndrome and the multiple nevoid basal cell carcinoma syndrome (Gorlin syndrome) are known to predispose to the development of brain tumors in affected children. As far as we know, there is no association of medulloblastoma with neurofibromatosis or tuberous sclerosis, as is the case for other types of brain tumors like glioma. There is however an association of medulloblastoma with the multiple nevoid basal cell carcinoma syndrome \(^19-21\) and the Turcot syndrome, in which patients suffer from polyposis coli and neural tumors \(^22,23\).
An association between the occurrence of renal embryonal neoplasms (malignant rhabdoid tumor and Wilms' tumor) and brain tumors, including medulloblastoma, was found by Bonnin \textit{et al.} in 7 children \(^24\).
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4) Prognostic markers

Reported 5-year survival rates of children with medulloblastoma vary greatly in literature: 39 - 70\% \cite{25-28}. In one study, Packer \textit{et al.} even found survival rates of over 80\% \cite{29}. The reason for this great variation may be selection of patients in some studies, small patient numbers or treatment in a single institution. In the SEER program, these problems are bypassed, and survival rates for children with medulloblastoma range from 40 to 50\%, according to different age groups \cite{4}. All this means that some children, despite very intensive therapy consisting of neurosurgery, craniospinal radiotherapy and sometimes chemotherapy, do very badly. In addition, the therapy of these tumors is responsible for important toxicity and long-term effects, which seriously affect the quality of life in a later stage. Therefore improving the treatment for this type of tumor must encompass improvement of the survival as well as decrease of the toxicity of the therapy. To attain this goal, prognostic factors need to be identified that allow the children to be assigned to different treatment schedules according to their predicted outcome. Laborious studies have been undertaken to identify such prognostic factors, unfortunately often without consistent results.

\textit{Patient and tumor related prognostic factors.}

Age at diagnosis is a very debated prognostic marker. Some authors found a prognostic significance in favor of older age \cite{30,31}, while others didn't see an influence of age \cite{32-34}. Most authors did not find a statistical significant difference in survival for sex \cite{32,33,35,36}, although this is contradicted by others \cite{4,7,26}, in favor of females. T- and M-stage are more often found to be of prognostic significance \cite{32,34,35,37,38}, although not by all \cite{28,36}. Aneuploid tumors had a better prognosis in some studies \cite{39,40}, while the opposite was found in others \cite{32}. Tait \textit{et al.} \cite{33} did not see an influence of DNA ploidy. Gilbertson \textit{et al.} found the mitotic percentage index, which is the percentage of tumor cells in mitosis, to be a prognostic factor in multivariate analysis \cite{41}. Some authors found a better prognosis for tumors of the desmoplastic type, but a worse prognosis for patients with a bad postoperative performance status \cite{42}.

\textit{Therapy related prognostic factors.}

Survival is often related to the extent of resection \cite{32-34,38}. Some studies \cite{36,38} showed that the need for CSF shunting worsens the chance on survival. Zerbini \textit{et al.} \cite{32}, Carrie \textit{et al.} \cite{42}, and Khafaga \textit{et al.} \cite{38} found the radiation dose to be of prognostic value. Grabenbauer \textit{et al.} found in multivariate analysis that the adequate coverage of the target volume by external radiotherapy was more important than the radiation dose to the posterior fossa \cite{43}.
The influence of chemotherapy on prognosis will be discussed in detail in the chapter of therapy of medulloblastoma.

In conclusion, reliable prognostic markers that apply to the majority of medulloblastoma patients are very hard to find. The presence of metastases at diagnosis is generally accepted as a predictor of poor survival, but this represents only a small number of patients. Administration of adequate doses of radiotherapy (50 Gy to the posterior fossa and 30 Gy to the spinal canal) seems to be necessary to improve survival of these patients. Other clinical markers however do not unequivocally predict prognosis and are therefore difficult to use in practice. More reliable markers need to be identified to solve this problem.

5) Histogenesis, pathology and classification

Histogenesis
The histogenesis of medulloblastoma has been a matter of debate for a long time. It is generally accepted that the tumor is embryonal, i.e. derived from an immature precursor cell. Three main sources for the origin of this tumor have been described: a) the external granular layer, which is a cell layer present in the cerebellum until approximately one year of age. These primitive cells migrate and differentiate to form the neurons of the internal granular layer; b) the cells of the internal granular layer. This origin is consistent with the fact that medulloblastomas frequently show neuronal differentiation in immunohistochemical studies; c) cells of the posterior medullary velum, part of the roof of the fourth ventricle.

Pathology
On examination, medulloblastomas are most often grayish-white or pink tumors, located in the vermis of the cerebellum and occupying the cavity of the 4th ventricle. They are soft and friable and moderately demarcated from the normal tissue. Areas of necrosis may be present, but calcification is rare. Medulloblastomas are known for their involvement of and spread via the leptomeninges, which has its consequences for therapy.

Microscopically, this tumor is characterized by a dense population of small cells with scanty cytoplasm, and round to oval nuclei with coarse chromatin. The presence of mitotic activity may vary considerably. Beside the classical or undifferentiated medulloblastoma, signs of differentiation are present in approximately 50% of the cases.
**Medulloblastomas with neuronal differentiation**
This is the route of differentiation most frequently seen, and it is characterized by some degree of positivity for synaptophysin and neuron specific enolase (NSE) in immunohistochemical studies. Neuronal differentiation can be expressed as pale islands or nodules of better differentiated cells, Homer Wright rosettes or ultimately as mature ganglion cells. The formation of "neuronal" nodules is the most frequent type of neuronal differentiation. A variant of this type, with reticulin-rich regions separating the reticulin-free islands, is referred to as desmoplastic medulloblastoma. Another characteristic of neuronal differentiation, though not as frequent, is the formation of Homer Wright rosettes. These consist of a central region of fibrillar processes emerging from surrounding neoplastic cells, of which the nuclei lie radially around the center. These centers show positivity for neuronal markers.

**Medulloblastomas with glial differentiation**
The true incidence of glial differentiation is hard to establish, as medulloblastomas contain reactive astrocytes. True glial differentiation however would mean that neoplastic cells would be positive for a glial marker such as GFAP. As it is very difficult to prove whether immunoreactive cells are neoplastic or reactive, the incidence of glial differentiation varies greatly among authors.

**Medulloblastomas with mixed differentiation**
This category includes tumors in which true neoplastic glial cells are found in a medulloblastoma with signs of neuronal differentiation. As a consequence of the highly varying incidence of glial differentiation, the same variability is found in the incidence of mixed medulloblastomas.

Three characteristic variants of medulloblastoma are described: the desmoplastic, the melanotic and the medullomyoblastoma. The most frequent variant is the desmoplastic type, which accounts for approximately 10% of childhood medulloblastoma. This type has often a more lateral localization, i.e. the lateral lobes of the cerebellum, and shows frequent infiltration in the overlying meninges. Microscopically this tumor is placed in the category of medulloblastomas with neuronal differentiation, although some authors believe that some glial differentiation is also present. Rare forms are the melanotic medulloblastoma, a form of medulloblastoma containing melanin pigment, and the medullomyoblastoma, in which striated muscle cells can be detected.
Chapter 1

Classification

Medulloblastoma-like tumors are sometimes found in the cerebral hemispheres. Hart and Earle proposed in 1973 that these tumors be called Primitive NeuroEctodermal Tumors (PNETs) \(^52\). In the assumption that more embryonal CNS tumors arise from one common immature precursor cell, Rorke proposed in 1983 \(^53\) that these tumors (i.e. ependymoblastoma, pineoblastoma and cerebral neuroblastoma) also be called PNET. However, in the latest WHO classification of brain tumors (1993) \(^54\), the latter three are classified separately and the term PNET is reserved for the cerebellar medulloblastomas and those tumors that are morphologically indistinguishable from the medulloblastomas but are located elsewhere in the CNS.

6) Cytogenetics and molecular biology

Numerous studies have shown genetic alterations in childhood PNETs and medulloblastomas. These alterations involve both the total DNA content of the cells as well as specific chromosomes, i.e. chromosomes 1, 6, 7, 8, 9, 10, 11, 16 and 17. Regarding the DNA content of the tumor cells, various studies show different levels of aneuploidy. Tomita et al. and Tait et al. found about half of the cells to be aneuploid \(^3\), while Gajjar et al. \(^55\) and Zerbini et al. \(^32\) respectively found 9 of 34 tumors and 12 out of 58 tumors that were aneuploid. The correlation of aneuploidy to prognosis is not clear: in the studies of Tomita et al. and Gajjar et al. patients with aneuploid tumors seemed to do better, while the opposite was found by Zerbini et al. and no influence on survival was seen by Tait et al.

Analysis of tumor karyotypes reveals that the most consistent finding is deletion of the short arm of chromosome 17, whether or not in combination with duplication of 17q (isochromosome 17q, i(17q)). The reported frequencies of this deletion go up to 46\% \(^56\)\(^-\)\(^68\). As the tumor suppressor gene (TSG) p53, which is involved in many tumor types, is localized on 17p13, deletion of this TSG was thought to be important in the development of medulloblastoma. However, evidence of a tumor related locus more distal of p53 became available \(^69\)\(^-\)\(^70\), and several authors showed that mutations in p53 are rare in medulloblastoma/PNET \(^69\)\(^-\)\(^73\).

Loss of 17p has a negative impact on prognosis according to some authors \(^58\)\(^-\)\(^70\). However, this finding is not verified by others \(^66\).

As previously mentioned, patients with the nevoid basal cell carcinoma syndrome (NBCCS), or Gorlin syndrome, have a predisposition to develop medulloblastomas.
The gene for NBCCS, Patched (PTCH), is located on chromosome 9q. Previously, Schofield et al. 74 already showed that loss of heterozygosity of 9q was only seen in medulloblastomas of the desmoplastic type, and the 3 medulloblastomas occurring in patients with Gorlin syndrome were all desmoplastic. Raffel et al. 75 also found LOH of PTCH in non-desmoplastic sporadic medulloblastomas. Pietsch et al. 76 screened 64 tumors and 4 cell lines of sporadic medulloblastomas for PTCH mutations. None of the 57 "classical" medulloblastomas carried mutations, in contrast to 3 out of 11 desmoplastic variants.

N-myc amplification is sporadically described in medulloblastoma, and these tumors seem to be unresponsive to therapy 65,77,78.

Scheurlein et al. found amplification of c-myc to be more frequent in central PNET (8 of 32 tumors) 68. This is in agreement with Brugger et al. 79, who found that c-Myc protein expression is common in medulloblastoma/PNET. In the first study, combination of LOH of 17p and c-myc amplification seemed to predict a very bad survival for the patients.

More recently, studies have focused on gene and protein expression in medulloblastoma and the prognostic impact of differences in expression. One of the proteins studied is the c-erbB-2 oncogene product 80,81. This oncogene is located on chromosome 17q, which is frequently amplified in medulloblastoma [i(17q)]. Although the number of medulloblastomas that was positive for this protein differed in the 2 studies (83.6% versus 13%), both authors found an inverse correlation between c-erbB-2 expression and survival.

Gilbertson et al. 82 found that co-expression of 2 members of the Epidermal Growth Factor Receptor (EGFR) family, HER2 and HER4, occurred in approximately half of the medulloblastomas investigated, and was an independent predictor of poor survival. Another growth factor, neurotrophin 3, was consistently expressed in medulloblastomas, as well as its receptor, TrkC 83. Although the level of expression was highly variable in different tumors, patients with a high expression had a significant better progression free survival and overall survival.

Transcription factors are other candidates for deregulation of their expression in tumors. Rostomily et al. analyzed the expression of NEUROD1, a member of the NEUROD/atohal family which regulates neurogenesis, and found that all 12 medulloblastomas investigated showed expression 84. The PAX gene family also codes for transcription factors. Deregulated expression of PAX5 in medulloblastoma was found by Kozmik et al. 85. PAX6 was also consistently expressed in medulloblastoma, but in contrast to PAX5, PAX6 was also expressed in normal cerebellar tissue. Deficiencies in the DNA mismatch repair (MMR) system play a role in some types of cancer as hereditary nonpolyposis colorectal cancer (HNPCC). Analysis of 22 medulloblastomas showed that the MMR system is not commonly deficient in these tumors 86.
7) Clinical presentation and diagnosis

The symptoms and signs of a child with a brain tumor are dependent on the age and developmental stage of the child and the localization of the tumor. In general, complaints of raised intracranial pressure (ICP) are often the first ones, consisting of headaches and vomiting in the morning, ataxia and lethargy. These symptoms can however be vague and slowly progressing.

In young children non-specific signs of anorexia and irritability are often seen, together with developmental delay or loss of acquired skills. Children with an open fontanel may develop macrocephaly. Papilledema may be absent on fundoscopy. Older children more often complain of headache and vomiting, which does not always present as the classical morning headache, relieved by vomiting. Extreme fatigue, poor school performances and personality changes can be present.

Most of the central PNETs will be located in the posterior fossa. This causes signs of disturbances in balance as ataxia -often accompanied by nystagmus-, coordination problems and cranial nerve deficiencies, mostly of n. V, VI, VII and IX. Supratentorial tumors will cause symptoms according to their location and size. The first signs however are often not site-specific, since headache is the most common symptom, followed by seizures. The latter are most often of the grand-mal type, and occur as first symptom mostly in slow-growing tumors. Dependent on the localization of the tumor, hemiparesis, sensory loss and signs of raised ICP may occur. More specific signs may lead the diagnosis to very specific locations, as visual defects in tumors of the optic pathway.

PNETs have the propensity to spread via the leptomeninges in about 15% of cases. Sometimes these metastases are responsible for the first symptoms, such as radicular pain or bladder dysfunction in children with metastases in the spinal canal. Extraneurial spread also occurs, although it is rare at diagnosis. The most common site is bone, but also bone marrow, lungs, lymph nodes and liver may be involved.

The major tools to confirm clinical suspicion on a brain tumor are CT and MR scans. CT scan with and without contrast will reveal 95% of the brain tumors. MR scan however has some advantages over CT scan, such as no radiation exposure, the ability to reconstruct images in different planes (transversal, sagittal and coronal), less bone artifacts, a greater sensitivity in detection of early infiltration and a better visualization of brain stem lesions. On the other hand, MR takes a much longer scanning time, is more prone to movement artifacts and can not differentiate between edema and tumor, which has consequences if MR is performed to evaluate postoperative tumor rest. Figure 1 shows the MR scan of a medulloblastoma in an 11-year-old girl.
In search for leptomeningeal metastases, myelography was the diagnostic procedure most often performed. The advantage of this technique is the availability of CSF, which can be examined for the presence of tumor cells. However, there may be a risk in performing a myelography, especially in posterior fossa tumors. Therefore, this method is replaced more often by a MR scan with Gadolinium-DTPA, which is a reliable technique for detection of spinal leptomeningeal spread. This does however not solve the problem of the CSF examination, which should still be performed. One must thereby take into account that negative CSF examination can occur with obvious metastases on imaging, and vice versa, a few tumor cells in the CSF will not be visible on imaging.

**Table 1**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DEFINITION</th>
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<tr>
<td><strong>Tumor</strong></td>
<td></td>
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<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Tumor &lt; 3 cm in diameter and limited to the midline position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres</td>
</tr>
<tr>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Tumor &gt; 3 cm in diameter, further invading one adjacent structure or partially filling the fourth ventricle</td>
</tr>
<tr>
<td>T&lt;sub&gt;3a&lt;/sub&gt;</td>
<td>Tumor 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>T&lt;sub&gt;3b&lt;/sub&gt;</td>
<td>Tumor arising from the floor of the fourth ventricle or brain stem and filling the fourth ventricle</td>
</tr>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Tumor further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumor extending to the upper cervical cord</td>
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**Figure 1** MR scan of a medulloblastoma in an 11-year-old girl

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*Continued*
Table 1 - continued

<table>
<thead>
<tr>
<th>Metastases</th>
<th>Description</th>
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<tr>
<td>M₀</td>
<td>No evidence of gross subarachnoid or hematogenous metastasis</td>
</tr>
<tr>
<td>M₁</td>
<td>Microscopic tumor cells found in cerebrospinal fluid</td>
</tr>
<tr>
<td>M₂</td>
<td>Gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space or in the third or lateral ventricles</td>
</tr>
<tr>
<td>M₃</td>
<td>Gross nodular seeding in the spinal subarachnoid space</td>
</tr>
<tr>
<td>M₄</td>
<td>Extraneuroaxial metastases</td>
</tr>
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Table 1.
Chang staging system for posterior fossa medulloblastoma.

A classification system of posterior fossa medulloblastoma was proposed by Chang et al. 87, and is shown in Table 1. The usefulness of this staging system for designation of patients to different prognostic subgroups can be a subject of debate. As stated in the paragraph of prognostic markers, the prognostic value of the T-stages is not equivocal, especially in the case of low T-stages. The M-stage has much more value in predicting prognosis. A new staging system should take into account molecular markers that have shown to be reliable prognostic factors such as c-erbB-2 or TrkC. However, before these markers can be applied more longitudinal studies need to be performed.

8) Therapy

Neurosurgery
Therapy of cPNETs consists in the first place of neurosurgical removal of the tumor. The main attempt is to come to complete resection, thereby trying to minimalise the risk on postoperative morbidity and mortality. The application of the operation microscope and ultrasonic surgical aspirator is of great value hereby and has increased the number of patients in which this goal is achieved.

A specific problem is the need for CSF diversion due to raised intracranial pressure caused by obstruction of the CSF circulation by the tumor. Several cases of systemic spread of medulloblastoma after CSF shunting procedures were described in literature, and reviewed by Jamjoom et al. 88. The general conclusion of these authors is that the shunting procedure is only rarely responsible for the systemic spread (in less than 7% of cases with metastases), and furthermore, the survival of these patients is seldom adversely affected by the systemic spread, but is in most cases determined by the intracranial tumor itself. Thus, shunting procedures before surgical removal of the tumor should be performed when necessary. Nevertheless, to reduce the risk of systemic spread of tumor cells to a minimum, external ventricular drainage is preferred.
Radiotherapy
Radiotherapy after surgical resection is still the standard adjuvant therapy for medulloblastoma, as this tumor is one of the most radiosensitive brain tumors in childhood. There is a general consensus about the need for total neuraxis irradiation, in view of the propensity for leptomeningeal spread. A series of studies have shown the need for a dose of 50 to 55 Gray on the tumor and 30 to 35 Gray on the rest of the brain and spinal canal. Lowering this dose had no influence on survival in some studies, although most of these studies were performed on a selected group of patients. Randomized trials on large groups of patients contradict this finding. This is a huge problem in children under the age of 3 years, as in this group such a high dose of radiation has even more disastrous effects on the long term than in older children. At present, hyperfractionated radiotherapy is being tested in an attempt to increase the dose of radiotherapy without increasing the side effects. In one study, hyperfractionated radiotherapy was combined with chemotherapy for children with high T or M stage medulloblastoma. The dosages administered were 72 Gray to the intracranial tumor and 36 Gray to the craniospinal axis as prophylaxis. Survival was excellent for children with high T stage who had no metastases at diagnosis, but not for children with high M stage. In a second study however, where no chemotherapy was added for standard-risk medulloblastoma, results were much more disappointing.

In this study the dose administered to the primary tumor was 72 Gray, with 30 Gray to the craniospinal axis. Survival of standard-risk patients was comparable to that achieved with single-fraction radiotherapy (3-year PFS of 63%), but with a high number of failures outside the primary site. The high-risk patients in this study also received chemotherapy, so the role of hyperfractionated radiotherapy in their high survival rates (60% 3-year PFS) can not be correctly assessed.
In a separate paragraph some of the long-term sequelae of treatment will be discussed.

Chemotherapy
Chemotherapy was introduced in the treatment of medulloblastoma in an attempt to improve survival of these children and diminish the long-term effects by trying to reduce the dose of radiotherapy or delaying radiotherapy until after the age of 3 years.
A number of chemotherapeutic agents are tested in childhood medulloblastoma. However, the number of single drug studies is limited. Often a combination of two or more drugs is tested, which hampers the interpretation of the therapeutic efficacy of each single drug.
Platinum derivatives. These drugs are known to be effective in the treatment of medulloblastoma. In recent years, more studies have been conducted using carboplatin instead of cisplatin because of a similar antitumor activity but with a better penetration of the blood brain barrier and less oto- and neurotoxicity of carboplatin. The majority of these studies show a clear effect of carboplatin. Combination of carboplatin with vincristine showed no encouraging results in the treatment of standard-risk medulloblastoma in a study by Bergman et al. Another combination however, which does show a good response rate, is carboplatin and etoposide.

Other alkylating agents. Medulloblastoma is also shown to be sensitive to cyclophosphamide. A concern however is the prolonged myelosuppression caused by this drug. As is stated later in this chapter, cyclophosphamide is used in studies evaluating the efficacy of high-dose chemotherapy with stem cell rescue in medulloblastoma.

A phase II study of high-dose ifosfamide, conducted by the Pediatric Oncology Group, only showed a poor response rate of medulloblastomas to ifosfamide. Thiotepa is another candidate for the treatment of medulloblastoma. This is a highly lipophilic drug, which penetrates the blood brain barrier very easily and produces high cerebrospinal fluid levels. It has shown some activity in medulloblastoma, but because of the severe myelosuppression, it is mostly studied in regimens of high-dose chemotherapy with stem cell rescue (see later).

Etoposide. Used as a single drug, etoposide also shows activity against medulloblastoma and other brain tumors. The best effect is seen in case of prolonged exposure to the drug, which can be achieved by repeated schedules of daily oral administration during 21 consecutive days, followed by a 7 days interval between courses. This administration schedule even produces antitumor effect in patients that have been previously treated with intravenous etoposide and showed resistance to this course of treatment.

Other drugs currently used in the treatment of medulloblastoma, like vincristine and methotrexate, are mainly studied in combination regimens with other cytostatics. This hampers the interpretation of their therapeutic value.
Combinations of drugs. Many different combinations of drugs have been studied in different patient groups. A few prospective randomized studies have been conducted by cooperative groups such as the Children’s Cancer Study Group (CCSG) \(^{27}\) and the Société International d’Oncologie Pédiatrique (SIOP) \(^{26,94}\). In the first SIOP trial \(^{26}\), chemotherapy consisted of vincristine during and vincristine and CCNU after the radiotherapy. A benefit of adjuvant chemotherapy was only seen in some subgroups of patients i.e. partial or sub-total resection, brainstem involvement and stage T3 and T4 disease. In the following SIOP study \(^{94}\) children were divided into low or high-risk patients, according to the extent of tumor removal or the presence of invasive brain stem involvement or metastatic disease. All patients were randomized to receive, or not, chemotherapy consisting of procarbazine, vincristine and methotrexate with prednisolone preceding the methotrexate infusion to prevent cerebral edema. This chemotherapy course was given before start of the radiotherapy. High-risk patients continued with chemotherapy, consisting of vincristine and CCNU, post-radiotherapy. No benefit of this treatment regimen was seen in this study, even in different subgroups. Children treated with chemotherapy followed by a reduced dose of radiotherapy even had a worse prognosis.

In a prospective randomized trial of the CCSG, Evans et al. \(^{27}\) concluded that patients with more extensive tumors may benefit from the addition of chemotherapy. They used chemotherapy consisting of weekly vincristine during radiotherapy and vincristine, CCNU and prednisone after radiotherapy. This cycle was given every 6 weeks for a total of 8 cycles. The best results of addition of chemotherapy are reported by Packer et al. \(^{28,29}\), who assigned patients prospectively to risk groups, based on the extent of the tumor and the degree of surgical resection. Poor-risk patients seemed to do significantly better when given adjuvant chemotherapy, consisting of vincristine weekly during radiotherapy and vincristine, CCNU and cisplatin post-radiotherapy. This regimen offered a 5-year progression free survival rate of 90% for patients with localized disease at the time of diagnosis, and 67% for patients with metastases. However, not all studies show such a clear advantage of the addition of chemotherapy.

A Pediatric Oncology Group (POG) study, using vincristine, cisplatin and cyclophosphamide, showed some activity against medulloblastoma, but disease progression during preradiation chemotherapy was seen in some patients \(^{117}\). Similarly, the "8 drugs in 1 day" regimen (consisting of vincristine, carmustine, procarbazine, hydroxyurea, cisplatin, cytarabine, prednisone and cyclophosphamide) did not show convincing results in a study conducted by the CCG \(^{118}\) or in the French Cooperative Study \(^{119}\). Comparison of this "8 drugs in 1 day" chemotherapy plus radiotherapy to a regimen containing vincristine, CCNU and prednisone plus radiotherapy in high-risk children over 1.5 years of age, revealed a superior survival of the last combina-
tion in a study conducted by the CCG \cite{120}. In contrast, the German Pediatric Brain Tumor Study Group achieved good results with a combination of Procarbazine, Ifosfamide, Etoposide, high-dose Methotrexate, Cisplatin and Cytarabine, as 2/3 of patients with high-risk medulloblastoma responded \cite{121}.

*Pre-operative chemotherapy.* Another possibility, which is being explored at present, is the administration of chemotherapy pre-operatively. The rationale behind this is the idea that pre-operative chemotherapy might facilitate the surgical removal of the tumor by reducing the size of the tumor and making it more firm, and thus sharpen the border between normal and tumor tissue. In several pediatric tumors this approach is already used, such as Wilms' tumor and osteosarcoma. Two studies have been published on this subject \cite{104,122}. In the first study chemotherapy consisted of carboplatin. Regression of the tumor was seen in 3/3 cases. In the second study chemotherapy consisted of vincristine, procarbazine, dibrum dulcitol and methotrexate. Here, regression was seen in 8 out of 10 cases. In both studies the authors state that the preoperative chemotherapy facilitated the surgical removal of the tumor. At this moment, this issue is studied more extensively by a Danish-British study that started in 1995, in which a combination of drugs is used, according to the age of the child. Children less than 3 years receive vincristine, high-dose methotrexate, cyclophosphamide, carboplatin and cisplatin preoperatively, while children older than 3 years receive vincristine, carboplatin, etoposide and cyclophosphamide.

*High-dose chemotherapy followed by stem cell rescue.* In recent years, several studies have been conducted, using high-dose chemotherapy with stem cell rescue in the treatment of malignant brain tumors, in an attempt to improve the survival of poor prognosis brain tumors, to avoid or delay radiation therapy in young patients or as curative option for recurrent brain tumors. Chemotherapy combinations used are: thiopeta/etoposide with or without carboplatin or BCNU \cite{123-126}, melphalan/cyclophosphamide \cite{127,128}, busulfan/melphalan \cite{128}, carboplatin/etoposide \cite{128}, cyclophosphamide \cite{110}, busulfan/thiopeta \cite{129}, cyclophosphamide/thiopeta \cite{130} or etoposide/carboplatin/thiopeta with cyclophosphamide or BCNU \cite{131}.

Although follow up is too short in most studies to draw any definite conclusions, survival of these patients looks promising and warrants further investigation, especially in the case of recurrent medulloblastoma where minimal residual disease is achieved at the time of administration of high-dose chemotherapy.
The general conclusion to date is that some groups of patients may benefit from the addition of chemotherapy (patients with high-risk tumors or recurrent tumors), but this advantage is not clear for children with standard-risk medulloblastoma. As many studies use different chemotherapy protocols with different results, the optimal combination and dosage of the drugs is still not established. Further studies are needed to point out which combination of drugs shows the best results, and which patients benefit from chemotherapy. The drugs that seem to be most promising to date are carboplatin, etoposide, cyclophosphamide and thiotepa, the latter perhaps only to be used in high-dose regimens with stem cell rescue in view of the severe myelosuppression.

Some problems pose a special challenge, to be addressed in the near future. One of them is trying to minimize or postpone radiotherapy for children under 3 years of age. Some studies show promising results, but more research has to be focused on this issue. The second one is the administration of pre-operative chemotherapy, in order to facilitate tumor removal. A combination of e.g. carboplatin, etoposide and/or cyclophosphamide can be used. And last but not least, special interest should be paid to the therapy of recurrent medulloblastoma. Although further evidence is needed to prove that high-dose chemotherapy is of value for these patients, no other therapies studied so far have shown similar results on survival. Therefore it is justified to offer this high-dose therapy to patients that are in second complete remission or minimal residual disease.

9) Long-term sequelae

Apart from the late effects that patients who have received treatment for cancer in childhood can develop, as cardiac toxicity after receiving anthracyclines, diminished fertility due to alkylating agents and increased risk on secondary tumors post chemo- and radiotherapy, some long-term sequelae are specifically found in patients treated for brain tumors.
Shunt problems
Although the majority of children with medulloblastoma need a CSF diversion only temporarily or not at all, those who do need one for a longer period of time can be confronted with 2 major problems: infection and obstruction. Infection occurs in about 10% of patients and is usually staphylococcal. Symptoms are fever, irritability and anorexia and treatment usually consists of antibiotics, but removal of the shunt is often necessary. Shunt obstruction leads to symptoms and signs of raised intracranial pressure (headache, nausea, and lethargy). Patients with these symptoms should be evaluated by CT scan for the presence of hydrocephalus, and shunt revision should be undertaken if necessary.

Neuropsychological sequelae
Numerous studies have been undertaken on neuropsychological sequelae and quality of life of long-term survivors, showing that these patients have deficits in intelligence, academic skills, memory, language and attention, perception, motor function and bulbar function. Emotional and behavioral disturbances are also common.

Intelligence: In general, these studies show a mild to serious deterioration of intelligence in a great majority of patients (85 - 100%), as demonstrated by lower IQ scores in comparison to siblings, historical controls or children with brain tumors not receiving radiotherapy. This is the case for full-scale intelligence (FSIQ) as well as verbal IQ (VIQ) and performance IQ (PIQ). Some authors find that impairment of PIQ is related in the first place to age at diagnosis and treatment, while VIQ deterioration is increasing with the time since treatment is given. The latter is determined in a lesser degree by the age at diagnosis. The main cause of the intellectual impairment is primarily radiotherapy - in which higher doses administered cause more toxicity - although the tumor itself, the raised intracranial pressure often present, the surgery and chemotherapy may all contribute to late effects. The age at diagnosis and treatment is also an important factor: the younger the children, the more impairment is seen. As a standard rule, radiotherapy is - whenever possible - avoided under the age of 3 years, the age on which myelinization is thought to be complete. However, severe late toxicity can be seen in children as old as 7-8 years at diagnosis. Second important factor is the time delay between treatment and intelligence testing. An ongoing deterioration is seen 5 to 10 years after treatment, so testing must continue longer than that time period.
Endocrinological sequelae

A substantial amount of patients receiving craniospinal radiotherapy will develop endocrinological deficiencies after therapy. Growth hormone and/or thyroid hormone levels are most frequently affected. The former is due to direct irradiation of the hypothalamic-pituitary region while the latter is more frequently caused by indirect irradiation of the thyroid when administering radiotherapy to the cervical spine.

Growth hormone deficiency. Decreased growth velocity is seen in a majority of patients, starting from 3 months till 4 years after therapy. Growth hormone (GH) responses on provocation tests however can be normal in these patients. The reason for the poor growth rate in these children might be due to a reduction of spontaneous GH pulses, which is not detectable on provocation tests, and which is called a "functional" GH deficiency.

Hypothyroidism. Irradiation of the cervical spine at a dose of 35 Gray causes indirect irradiation of the thyroid gland of about 24 Gray, resulting in primary hypothyroidy. Development of abnormal thyroid hormone levels can occur as soon as a few months after therapy, or can take years, and is mostly characterized by an elevation of TSH level. Rarely, hypothalamic hypothyroidism is observed. Some authors find that administration of hyperfractionated radiotherapy causes a significant decrease in the occurrence of hypothyroidy later on.

Precocious puberty. The onset of puberty may develop at an earlier age by disturbances in the hypothalamic-pituitary-gonadal axis. Obvious precocious puberty was seen in a study in nearly one fourth of patients and was directly correlated to the age of irradiation: the younger the patient at irradiation, the earlier the puberty. Obviously, hypothyroidism as well as precocious puberty also affect the final length of the child, besides growth hormone deficiency. Furthermore, spinal radiotherapy is responsible for a reduced growth of the spine, which results in a shorter final length and a disproportional growth of the upper versus the lower body segment.

Other endocrine disturbances. Overt adrenal insufficiency and panhypopituitarism are rarely seen in these children.

Therapy. Therapy consists of hormonal substitution. In case of decreased growth rate with normal GH responses on provocation tests, this might pose a problem. However, some authors showed that even children with this "functional" GH deficiency may benefit from GH therapy. As some children have earlier onset of puberty after therapy, more effect can be expected in combining efforts to delay onset of puberty combined with GH therapy.
10) Conclusion

It is clear that the treatment of medulloblastoma in childhood still poses a big challenge to all the people of the different disciplines involved in it, i.e. the neurosurgeon, the radiotherapist, the pediatric oncologist and the psychosocial team, not only to improve the survival of these children, but also to adjust the therapy in an attempt to guarantee a good quality of life for survivors, without jeopardizing the survival rates. To attain this goal, a very intense cooperation of the different treatment groups is absolutely necessary.

For those subgroups in which chemotherapy seems to improve survival or is able to postpone radiotherapy, new drug combinations must be tested. Further studies must be undertaken to evaluate the advantages and disadvantages of pre-operative chemotherapy. For those subgroups in which chemotherapy does not seem to be of great value, other treatment strategies must be developed, such as other modalities of radiotherapy or immunotherapy. For all children, urgent attempts must be made to diminish the long-term sequelae. A big step forward in these efforts would be the identification of reliable prognostic markers, which would enable us to adjust therapy to the predicted good or bad prognosis. As for the majority of children with medulloblastoma no reliable clinical markers are currently available, studies must be directed toward finding them. Molecular biological markers might prove to be more reliable.

Finally, children who were treated for medulloblastoma must be checked regularly for a long time to trace late effects caused by the tumor or its treatment, in order to get a full picture of these effects and correlate them to the treatment given. This will allow us to adjust the treatment, which might eventually improve the survival and quality of life of the children yet to come.
References

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83. Segal RA, Goumerrova LC, Kwon YK, Stiles CD, Pomeroy SL. Expression of the neurotrophic receptor TrkC is linked to a favorable outcome in medulloblastoma. Proc Natl Acad Sci USA 1994; 91:12867-12871.

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