

Medulloblastoma in Adults

Treatment Protocol

**Dutch Society for Neuro-Oncology
(Landelijke Werkgroep Neuro-Oncologie, LWNO)**

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Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht

1 Working group

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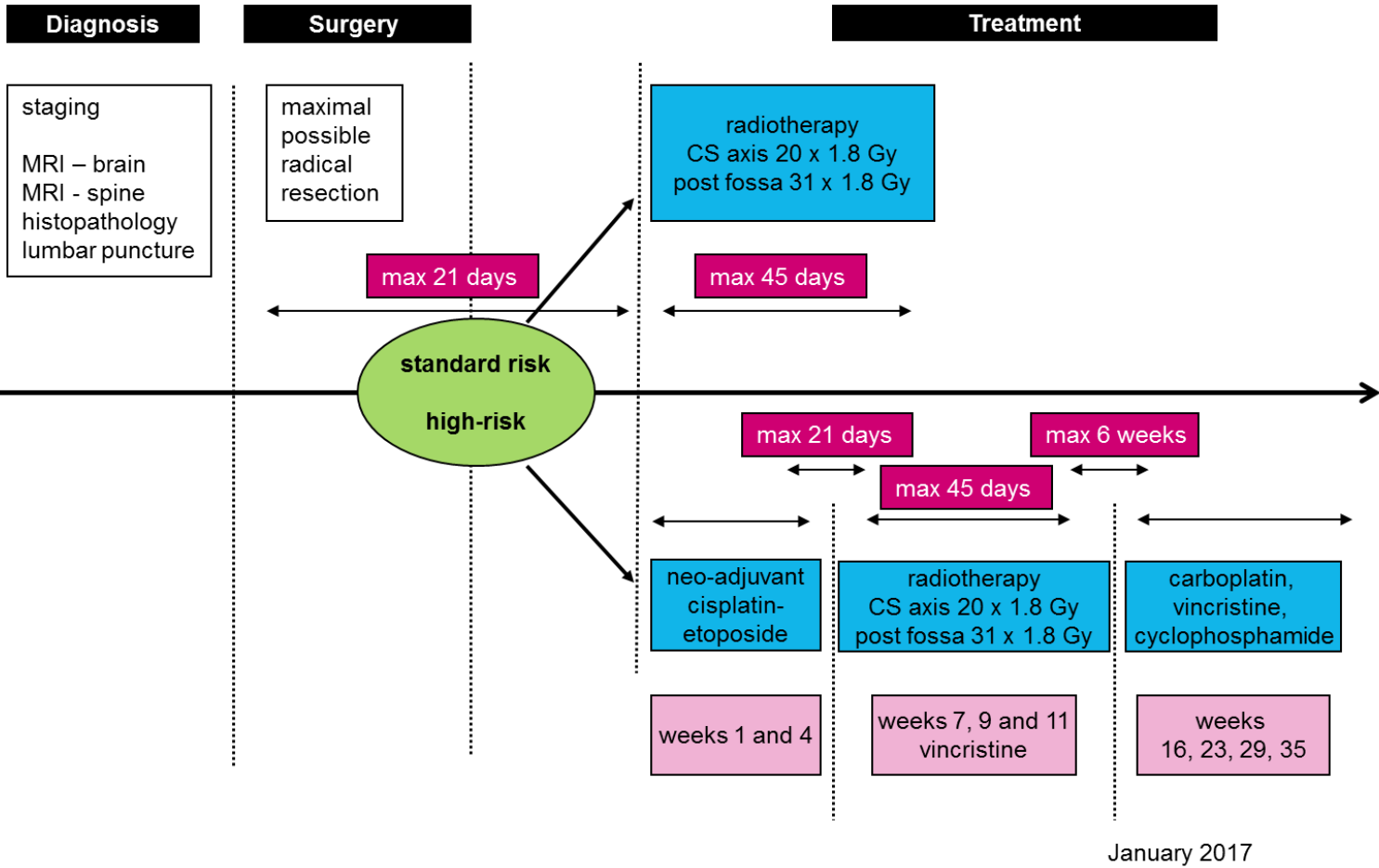
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3 Summary, flowcharts and time schedule



4 Background

4.1 Introduction

The term medulloblastoma was coined in 1925 when Bailey and Cushing reported clinical and pathologic features in 29 patients with "a very cellular tumor of a peculiar kind". Most of these 29 patients were children, and the tumors were usually located in the cerebellar vermis over the roof of the fourth ventricle (1). Medulloblastoma is a rare tumor in adult patients, accounting for only 1-2% of primary brain tumors in adults and with an estimated incidence of 10-20 patients per year in The Netherlands. As a consequence only retrospective studies have been published on this disease, with the exception of one small prospective, single arm study, the latest long term follow-up results of which were published in 2007 (2). Most data on medulloblastoma in adults are extrapolated from data obtained from children despite the fact that differences in the behavior of the disease and in the tolerance of treatment at different ages appear to exist. Because of the rarity of the disease prospective studies are difficult to perform. Therefore a protocol has been set up for diagnosis and treatment based on the available literature to achieve uniform treatment of adult medulloblastoma patients within The Netherlands and allow prospective toxicity and efficacy data to be collected for a larger number of patients than is feasible in a single center.

4.2 Pathology and Genetics

Medulloblastomas (MBs) are high grade malignant (WHO grade IV), "embryonal" tumors of the cerebellum with immunohistochemically predominantly neuronal differentiation, and a tendency to metastasize via CSF pathways (3). MBs preferentially manifest in children, with a peak incidence at 7 years of age. Less than 1% of malignant CNS tumors in adults is MB, but 29% of the MBs occurs in adults (85% of these between 21-40 years of age, 65% in male patients) (4). In most children, the tumor is located in the vermis. In adults, the cerebellar hemispheres are more often involved (5-6). The clinical manifestations depend on the location of the tumor and include ataxia, disturbed gait and intracranial hypertension due to CSF flow obstruction with headache, vomiting, and lethargy.

Histopathology

Like in children, in adults several MB subtypes are described, but with a different frequency compared to the pediatric age group. The following subtypes, which may differ in molecular abnormalities and clinical behavior (3,7), are recognized:

1. Classical ("undifferentiated") MBs; these tumors are composed of densely packed cells with round nuclei surrounded by scant cytoplasm. Neuroblastic rosettes, ganglion cells, necrosis, calcifications, intratumoral hemorrhages and infiltrative behavior can be found. Most childhood cases are classic MB (80%).
2. Desmoplastic/nodular MBs are more frequent in adults than in children (25-40% versus 15-20%, resp.), and are more often located in the cerebellar hemispheres (5). Histologically these tumors are characterized by the presence of reticulin-free nodules ("pale islands") with lower cellularity and more prominent neuronal differentiation of the tumor cells within these islands. While there is evidence that these tumors are biologically less aggressive (6,8), the prognostic significance of the desmoplastic phenotype is not yet clear (8-10).
3. Large cell/anaplastic MBs; these neoplasms represent 2-4% of the MBs in children, are rare in adults (11) and carry a relatively poor prognosis (12-13). Histologically these large cell and anaplastic MBs are characterized by pronounced and widespread large-cell and/or anaplastic features (relatively large, partly vesicular nuclei with prominent nucleoli and a variable amount of eosinophilic cytoplasm and/or markedly pleiomorphic tumor cell nuclei with nuclear moulding, cell-cell wrapping and high mitotic activity).

4. MBs with extensive nodularity; these tumors occur predominantly in infants and are very rare in adults; this variant histologically shows very extensive formation of (often confluent) nodules and carries a significantly better prognosis than classic MBs (3).
5. MBs with not only neuronal but also glial differentiation are rare but more frequently found in adults than in children; the prognostic significance of this feature is not clear (8). Discrimination of this subtype from malignant gliomas in the posterior fossa with PNET-like component is difficult (14).

For histopathological diagnosis in daily practice it is important to note that discrimination between these MB variants can be difficult because of the lack of unequivocal histopathological criteria. According to “experts in the field” a desmoplastic subtype can be diagnosed when clear-cut reticulin-free zones (‘pale islands’) are present albeit only focally. In contrast, for the diagnosis of large cell and/or anaplastic medulloblastoma the large cell/anaplastic features should be pronounced and widespread (esp. focal anaplastic change is a very frequent feature in almost all medulloblastomas).

Genetics

Multiple molecular/genetic abnormalities have been discovered in MBs, the most common being isochromosome 17q (present in 30-40% of tumors), MYC amplification in esp. anaplastic MBs, and genetic abnormalities in de SHH-PTCH and Wnt/WG pathways (3,15). The Hedgehog signaling pathway controls the development of cerebellar granular progenitor cells in the external granular layer, which plays an important role in the pathogenesis of MB. PTCH, a tumor suppressor gene on chromosome 9, is an inhibitor of the Hedgehog pathway. SHH, secreted by Purkinje cells, is a ligand for the transmembrane receptor Patched (encoded by PTCH), which is a negative growth regulator inhibiting Smoothed (SMO). Binding of SHH results in inhibition of Patched, expression of SMO, transcription of specific target genes, and development of MBs (3). Abnormalities in the multiple genes involved in this pathway are found, mainly in the desmoplastic subtype of MBs (3,16-17). The Wnt pathway involves the APC (adenomatous polyposis gene), which is a negative regulator. APC forms a complex with several other factors and is inactivated in the presence of ligands, allowing β -catenin to enter the nucleus and to regulate the transcription of growth factors (3). Activation or inactivation of the factors involved in this pathway by genetic mutations are reported in esp. the classic subtype of MBs (3). Less than 5% of MBs occur due to a germline mutation, e.g. in the context of Li Fraumeni (TP53), Turcot (APC), Gorlin (PTCH) syndrome (18). Other hypotheses include an origin of MBs from the subependymal matrix cells, and a dual origin from the external granular layer (esp. desmoplastic MBs) and from the subependymal matrix cells (esp. classic MBs).

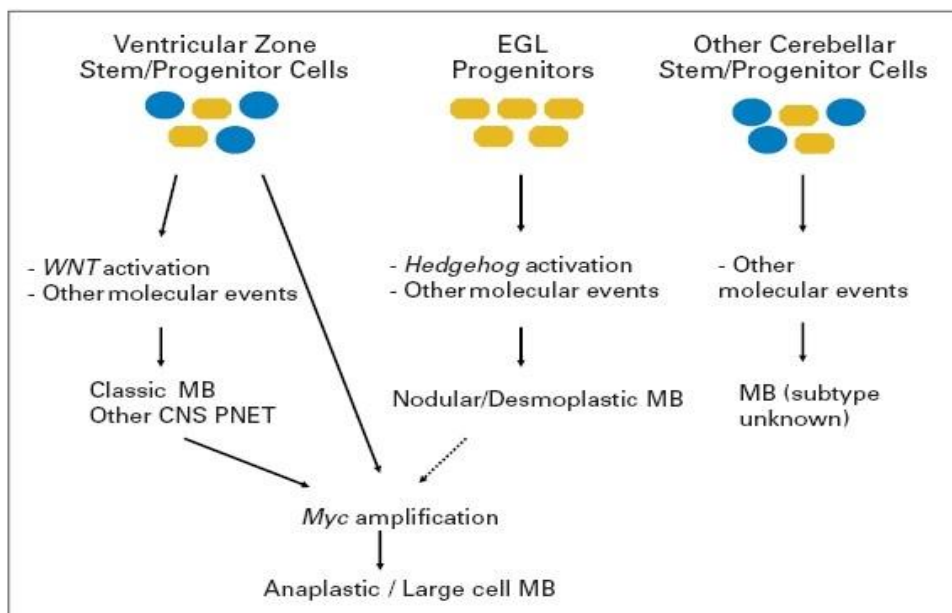


Figure 1. Mutations activating Wnt have been identified primarily in the classic medulloblastoma subtype, which is thought to derive primarily from stem and/or progenitor cells of the ventricular zone. The external germinal layer (EGL) is thought to give rise to nodular/desmoplastic medulloblastoma commonly associated with Hedgehog activation (19).

Pathologic prognostic factors

Most studies reported no significant difference in survival between children and adults with MB (8,10,20), although some found a worse survival in children due to early recurrences without therapeutic options (5).

An unfavorable prognostic pathologic factor in adults is large cell/anaplastic subtype, location of the tumor in the cerebellar hemisphere is a favorable prognostic factor (5,13).

Prognostic genetic markers are reported in children; TrkC and genes associated with cerebellar differentiation and extracellular matrix, and nuclear accumulation of β -catenin (associated with activation of the Wnt/WG pathway) are markers for favorable prognosis, while p53 and EGFR overexpression and MYC amplification are unfavorable. In future pediatric protocols risk group stratification will also be based on a β -catenin and MYC amplification (21). In adults, MDM2 overexpression has been reported as a marker for unfavorable prognosis (12,16,22-23).

In summary

Compared to the pediatric age group, MBs in adults are more often located in the cerebellar hemispheres, are more frequently of the desmoplastic subtype, and on average tend to be biologically somewhat less aggressive. The large cell/anaplastic subtype is an unfavorable prognostic factor both in adults and children.

4.3 Clinical prognostic factors

The staging process of medulloblastoma is based on the knowledge of favourable and adverse prognostic factors. Treatment in children is tailored to risk factors with a division into standard risk and high risk categories. Since data on these prognostic factors are scarce in adult medulloblastoma, the risk profile has been extracted mainly from data on childhood medulloblastoma.

The risk profile is composed of information about the stage of the disease determined firstly by investigating metastatic and / or residual disease and secondly by histopathologic classification of the tumor; this latter aspect has been outlined in the previous section (4b).

The degree of tumor resection is related to outcome of medulloblastoma, where 5 year PFS in patients more than 3 years of age was 78% in children with tumor residue < 1.5 cm² and 53% in patients with larger tumor residue (24). In adults, the advantage of gross total resection has also been shown in a cohort of 454 patients analyzed within the SEER database (13).

The relevance of leptomeningeal spread of medulloblastoma is reported in several studies (25-26). This concerns tumor cells in the CSF only (M1) as well as localized metastatic disease visualised with MRI. The study of 86 patients of Miralbell et al. revealed prognostic differences according to staging for 5- and 10 years survival being 76/54% for M0, 68/50% for Mx (denoting unknown cytology), 36/25% for M1 and 22/22% for M2-3 disease (27). Zeltzer et al. studied 203 patients with medulloblastoma and the differences in 5-year progression free survival in M0, M1 and M2+ was significant being 70%, 57% and 40% respectively (28).

The prognostic relevance of macroscopic metastatic disease has been confirmed in the analysis of 454 patients reported by Lai (13) and 251 patients reported by Padovani et al. (29). Fouladi et al. studied 106 consecutive patients, in which 17% of leptomeningeal spread would have been missed if no CSF were studied (30).

Although retrospective, the information about M1 disease consistently points to a worse prognosis compared to M0. This prognostic relevance confirms the need to stage CSF in medulloblastoma for M1 according to strict rules. The time point to study lumbar CSF in this protocol is set at day 15 after surgery to prevent contaminating non-vital cells post-surgery with an accepted delay of up to 3 days later.

Extraneural disease is an exception, but should not be overlooked in the staging procedure. In case of complaints or abnormalities on physical examination additional imaging procedures should be performed to rule out extraneural metastases.

In line with the available literature, both pathological and clinical prognostic factors will be used to categorize patients as standard or high risk in this protocol.

4.4 Surgery

The surgical management of medulloblastomas has two goals. The first goal is to ameliorate the symptoms of obstructive hydrocephalus, and the second goal is to achieve maximal surgical resection (31). Controversy exists regarding the initial management of patients with a medulloblastoma. Some neurosurgeons advocate shunting the hydrocephalus routinely as the first step before tumor removal. They claim that there is lower morbidity and mortality and a better surgical field after the intracranial pressure is relieved for a period of several days to a few weeks. A disadvantage is potential dissemination of tumor cells to the peritoneal cavity or systemically after shunting: in some studies an incidence of up to 19% of extracranial metastasis has been reported (32). A second problem with early shunting is that decreasing the pressure in the supratentorial system by draining the hydrocephalus can produce an upward herniation of the tumor, which would necessitate an emergency decompression of the posterior fossa and removal of the mass. Endoscopic perforation of the floor of the third ventricle may alternatively be performed, which provides internal shunting without the risk of extradural seeding. Furthermore, this leads to more gradual decrease of intracranial pressure and is perceived to have a lower risk of upward herniation. Others prefer to treat the increased intracranial pressure with large doses of corticosteroids for a short period of 2-3 days before surgical intervention instead of shunting. This usually produces a remarkable improvement in the symptoms and often the results of neurological examination will revert to normal.

In the paediatric setting, the extent of resection has been shown to be of prognostic importance (12,24), and although there is a lack of such data in adults, it is accepted that extent of resection is also a prognostic factor in adults (33). Immediate postoperative imaging is necessary to define the extent of resection, since intra-operative judgement of residual tumor is insufficiently reliable. Second-look surgery (defined as reoperation within 2 weeks after the first surgery, aimed at resection of residual tumor) may improve survival by reducing the tumor residue, but the morbidity of the procedure is not known. There are no prospective studies on this topic, only case reports have been published in which this protocol was used (34). Although the extent of resection has been shown to affect survival, only one study has specifically addressed second look surgery. The authors conclude that second-look surgery has an acceptable morbidity and should be considered in patients with residual tumors (35).

4.5 Radiotherapy

Standard therapy for adult medulloblastoma consists of gross total surgical removal of the primary tumor followed by radiation. Because of the propensity of medulloblastomas to disseminate with the cerebrospinal fluid, postoperative radiotherapy should be given to the entire craniospinal axis with a boost to both the primary tumor site and focal CNS metastatic sites (36-38). The radiation dose to the posterior fossa should be at least 54 Gy (39). The dose to the spinal axis depends on the presence or absence of microscopic or macroscopic metastases. 3D-image guided radiotherapy is a prerequisite for optimal tumor control.

Two large series of adult medulloblastoma patients derive from the Royal Marsden Hospital, London, UK (40), and the Princess Margaret Hospital, Toronto, Canada (41). Both studies included about 50 patients treated over a 30-year period from the 1950's to the 1980's. The 5-year survival is about 50-60% and 10-year survival is about 40%.

Herrlinger et al. reported an influence on survival of the interval between surgery and the start of radiotherapy (36). Other studies have shown a correlation between improved posterior fossa control and shorter periods for the completion of radiotherapy (42-43). An overall treatment time of less than or equal to 45-48 days was therefore proposed (44-45). Concerning time intervals, another study found a significant better survival if the time interval between surgery and start of radiotherapy was

kept below 25 days (39). Chan et al. reported a 5-year posterior fossa control rate of 81% for patients who completed radiotherapy in less than 48 days, compared to 51% for patients who completed radiotherapy in 48 days or more (42).

In case of recurrence or residual disease, re-irradiation with (hypofractionated/radiosurgical) stereotactic radiotherapy results in good local control without significant toxicity (46).

Thus, radiotherapy is an essential part of the primary treatment of patients with medulloblastomas. Due to the risk of craniospinal metastases, the whole craniospinal axis should be irradiated with higher doses to the primary tumor site and metastases.

Late toxicity

Long-term permanent toxicity after cranial irradiation, including cognitive deterioration and cerebellar dysfunction, have been described (47). There are, however, differences in terms of long-term toxicities between adult and pediatric patients: the development of the growing brain and myelination are correlated with age. Neurocognitive deficits and a decrease in IQ after whole brain irradiation (WBRT) are more dramatic and more eminent in children. A decline in IQ in children of different ages who received craniospinal radiation has been demonstrated (48-50). Another study reported a greater decline in IQ in patients who received a dose of approx. 33 Gy compared to patients who received approx. 24 Gy (51).

Data in adults are scarce and inconclusive. De Angelis et al. suggested that as many as 11% of long-term (1-12 months) surviving patients with brain metastases treated with WBRT develop dementia (52). Radiotherapy is known to cause delayed leuko-encephalopathy with cognitive dysfunction and radiation necrosis (53-55). A survey on cognitive deficits in progression-free survivors of low-grade glioma did report a relation between the daily radiotherapy fraction size used: patients treated with a higher dose than 2Gy showed evidence of increased cognitive dysfunction (56).

4.6 Chemotherapy

In children with medulloblastoma, chemotherapy has been used for years in order to improve outcome for poor prognosis patients, or to decrease radiotherapy dose in standard prognosis patients. In adults with high-risk medulloblastoma, prognosis seems to be similar to that in children for those patients treated with both radiotherapy and chemotherapy. Adult patients with medulloblastoma treated with radiotherapy only fare worse than children in retrospective studies (42;57). However, retrospective series of adolescents and adults with medulloblastoma suggest poor tolerance of chemotherapy after craniospinal irradiation (58-59). In addition, increased and irreversible vincristine-induced neuropathy has been prospectively documented in adults at doses that are common in pediatric protocols (60).

Neoadjuvant chemotherapy, i.e. after surgery but before radiotherapy, has the advantage of increased tolerance because of uncompromised bone marrow reserve, and increased delivery due to the decreased blood-brain barrier after surgery. It also provides an in vivo assay of chemotherapy efficacy in patients with residual disease after surgery. Disadvantages of neoadjuvant chemotherapy are the inevitable delay of initiation of radiotherapy. In children, randomized studies showed a disadvantage for neoadjuvant chemotherapy when an ineffective regimen was used (28), or when radiotherapy was postponed for more than 20 weeks after surgery (61).

The only prospective medulloblastoma study in adults, however, used both neoadjuvant and adjuvant treatment after radiotherapy in high-risk patients. Not only was prognosis exceptionally good and comparable to that in children in this phase II study, but also toxicity appeared to be acceptable (2,26). Apart from manageable haematological toxicity, the main problems arose from otovestibular and neurological side-effects of cisplatin.

Given the data mentioned here, treatment of adult patients with poor-risk medulloblastoma with chemotherapy in adjunction to radiotherapy seems warranted, although direct extrapolation of childhood protocols is not feasible.

In order to both deliver adequate dose-intensity chemotherapy and to manage toxicity, substitution of cisplatin with carboplatin was proposed, as well as introduction of two courses of neoadjuvant chemotherapy before radiotherapy. The efficacy of carboplatin combined with etoposide in medulloblastoma is well established, in both neoadjuvant and adjuvant setting (62-64). After treatment of 16 patients with this neo-adjuvant schedule in the first version of the protocol, myelotoxicity was impressive, and led to both postponement of the second course, and postponement of the start of radiotherapy (oral communication, unpublished data). It was therefore decided to switch to cisplatin for the neo-adjuvant courses, as no severe ototoxicity, nor neurotoxicity and less myelotoxicity is to be expected. For the maintenance courses adjuvant carboplatin was kept as part of the protocol, in order to prevent ototoxicity and neuropathy (after radiotherapy). During radiotherapy, vincristine dose is limited to fortnightly rather than weekly doses in order to prevent irreversible neuropathy.

After radiotherapy, four courses of maintenance chemotherapy will be administered according to the well-tested arm B of the Children's Oncology Group (COG) Study A9961 (65), albeit with the substitution of carboplatin for cisplatin, and a 25% dose reduction of the cyclophosphamide dose in order to prevent dose delays due to myelosuppression. The total number of six courses (two neoadjuvant and four after radiotherapy) is equivalent to that in the small prospective phase II study of Brandes et al. (2), and to what is common to all pediatric schedules.

Thus, for this protocol the principles of successful childhood medulloblastoma treatment have been adapted to what is considered feasible in adults with medulloblastoma. Prospective registration of treatment and toxicity data will establish whether this strategy can and will be justified by patient outcome.

4.7 Follow-up

Whether surveillance-imaging improves survival in patients with medulloblastoma is strictly unknown. The only published studies specifically addressing this issue were retrospective series concerning children with medulloblastoma. However, almost all of these series show better survival after asymptomatic recurrence (10-44 months) compared to symptomatic recurrence (2-12 months) (66-70). Furthermore, recent epidemiologic data suggest similar survival in children and adults, with only infants faring worse (57). The interval between primary disease and recurrence varies greatly. In published retrospective series on adult patients, most recurrences were reported after an interval up to 6 years, with median intervals ranging from 24-50 months (20,33,36,42,71), although isolated recurrences have been reported after 18 years (33). In the only published prospective series, median PFS was 6-7 years (2).

It seems reasonable to perform surveillance imaging most intensively in the first 2 years after treatment, reducing frequency after this time and continuing surveillance until 10 years after treatment. Given the data of Bartels et al, who found spinal recurrence only in combination with intracranial recurrence, routine spinal imaging seems unnecessary unless symptoms are present (70).

5. Objectives

The objectives of the current protocol are to:

1. treat all adult medulloblastoma patients in The Netherlands through a comprehensive protocol with separate strategies for standard-risk and high-risk tumors;
2. document the feasibility of this treatment protocol by recording side-effects and actually administered treatment in a standardized fashion;
3. document the outcome of adult medulloblastoma in EFS and OS after treatment in this standardized treatment protocol;
4. collect tumor material and peripheral blood for translational research studies.

To this end, all patients will be prospectively registered in a central database.

6. Eligibility for registration

a. Inclusion criteria

- pathological diagnosis of medulloblastoma, whenever possible confirmed by central review (see also section 8c)
- age \geq 18

b. Exclusion criteria

- pregnancy

7 Registration

After diagnosis patients should be registered at the IKMN Trial bureau (Integraal Kankercentrum Midden Nederland), c/o UMCU huispost F02-162 postbus 85500 3508 GA Utrecht. Tel: 088-755 6286, fax: 088-755 5462

At least the following information should be registered for each patient: date of birth, sex, patient hospital registration number, treating physician, and date of registration.

8 Treatment

8.1 Diagnostic work-up

Staging of disease and categorization into standard or high-risk will be performed according to the following table:

Table 1. Risk profile for medulloblastoma in adults

| Investigation | | Standard-risk | High-risk |
|--|---|---------------------------------------|-----------------------------------|
| 1. MRI brain and myelum with contrast | | unifocal disease cerebellum | M2-3 |
| 2. Within 72 hr postoperative MRI brain | <i>If > 1.5 cm² perform second look surgery</i> | R0 R1 ≤ 1.5 cm ² residu | R2 (after second look surgery) |
| 3. History and physical examination | <i>If indicated bonescintigrapy, bone marrow aspirate, bone biopsy, biopsy other suspicious lesions</i> | M0 | M4 |
| 4. Histology | | desmoplastic classical | large cell/anaplastic |
| 5. CSF lumbar puncture day 15 post surgery | | M0 | M1 |

Residual disease: R0 = no residual cerebellar tumor; R1 = residual tumor ≤1.5 cm²; R2 = residual tumor > 1.5 cm²

Metastatic disease: M0 = no metastasis; M1 = tumor cells in CSF at day 15; M2 = additional tumor locations in the brain on MRI; M3 = spinal metastasis; M4 = extra-neural disease.

In addition at baseline full blood counts, liver and renal function, electrolytes and blood glucose concentration should be performed. Other investigations are performed when required.

8.2 Treatment with neurosurgery

The surgery is usually performed with the patient in the prone position, allowing good visualization of the region of the cisterna magna, foramen of Magendie and fourth ventricle. A posterior fossa craniectomy is commonly performed, including the rim of the foramen magnum. If necessary, the posterior arch of C1 is resected. Frequently the tumor is visible in the cisterna magna upon opening the dura mater. Sometimes, "sugar coating" of the cerebellum and arachnoid can be seen. Some neurosurgeons prefer the sitting position, although the risk of air embolism does exist. The extent of tumor resection is a prognostic factor. The surgical goal is therefore to perform total gross removal of the tumor, which can frequently be done in a piecemeal fashion, avoiding traction on the vital structures of the brain stem and cerebellar peduncles. The use of bipolar coagulation, microscope, self-retaining retractors, a high-frequency ultrasonic aspirator, and a laser has greatly improved the chances of obtaining satisfactory removal of the tumor without damage to the surrounding structures. Furthermore, by decreasing the amount of manipulation of the structures surrounding the tumor, morbidity such as swallowing difficulties, involvement of speech mechanisms, and other cranial nerve palsies is decreased. After the tumor is removed, the floor of the fourth ventricle is inspected for infiltration, and cerebrospinal fluid is usually seen draining from the dilated aqueduct of Sylvius.

All available tumor material should be sent to the pathology department for formalin fixation or snap freezing according to the guideline in section 8c.

Since the amount of residual tumor is a factor determining further treatment and prognosis, a postoperative MRI should be performed within 72 hours post-surgery to delineate residual tumor from the postsurgical inflammatory changes that are visualized on MRI after this time. In case of more than 1.5 cm² residual tumor, second-look surgery (defined as reoperation within 2 weeks after first surgery) should be considered, and if judged feasible, it should be performed in order to resect this residu. However, severe morbidity as a result of surgery should be avoided since a poor performance status will compromise adjuvant treatment with chemotherapy and/or radiotherapy.

If the tumor is located in an eloquent area (for example growth into the brainstem), or in case the tumor is too large and disseminated in functional areas, biopsy is advised to confirm the diagnosis. In these cases attempts at neurosurgical removal leads to unacceptable surgical risks of morbidity and mortality.

Up to approximately 50% of patients require treatment of unresolving obstructive hydrocephaly. Since placement of a ventriculoperitoneal shunt may cause peritoneal tumor spread, third ventriculostomy is the preferred alternative.

8.3 Pathology

Collection of material for pathological diagnosis and translational research

- **Tumor tissue**

- Formalin-fixed, paraffin-embedded tissue: Sufficient representative tumor tissue needs to be formalin-fixed and paraffin-embedded to allow for optimal microscopic (including immunohistochemical) analysis and neuropathological diagnosis
- Snap frozen tissue: Whenever possible, at least 2 (viable) tumor fragments of 3x3x3 mm, but preferably as much as possible representative tumor tissue should be snap frozen and stored at -80 °C for translational research (e.g. to identify β -catenin mutations and MYC amplification status)
- Optional: Electron-microscopy; some small tumor fragments may be fixed for electron-microscopic studies (e.g. in glutaraldehyde)

- **Peripheral blood**

- Either before operation, or at any moment after 24 hours after surgery 1 EDTA-tube with at least 10 ml peripheral blood should be taken for translational research (esp. to allow for comparison with the molecular/genetic features in the tumor tissue sample); this tube should be stored at 4°C for 24-48 hours for transport and then stored at -80°C

- **CSF cytology**

- CSF samples at day 15 need to be prepared for optimal cytological analysis of the presence/absence of tumor cells, ideally allowing for additional immunocytochemical analysis of the samples

Review of histopathological diagnosis

The diagnosis medulloblastoma + histological subtype by the local pathologist will be reviewed by the neuropathology panel for pediatric brain tumors as organized by SKION/The Hague (expected to be operational in the course of 2010), ideally, before the start of radio- and/or chemotherapy; until this neuropathology panel is operational a review diagnosis can be obtained from: Prof. dr. Pieter Wesseling, Radboud University Nijmegen Medical Center, and Prof. dr. Johan M. Kros, Erasmus Medical Center Rotterdam.

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Transport of tumor material and blood for translational research

Snap frozen tumor tissue and an EDTA-tube with peripheral blood for translational research should be sent on dry ice to the contact person for this research:

Dr. Marcel Kool (alternative: Peter van Sluis)
Dept. of Human Genetics, Room nr. M1-130
Academic Medical Center
Meibergdreef 9
1105AZ Amsterdam
Tel. 020-5665170 / 06 55364115 (alt. 020-5665224 ; beeper 59085)
Email: m.kool@amc.uva.nl

8.4 Chemotherapy: schedules and management

8.4.1 Chemotherapy for standard risk medulloblastoma

Adults with standard risk medulloblastoma will not receive chemotherapy, but radiotherapy only. When and if the feasibility of chemotherapy in the high-risk group has been established, the protocol may be amended to treat standard risk patients with this schedule in order to decrease the radiotherapy dose.

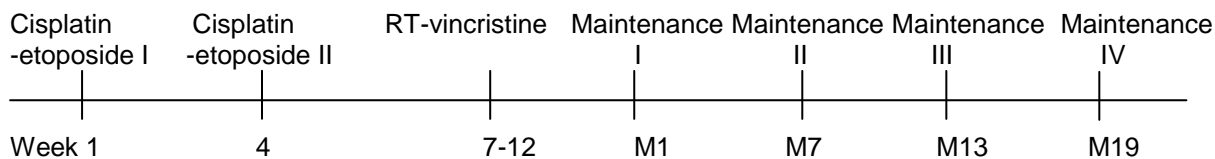
8.4.2. Chemotherapy for high-risk medulloblastoma

8.4.2.a Treatment plan overview

All patients will receive two courses of neoadjuvant chemotherapy with cisplatin-etoposide, followed by radiotherapy with biweekly vincristine, followed by four maintenance courses of chemotherapy according to the B-arm of COG A9961 with carboplatin (rather than cisplatin), vincristine and cyclophosphamide (75% dose), supported by PEG filgrastim. Neo-adjuvant chemotherapy will start as soon as the patient has recovered from surgery and staging has been completed, but preferably within 21 days after surgery. Post-radiotherapy (maintenance) chemotherapy will start after recovery from radiotherapy, preferably 4-6 weeks after the last radiotherapy fraction.

Week 1 is the start of chemotherapy treatment. Since delay after radiotherapy may vary, the start of maintenance chemotherapy is denoted as week Maint1, start of second cycle week M7 etc.

Overview of treatment schedule and time line



All drugs may be administered according to local protocol, but suggested schedules are given for administration, hydration and supportive care for all cycles.

Fertility preservation

Male patients will be encouraged to cryopreserve sperm before start of chemotherapy treatment. Female patients may be prescribed oral contraception or GH-RH agonists for the duration of treatment, in order to maximize the likelihood of preserved fertility after completion of treatment. Contact may be sought with the local fertility department to explore the possibility of vitrification-technique cryopreservation of oocytes.

8.4.2.b Neoadjuvant courses

Neoadjuvant doses

Cisplatin 80 mg/m² d.1 IV
Etoposide 100 mg/m² d.1-3 IV

Repeat cycle after 21 days, for a total of 2 cycles

Administration of neo-adjuvant chemotherapy

Cisplatin will be dissolved in 1000 ml NaCl 0.9% and administered over 1–4 hours, according to local protocol.

Etoposide will be administered in 500 ml NaCl 0.9% and administered over one hour.

Suggested premedication and supportive care for neo-adjuvant chemotherapy

Anti-emetics:

5HT3 antagonist (e.g. ondansetron 8 mg PO or IV or granisetron 1 mg PO or IV) day 1 and 2 prior to infusion of cytostatic drugs, to be repeated in the evening and on d.3 in case of nausea.

Dexamethasone 10 mg IV prior to infusion of cytostatic drugs on day 1 and 2
Metoclopramide 20 mg up to 3 dd in case of nausea/vomiting

Hydration: at least 2000 mL NaCl 0.9% per day, in addition to the fluids in which treatment is administered.

Growth factors: only in case of febrile neutropenia in the first course (see hematological toxicity)

Toxicity and dose modifications of neo-adjuvant chemotherapy

Hematological toxicity

At the start of each cycle of chemotherapy the absolute neutrophil count (ANC) should be $\geq 1 \times 10^9/L$, and platelets $\geq 100,000 \times 10^9/L$. In case count recovery is delayed then monitor counts on a twice weekly basis. As soon as counts recover (but within 2 weeks), the second cycle is administered *at the original dose*. If febrile neutropenia has occurred, PEGfilgrastim should be administered on day 3 of the second course. No dose reduction for haematological toxicity is foreseen. In case chemotherapy has to be delayed for 2 weeks or more, the second neo-adjuvant course will not be delivered and radiotherapy will be started instead. In that (unlikely) case, an extra course of maintenance chemotherapy may be substituted at the physician's discretion.

Premenopausal females may be prescribed ornametril in case of grade 3-4 thrombopenia (i.e. platelets $< 50 \times 10^9/l$) during treatment, in order to minimize menstrual blood loss. Because the majority of female patients will be on either oral contraceptives or LH-RH agonists, the chances of heavy menstrual bleeding seem remote.

Non-hematological toxicity

For grade 3 or 4 mucositis, the next course will be delayed until recovery to grade 0 or 1. The second cycle may be administered at 80% of the etoposide dose (i.e. $120 \text{ mg/m}^2 \text{ d.1 and 2}$), with 100% of the cisplatin dose. All other toxicities (save alopecia) should resolve until grade 1 or 0 before the second course is started. In case of dose delay of 2 or more weeks, the second neo-adjuvant course must be cancelled and radiotherapy should start. An extra course of maintenance chemotherapy may then be substituted at the physician's discretion.

8.4.2.c Chemotherapy during radiotherapy

Dose and administration of vincristine during radiotherapy

Vincristine 1.5 mg/m^2 with a maximum of 2 mg will be administered fortnightly as an IV bolus during radiotherapy, for a total of 3 doses.

Toxicity and dose modifications of vincristine during radiotherapy

Vincristine neurotoxicity

Before *each* dose of vincristine, patients should be checked for neurotoxicity. In case of toxicity $>$ grade 1, a neurologist should be consulted. It is recommended to err on the safe side when in doubt about continuation of vincristine or vincristine dose.

Grade 1: continue at full dose
Grade 2 or higher: hold dose, resume vincristine at 1 mg/m^2 (1.5 mg maximum) when resolution to grade 1, and then escalate to full dosage when symptoms resolve.

For seizures, hold one (1) dose, then reinstitute at 1.0 mg/m^2 (1.5 mg maximum) while anticonvulsants are continued. If seizures do not recur, then escalate to full dosage. Rule out syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a cause of seizures.

Vincristine gastro-intestinal toxicity

Constipation should be anticipated and promptly treated with laxatives such as magnesium or fibers, while adequate fluid intake is guaranteed. In case of ileus, vincristine dose should be held until resolution, then resumed at 1 mg/m^2 (1.5 mg maximum). Escalate to full dosage when symptoms do not recur.

8.4.2.d Maintenance chemotherapy

Maintenance chemotherapy should start when it is considered feasible by the treating physician, based on recovery of blood counts and performance status (which may be compromised due to fatigue, asthenia and general malaise). WHO-ECOG performance status should be 0, 1 or 2 at the start of maintenance chemotherapy. It is expected that patients will be able to start 4 weeks after the end of radiotherapy, and preferably not later than 6 weeks after the last radiotherapy fraction.

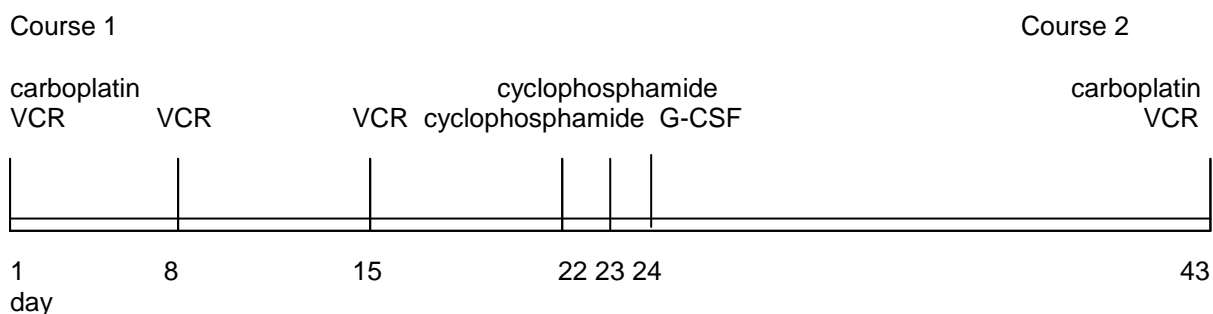
Doses and overview

Carboplatin (CBDCA): AUC 6 mg/ml, min d. 1
 Vincristine (VCR): 1.5 mg/m² (maximum dose 2.0 mg) d. 1, 8, 15
 Cyclophosphamide (CPM): 750 mg/m² d. 22, 23

Repeat cycle after 42 days (6 weeks), for a total of 4 cycles

Carboplatin dose will be calculated as follows:

Dose = 6 x (creatinine clearance + 25) mg. The creatinine clearance may either be measured or calculated according to the Cockcroft formula.



Administration and supportive care of maintenance chemotherapy

Suggested anti-emetic regimens during maintenance chemotherapy

5HT₃ antagonist (e.g. ondansetron 8 mg PO or IV or granisetron 1 mg PO or IV) prior to infusion of carboplatin (d. 1) and cyclophosphamide (d. 22 and 23)

Dexamethasone 10 mg IV prior to infusion of carboplatin (d. 1) and cyclophosphamide (d. 22 and 23)

Metoclopramide 20 mg up to 3 dd in case of nausea/vomiting

In case of intractable nausea or vomiting, dexamethasone may be continued for a few days at a lower dose, as may the 5HT₃ antagonist. There is insufficient proof for the use of aprepitant with this regimen.

Carboplatin administration during maintenance chemotherapy

Carboplatin will be dissolved in 500 ml glucose 5% and administered over one hour on day one of each cycle.

Vincristine administration during maintenance chemotherapy

Vincristine 1.5 mg/m² with a maximum of 2 mg will be administered on day 1, 8 and 15 of each cycle as an IV bolus

Cyclophosphamide administration, suggested hydration and mesna schedule during maintenance chemotherapy

Cyclophosphamide will be dissolved in 500 ml of NaCl 0.9% and administered over 1 hour on day 22 and 23 of each cycle.

Patients will be prehydrated with 1000 ml of NaCl 0.45%/Glucose 2.5% over 2 hours. After each cyclophosphamide dose 2000-2500 ml of hydration will be continued for 24 hours. Hydration fluid will contain 20 mEq/L KCl.

Mesna 500 mg (total dose) will be given 15 minutes prior to cyclophosphamide as an I.V. push. After cyclophosphamide, mesna 750 mg/m² will be administered, either in two doses of 375 mg/m² 3 and 6 hours post cyclophosphamide, or continuously in the posthydration fluid.

Administration of growth factors during maintenance chemotherapy

All patients will receive PEGfilgrastim (Neulasta[®]) 6 mg SC on day 24 of each cycle.

Toxicity and dose modifications during maintenance chemotherapy

Hematopoietic toxicity during maintenance chemotherapy

At start of course (i.e. day 1)

At the start of each cycle of chemotherapy ANC should be $> 1 \times 10^9/L$, and platelets $> 100,000 \times 10^9/L$. In case count recovery is delayed then monitor counts on a weekly basis. If count recovery takes place by Day 49 (i.e. an extra week) then do not reduce the dose of cyclophosphamide. If after day 49 ANC $\geq 0.75 \times 10^9/L$, start the next cycle of chemotherapy. Maintain the same dose of carboplatin and vincristine but reduce the dose of cyclophosphamide by 25%.

If after day 49 ANC $< 0.75 \times 10^9/L$ and platelets $< 100,000 \times 10^9/L$, then continue to monitor weekly counts (or twice weekly if feasible), and follow guidelines as outlined above for resuming chemotherapy.

If delayed count recovery continues to be a problem with subsequent cycles then reduce the dose of cyclophosphamide by 10% each time (25% initial reduction + 10% additional reduction = 35% total reduction). If the patient requires more than 2 cyclophosphamide dose reductions, it is suggested that contact should be sought with the working group.

At day 22 (i.e. before cyclophosphamide dose)

During each cycle administer Cyclophosphamide (on Day 22 and 23) when the ANC $\geq 0.75 \times 10^9/L$ and platelets $\geq 75,000 \times 10^9/L$. If there is a >1 week delay in administering the Day 21, 22 chemotherapy then reduce the Carboplatin dose to AUC 5 mg/ml,min in the next cycles. If delayed count recovery continues to be a problem with subsequent cycles, then reduce the dose of carboplatin further by 1 mg/ml,min AUC.

Febrile neutropenia

After febrile neutropenia, prophylactic antibiotics may be prescribed for subsequent courses. Carboplatin dose may be reduced by 1 mg/ml,min if febrile neutropenia re-occurs before day 21 in spite of antibiotic prophylaxis. Cyclophosphamide dose may be reduced by 25% if febrile neutropenia re-occurs after day 22 in spite of antibiotic prophylaxis.

In case of repeated dose delays ≥ 2 weeks at either day 1 or 22

If dose reductions have not succeeded in timely administration of courses, contact should be thought with the working group. Carboplatin may be replaced by cisplatin (75 mg/m²) in such cases at the physician's discretion and in the absence of significant neurotoxicity.

Vincristine neurotoxicity during maintenance chemotherapy

Grade 1: continue at full dose

Grade 2 or higher: hold dose, resume vincristine at 1 mg/m² (1.5 mg maximum) when resolution to grade 1, and then escalate to full dosage when symptoms resolve.

For seizures, hold one (1) dose, then reinstitute at 1.0 mg/m² (1.5 mg maximum) while anticonvulsants are continued. If seizures do not recur, then escalate to full dosage. Rule out syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a cause of seizures.

Vincristine gastro-intestinal toxicity during maintenance chemotherapy

Constipation should be anticipated and promptly treated with laxatives such as magnesium or fibers, while adequate fluid intake is guaranteed. In case of ileus, vincristine dose should be held

until resolution, then resumed at 1 mg/m² (1.5 mg maximum). Escalate to full dosage when symptoms do not recur.

Other non-hematological toxicity during maintenance chemotherapy

All toxicity (save alopecia) should be resolved until grade 1 or less before day 1 or 22 of each course. Dose reductions due to unresolved other toxicities than those mentioned above are not foreseen, but may be necessary and executed at the physician's discretion.

8.4.2.e Recommended observations during protocol treatment

Please refer to chapter 9, page 24 for required clinical observations.

8.5 Radiation therapy

| Risk group | Regimen |
|------------------------|---|
| Standard-risk patients | radiotherapy only |
| High-risk patients | 1. combined modality: chemotherapy + radiotherapy 2. contraindications for chemotherapy: only radiotherapy |

Timing of Radiation Therapy

When no chemotherapy is planned, radiotherapy should start within 4 weeks of the operation but preferably within 2-3 weeks. The expected duration of radiotherapy is approximately 6 weeks (31 fractions).

In case of combined modality treatment the radiotherapy should start within 3 weeks of the second course of chemotherapy, but depends on bone marrow recovery. Weekly control of neutrophils and platelets should be performed taking the following stopping rules into consideration:

Start RT only if thrombocytes > 100 x 10⁹/l, neutrophils > 1 x 10⁹/l

Immobilisation mask

For accurate dose delivery and reproducibility an individual immobilisation mask will be made. The patient can be in prone or supine position, depending on the radiation technique. In this mask, a CT-scan for radiotherapy purposes will be generated. This radiotherapy CT-scan will be fused (image registration) with the MRI-scan that is performed within 72 hours of operation (if not available with the pre-operative MRI-scan).

Radiation technique

Most radiotherapy institutions will have their own craniospinal irradiation technique and protocol. A classical solution is that the patient is in a prone position and that 2 lateral opposing 4-6 MV photon beams will cover the head and the cranial cervical vertebrae/spine. The inferior border of these fields matches with the superior border of the spinal irradiation field. The spinal irradiation field is due to the length of the adult spinal cord divided into two parts. Most radiotherapy departments will use photons, but some will use electrons for the spinal coverage. After the craniospinal irradiation a boost will be given to the posterior fossa and metastases. The patient will then be placed in supine position.

Recent technical advances make it possible that IMRT (intensity modulated radiotherapy) can be used for both the irradiation of the spine as the boost.

Target volumes

Gross Tumor Volume (GTV): contrast enhancing lesion on MRI-scan. This accounts for both the primary tumor and the metastases. After complete excision the walls of the resection cavity will form the GTV.

Clinical Target Volume (CTV): is the GTV extended with that part of the CNS that is prone to subclinical microscopic disease. There are anatomical barriers such as the bone and tentorium. In the treatment of medulloblastoma multiple CTV's can be defined.

Planning Target Volume (PTV): is the CTV extended with a margin to compensate for movement and set-up inaccuracies.

Craniospinal Irradiation

CTV1: entire cranio-spinal axis

PTV1: cranium content (cave cribiform plate) + 5 mm margin; spinal canal including the the cal sac + 1,5 - 2 cm margin.

Boost to primary tumor

(3D-based treatment planning → conformal RT or IMRT)

GTV2 is based upon the pre-operative abnormalities and the changes after operation.

CTV2 is GTV2 plus a 1.5 cm margin but not going beyond the bone or tentorium.

PTV2 is CTV2 plus 0.3 - 0.5 cm margin.

Boost to cranial and spinal metastases

GTV3 is based upon staging MRI-scans

CTV3 cranial metastases: GTV3 + 0.5 cm margin

PTV3 cranial metastases: CTV3 + 0.5 cm margin

CTV3 spinal metastases: GTV3 + 1.0 - 1.5 cm margin

PTV3 spinal metastases: CTV3 + 1.0 cm margin

Radiation dose and prescription

Prescription

Prescription of dose is according to ICRU-50/63 guidelines

Dose

- standard risk patients and high risk patients treated with combined modality

PTV1: 20 x 1.8 Gy = 36 Gy

PTV2: 11 x 1.8 Gy = 19.8 Gy → total dose: 55.8 Gy

In case of metastases:

PTV3: 8 x 1.8 Gy = 14.4 Gy → total dose: 50.4 Gy (dependent on volume; too large: 45 Gy)

- high risk patients treated with radiotherapy only

PTV1: 22 x 1.8 Gy = 39.6 Gy

PTV2: 9 x 1.8 Gy = 16.2 Gy → total dose: 55.8 Gy

In case of metastases:

PTV3: 6 x 1.8 Gy = 10.8 Gy → total dose: 50.4 Gy (dependent on volume; too large: 45 Gy)

Aimed overall treatment time ≤ 45 days.

Weekly control of neutrophils, platelets should be performed during radiotherapy; in case of rapid decline control should be more frequent.

Interrupt RT if neutrophils < $0.5 \times 10^9/l$, or platelets < $25 \times 10^9/l$

Modifications due to hematological toxicity

Thrombocytopenia

If a platelet count of < $25 \times 10^9/L$ occurs, then radiotherapy should be interrupted. Platelet transfusions may be given when necessary according to local practices and guidelines. If the counts do not recover to > $50 \times 10^9/L$ unsupported by platelet transfusions after one week of interruption, only the posterior fossa boost will be given and the craniospinal irradiation (CSRT) will be postponed until after completion of posterior fossa boost. If counts have not recovered to > $50 \times 10^9/L$ by the end of boost radiotherapy CSRT may have to be abandoned.

Neutropenia

If a neutrophil count of < $0.5 \times 10^9/L$ occurs, then G-CSF 5ug/kg (s.c.) may be given daily to maintain a neutrophil count of > $0.5 \times 10^9/L$. If given, G-CSF should continue until the neutrophil

count rises to $> 1.0 \times 10^9/L$ for two successive days. CSRT will restart when the neutrophil count has recovered to $> 1.0 \times 10^9/L$ whether or not the patient is receiving G-CSF. Additionally, if a neutrophil count of $< 0.5 \times 10^9/L$ occurs radiotherapy should be interrupted. If the counts have not recovered after one week of interruption only the posterior fossa boost will be given and the craniospinal irradiation will be postponed until after completion of the posterior fossa boost. If counts have not recovered to $> 1 \times 10^9/L$ (?) by the end of boost radiotherapy CSRT may have to be abandoned.

Anaemia

The haemoglobin level should be maintained at a minimum level of 6.2 mmol/L RT by transfusion if necessary.

Organs at risk

ALARA (As Low As Reasonably Achievable) principle, ideally with the following maximum doses per organ at risk:

Whenever possible, without compromising CTV, attempts should be made to limit the dose to the optic chiasma to max 55 Gy, the brainstem to max 54 Gy, to the retina (eye) to less than 45- 50 Gy, the cochlea to 30-45 Gy, for the pituitary and hypothalamus < 45 Gy, for the optic nerves and chiasm to mean 56 Gy, normal spinal cord to 56 Gy. A direct irradiation of the thyroid by vertex fields should be avoided. Dose to the thyroid should be minimised. The lens dose should be minimized by avoiding direct fields and should not be higher than 5 Gy. The dose to the normal brain should be $< 60\%$ isodose (for the boost).

Portal imaging

According to institutional policies.

Acute side effects

Hematological (infections), bleeding, fatigue; skin; hair loss; nausea, hearing loss, Lhermitte's sign.

Late toxicity

Endocrinologic (hypopituitarism), neurocognitive (concentration, memory, character), benign tumors (meningioma), second malignancies (skin, thyroid, CNS), reduced hearing.

8.6 Follow-up

Imaging will be performed every 3 months in the first year and every 4 months in the second year starting 3 months after radiotherapy. Thereafter imaging will be performed twice a year for 3 years and yearly between 5 and 10 years after treatment. Only cranial MRI will need to be performed unless other localizations were present at presentation and unless new symptoms prompt additional or more extensive imaging.

9 Required clinical observations

Table 1. Required observations in standard-risk patients treated with radiotherapy only

| Observation | Postoperatively | Prior to RT | Follow-up ⁴ |
|--------------------------------|----------------------------|-------------|--------------------------------------|
| Physical and neurological exam | X | X | X |
| WHO performance status | X | X | X |
| NCI-CTC toxicity | | X | |
| MRI-brain ⁵ | X ≤ 72 hrs of operation | | X |
| MRI - spine | X | | If symptomatic or initially abnormal |
| CSF | day 15 | | o.i. |
| CBC | X | o.i. | o.i. |
| Liver function ¹ | X | o.i. | o.i. |
| Renal function ² | X | o.i. | o.i. |
| Electrolytes ³ | X | o.i. | o.i. |

¹ Bilirubin, ASAT, ALAT, gammaGT and alkaline phosphatase

² Creatinine and creatinine clearance calculation (or GFR)

³ Sodium, potassium

⁴ 3, 6,9,12,16,20, 24 months after the end of treatment. Thereafter twice a year for 3 years and yearly between 5 and 10 years after treatment

⁵ for details concerning imaging protocol see appendix E

Table 2. Required observations in high-risk patients treated with chemotherapy and radiotherapy

| Observation | Post-operatively | Prior to each neo-adjuvant CT | Prior to RT | During RT (weekly) | During maintenance CT | After maintenance CT ⁴ | Follow-up ⁵ |
|--------------------------------|----------------------------|-------------------------------|-------------|--------------------|--|-----------------------------------|------------------------|
| Physical and neurological exam | X | X | X | X | Every 3 weeks | X | X |
| Height | X | | | | | | |
| Weight | | X | X | X | D. 1, 8, 15, 22 of each cycle | | |
| WHO performance status | X | X | X | X | Every 3 weeks | X | X |
| NCI-CTC toxicity | | X | X | X | D. 1, 8, 15, 22 of each cycle | X | |
| MRI – brain ⁶ | X ≤ 72 hrs of operation | | X | | Before start [and in case of residual disease after RT: also after 2 nd maintenance course] | X | X |
| MRI – spine ⁶ | X | o.i. | o.i. | | | o.i. | o.i. |
| CSF | day 15 | o.i. | o.i. | | | o.i. | o.i. |
| CBC | X | X | X | X | Every 3 weeks | X | o.i. |
| Liver function ¹ | X | X | X | | Every 3 weeks | X | o.i. |
| Renal function ² | X | X | X | | Every 3 weeks | X | o.i. |
| Electrolytes ³ | X | X | X | | Every 3 weeks | X | o.i. |
| PA review | X | | | | | | |

¹ Bilirubin, ASAT, ALAT, gammaGT and alkaline phosphatase

² Creatinine and creatinine clearance calculation (or GFR)

³ Sodium, potassium

⁴ 0-14 days after day 21 of cycle 4

⁵ 3, 6,9,12,16,20, 24 months after the end of treatment. Thereafter twice a year for 3 years and yearly between 5 and 10 years after treatment

⁶ for details concerning imaging protocol see appendix E

10 Safety evaluations and adverse events reporting

Serious Adverse Events (SAEs) should be reported from the first study-related procedure until 30 days following the last dose of any drug or RT treatment from the protocol treatment schedule. Serious Adverse events occurring after 30 days should also be reported if considered at least possibly related to the treatment by the investigator.

SAE forms should be faxed (**fax 088-755 5462**) as soon as possible but preferably within 3 days to IKMN Trial bureau (Integraal Kankercentrum Midden Nederland), c/o UMCU huispost F02-162 postbus 85500 3508 GA Utrecht. Tel: 088-755 6286.

SAE: A Serious Adverse Event is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that:

- Results in death
- Is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient's hospitalization or prolongation of existing inpatients' hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Results in any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above), e.g. secondary malignancy, AE as a result of an overdose

The following situations are not considered to be SAEs and should not be reported on an SAE form:

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment
- Hospitalisation which was planned before the patient consented to study participation and where admission did not take longer than anticipated
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, palliative care, rehabilitation, overdose without occurrence of an adverse event)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

The severity of all adverse events (serious and non-serious) should be graded using CTCAE v 4.0 (<http://ctep.cancer.gov/reporting/ctc.html>)

11 Data collection

Data will be collected on Case Report Forms (CRF) to document eligibility, safety and efficacy parameters and compliance to treatment schedules. Data collected on the CRF are derived from the protocol.

Each CRF page will be identified by a unique combination of patient registration number (assigned at registration), hospital and patient name code (as documented at registration) to be filled out before completing the form.

The CRF will be completed on site by the local investigator or an authorized staff member. Each page must be dated and signed by the local investigator upon completion. All CRF entries must be based on source documents.

Copies of the CRF will be kept on site. The original CRF pages must be sent to the IKMN Trial bureau (Integraal Kankercentrum Midden Nederland), c/o UMCU huispost F02-162 postbus 85500 3508 GA Utrecht., fax: 088-755 5462, tel: 088-755 6286

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Appendix A: Common terminology criteria for adverse events

The grading of toxicity and adverse events will be done using the most recent version of the NCI Common Terminology Criteria for Adverse Events, CTCAE version 4.

A complete document may be downloaded from the following site:

<http://ctep.cancer.gov/reporting/ctc.html>

Appendix B: ZUBROD-ECOG-WHO Performance Status Scale

- 0 Normal activity
- 1 Symptoms, but nearly ambulatory
- 2 Some bed time, but to be in bed less than 50% of normal daytime
- 3 Needs to be in bed more than 50% of normal daytime
- 4 Unable to get out of bed

Appendix C: RTOG neurologic function status

- 0 No neurologic symptoms; fully active at home/work without assistance
- 1 Minor neurologic symptoms; fully active at home/work without assistance
- 2 Moderate neurologic symptoms; fully active at home/work but requires assistance
- 3 Moderate neurologic symptoms; less than fully active at home/work and requires assistance
- 4 Severe neurologic symptoms; totally inactive requiring complete assistance at home or institution - unable to work

Appendix D: MR imaging – minimal requirements

MRI scanner - minimally 1.0T (magnetic field strength)

MRI brain:

1. unenhanced T1W;T2W; axial; FLAIR axial or coronal.
 - slice thickness no more than 5 mm
 - DWI (diffusion) – optional
2. after gadolinium: T1 W axial; coronal, sagittal; slice thickness no more than 5 mm

MRI spine:

1. unenhanced T1W en T2W sagittal; slice thickness no more than 3 mm
2. after gadolineum: T1W sagittal; slice thickness no more than 3 mm
3. transversal slices at the level(s) of abnormalities

Appendix E: MINI MENTAL STATE EXAMINATION

Naam:

Patiëntnummer:

Datum :

Onderzoeker:

Visite:

Oriëntatie

1. Kunt u mij vertellen:

- Welke dag van de week het is? .../1
Welke maand het is? .../1
Welk jaar het is? .../1
Welke datum het vandaag is? .../1
Welk seizoen het is? .../1

2. Kunt u mij vertellen:

- Op welke afdeling u bent (in welke straat u woont)? .../1
In welk ziekenhuis u bent (op welk huisnummer)? .../1
In welke stad? .../1
In welke provincie? .../1
In welk land? .../1

Inprenting / registratie

3. Ik ga drie woorden opnoemen. Als ik ze alle drie gezegd heb, vraag ik u het rijtje te herhalen: "appel" "tafel" "stuiver"; onthoud deze woorden goed, want over een paar minuten zal ik u vragen het rijtje te herhalen .../3

Concentratie / Aandacht

4. Wilt u van de 100 zeven aftrekken en van wat overblijft weer zeven aftrekken en zo doorgaan tot ik stop zeg?
(herhaal eventueel driemaal als de persoon stopt, herhaal dezelfde instructie, geef maximaal 1 minuut de tijd; stop na 5 antwoorden)
Alternatief als patiënt niet wil/kan rekenen:
"Wilt u het woord worst spellen? Help de persoon hier evt bij zodat worst correct wordt gespeld
Zeg dan "Wilt u het nu van achteren naar voren spellen?
(1 punt voor elke correcte positie) .../5

Inprenting / herinnering

5. Kunt u dat rijtje van 3 woorden nog eens opnoemen?
(1 punt voor elk goed antwoord) .../3

Taal (Benoeming)

6. Laat een pen of een potlood zien: "Wat is dit?" .../1
Laat een horloge zien: "Wat is dit?" .../1
(1 punt voor elk goed antwoord)

Taal (Herhaling)

7. Wilt u de volgend zin herhalen? "Nu eens dit en dan eens dat" .../1
(1 punt als de complete zin goed is)

Taal (taalbegrip en motorisch uitvoerende functies)

8. "Ik ga u nu een stuk papier geven. Wilt u het vel papier met uw rechter hand aannemen (1 punt), het in tweeën vouwen (1 punt) en het op tafel leggen (1 punt) ? .../3

Taal (hardop lezen en begrijpen van gelezen taal)

9. "Wilt u dit lezen en opvolgen: "SLUIT UW OGEN?" .../1

Taal (schrijven)

10. "Wilt u voor mij een zin opschrijven?" .../1
(1 punt wanneer de zin betekenis heeft en een onderwerp en een lijdend voorwerp heeft)

Constructieve praxie

11. "wilt u deze figuur natekenen?" .../1
(1 punt wanneer de figuur correct is nagetekend)

(Er moet een vierkant te zien tussen de twee vijfhoeken)



TOTAAL SCORE

.../30

Appendix F: Collection, preservation and transport of material for pathological diagnosis and translational research

• Tumor tissue

- Formalin-fixed, paraffin-embedded tissue: Sufficient representative tumor tissue needs to be formalin-fixed and paraffin-embedded to allow for optimal microscopic (including immunohistochemical) analysis and neuropathological diagnosis
- Snap frozen tissue: Whenever possible, at least 2 (viable) tumor fragments of 3x3x3 mm, but preferably as much as possible representative tumor tissue should be snap frozen and stored at -80 °C for translational research (e.g. to identify β -catenin mutations and MYC amplification status)
- Optional: Electron-microscopy; some small tumor fragments may be fixed for electron-microscopic studies (e.g. in glutaraldehyde)

• Peripheral blood

- Either before operation, or at any moment after 24 hours after surgery 1 EDTA-tube with at least 10 ml peripheral blood should be taken for translational research (esp. to allow for comparison with the molecular/genetic features in the tumor tissue sample); this tube should be stored at 4°C for 24-48 hours for transport and then stored at -80°C

• CSF cytology

- CSF samples at day 15 need to be prepared for optimal cytological analysis of the presence/absence of tumor cells, ideally allowing for additional immunocytochemical analysis of the samples

Review of histopathological diagnosis

The diagnosis medulloblastoma + histological subtype by the local pathologist will be reviewed by the neuropathology panel for pediatric brain tumors as organized by SKION/The Hague (expected to be operational in the course of 2010), ideally, before the start of radio- and/or chemotherapy; until this neuropathology panel is operational a review diagnosis can be obtained from: Prof. dr. Pieter Wesseling, Radboud University Nijmegen Medical Center, and Prof. dr. Johan M. Kros, Erasmus Medical Center Rotterdam.

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Transport of material for translational research

Snap frozen tumor tissue and an EDTA-tube with peripheral blood for translational research should be sent on dry ice to the contact person for this research:

Dr. Marcel Kool (alternative: Dr. Peter van Sluis)
Dept. of Human Genetics, Room nr. M1-130
Academic Medical Center
Meibergdreef 9
1105AZ Amsterdam
Tel. 020-5665170 / 06 55364115 (alt. 020-5665224 ; beeper 59085)
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