

# **Medulloblastoma in Adults**

## **Treatment Protocol**

**Dutch neuro-oncology society  
(Landelijke Werkgroep Neuro-Oncologie, LWNO)**

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Comprehensive Cancer Centre the Netherlands (IKNL), Utrecht

# 1 Working group

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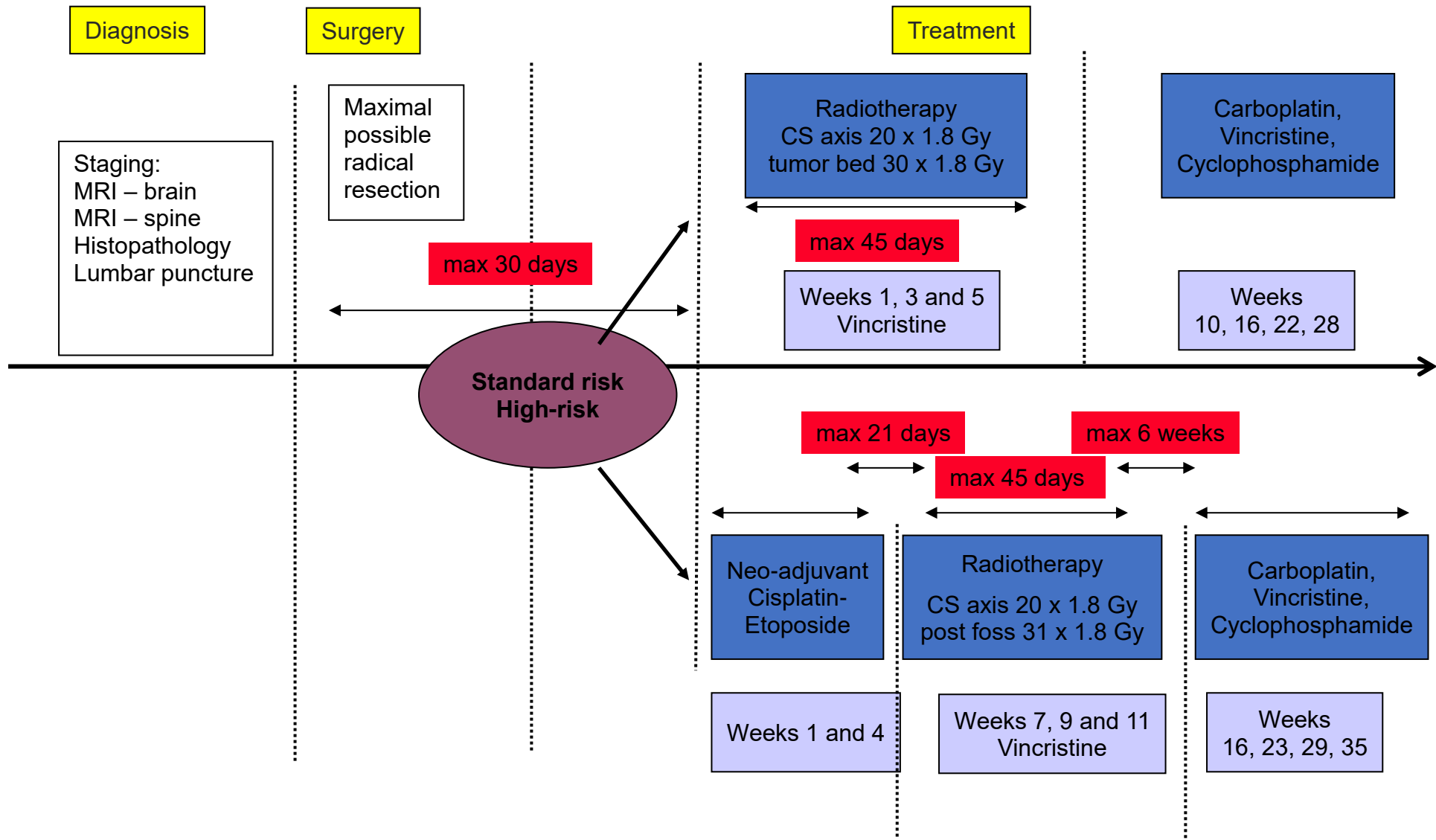
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### 3 Summary, flowcharts and time schedule



## 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 Molecular characteristics

#### Pathology of medulloblastomas

Medulloblastomas belong to the overarching group of embryonal tumors of the central nervous system (CNS), i.e. tumors characterized by (very) high cellularity, the densely packed and poorly differentiated appearing small cells often showing limited cytoplasm, variable nuclear pleomorphism and marked mitotic activity. Tumors with this phenotype in the posterior fossa are traditionally called medulloblastomas. In the 2007 (i.e. 4th) edition of the WHO classification of CNS tumors subgroups of medulloblastomas were histologically defined (3). More recent studies, however, revealed particular molecular medulloblastoma subgroups and showed that combination of molecular and histological data provide complementary, clinically relevant diagnostic information. Indeed, in the WHO 2016 CNS tumor classification (i.e. the updated 4th edition) an integrated diagnosis is proposed that combines histology with genetically defined tumours (4-6).

#### Histological subtypes

The histologic medulloblastoma subtypes described in the WHO 2016 classification have not substantially changed compared to the 2007 classification. The **classic** phenotype is by far the most frequent histologic subtype and shows bland microscopic features essentially as described above. The **desmoplastic/nodular** medulloblastoma is characterized by a nodular architecture, the reticulin-free nodules (often appearing as 'pale islands') surrounded by reticulin-rich desmoplasia. This subtype is closely associated with one of the SHH-activated groups of medulloblastoma (see below). An 'exaggerated' form of the desmoplastic/nodular subtype is medulloblastoma with **extensive nodularity** with many large nodules of more differentiated, neurocytic cells surrounded by reticulin-fibers. The desmoplastic/nodular and especially the extensive nodularity medulloblastomas are associated with a better prognosis. A diagnostic pitfall in this context is the classic medulloblastoma with a nodular architecture but without reticulin-rich desmoplasia completely surrounding the nodules, such tumors do not qualify as desmoplastic/nodular medulloblastomas. A fourth histologic subtype is the **large cell/anaplastic** variant (in the 2007 classification still described as two separate histologic

variants), this variant typically shows tumor cells with (a combination of) large nuclei, prominent nucleoli, cell wrapping, many mitoses and/or apoptotic figures (3-6). In cases in which the histological subtype cannot be assessed due to e.g. insufficient quantity or quality of the available tissue samples according to the WHO 2016 classification 'NOS' (histologically not otherwise specified) should be added to the diagnosis medulloblastoma.

## Molecular subtypes

Four molecular groups of medulloblastoma are recognized in the WHO 2016 classification:

- **WNT-activated**

The tumors in this group occur especially in childhood, encompass about 10% of medulloblastomas, and generally show the classic, occasionally the large cell/anaplastic phenotype. Over 90% of WNT-activated medulloblastomas carry a *CTNNB1* mutation (less frequently mutations in other components of the WNT signalling pathway such as *AXIN1* and *APC*, occasionally a germline *APC* mutation). The defect in the WNT-signalling pathway results in nuclear accumulation of beta-catenin as can be demonstrated by immunohistochemistry. About 85% of the tumors in this group show monosomy for chromosome 6. Children with WNT-activated medulloblastomas generally have an excellent prognosis, in adults this may be different (7, 8).

- **SHH-activated & TP53-wildtype**

About 30% of the medulloblastomas belong to the SHH-activated group, the vast majority of these are *TP53*-wildtype. The nodular/desmoplastic and the (much less frequently occurring) extensive nodularity histologic subtype (almost) exclusively are found in this molecular group. SHH-activated & *TP53*-wildtype tumors occur predominantly in infants and adulthood and are considered low risk, and especially in younger patients *PTCH1* or *SUFU* germline mutations may be found.

- **SHH-activated & TP53-mutant**

A small percentage of SHH-activated medulloblastomas is *TP53*-mutant, these tumors occur predominantly in childhood, often show the large cell/anaplastic phenotype and carry a poor prognosis. Up to half of the patients in this group have a *TP53* germline mutation (9).

- **non-WNT/non-SHH**

This last category encompasses the group 3 and group 4 molecular category as recognized in multiple studies (representing resp. about 20% and 40% of all medulloblastomas and occurring especially in infancy/childhood). As in many centers demonstration of these subcategories is so far difficult due to a lack of easily accessible diagnostic tools, group 3 and group 4 are still included under the umbrella of the non-WNT/non-SHH molecular category in the WHO 2016 classification (4). Histologically, these medulloblastomas are almost always of the classic or large cell/anaplastic phenotype.

Assessment of the molecular subtype of medulloblastoma can often be achieved by performing immunohistochemistry for (surrogate) markers like beta-catenin, GAB1, YAP1, p53, OTX2 and/or p75NGFR (10). Across different histologic and molecular medulloblastoma groups *MYC* and/or *MYCN* amplification may provide prognostic information, but the exact prognostic impact appears to be subgroup dependent (11, 12). In the near future, larger and/or more in depth studies may reveal even more clinically relevant medulloblastoma subgroups (12-14).

Minimum analysis should be subtyping by immunohistochemistry but preferably all patients should additionally be analysed molecularly by methylation array.

### 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 (4.2).

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 cm<sup>2</sup> and 53% in patients with larger tumor residue (15). In adults, the advantage of gross total resection has also been shown in a cohort of 454 patients analyzed within the SEER database (16).

The relevance of leptomeningeal spread of medulloblastoma is reported in several studies (17, 18). 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 (19). 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 (20).

The prognostic relevance of macroscopic metastatic disease has been confirmed in the analysis of 454 patients reported by Lai (16) and 251 patients reported by Padovani et al. (21). Fouladi et al. studied 106 consecutive patients, in which 17% of leptomeningeal spread would have been missed if no CSF were studied (22).

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 (23). 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 (24). 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 (15), 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 (25). Immediate postoperative imaging (within 72 hrs) 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 (26). 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 (27).

## 4.5 Radiotherapy

The basis of medulloblastoma treatment consists of surgery followed by radiotherapy. Being a radiosensitive tumour, clinical and radiological response can be observed shortly after start of treatment. Because of the high propensity of medulloblastomas to disseminate within the subarachnoidal space, the radiotherapy treatment volume should always include the entire craniospinal axis, even in absence of metastatic disease (28).

### *Timing and overall treatment time*

Several studies have shown improved posterior fossa control and/or survival after shorter intervals between surgery and start or completion of radiotherapy (29-31). An overall treatment time of less than or equal to 45 days was therefore proposed (30, 32, 33).

### *Technique*

The radiotherapy techniques most commonly used are 3D conformal therapy (3D CRT) or intensity modulated therapy (IMRT) including volumetric arc therapy (VMAT), using photons as the radiation delivery vehicle. In most scientific publications on the treatment outcome of medulloblastoma the radiotherapy is photon-based. Because, however, photons have an exit dose, treating the entire spine results in dose to almost every organ, including a large volume of the red bone marrow compartment. The hematological toxicity can interfere with treatment (and chemotherapy) tolerability.

In recent years proton therapy has gained significant ground worldwide and is now available in hospital-based settings. As from January 2018 proton therapy is available in The Netherlands. Due to the unique properties of protons, where there is no exit dose, significant treatment related toxicity (including hematological toxicity and likely late adverse effects such as reduced fertility, cardiovascular morbidity, endocrinopathies and secondary malignancies) due to dose outside the target volume can be avoided (34-37). The effects of proton therapy on the tumour are similar (38, 39). This makes proton therapy the preferred radiation modality for medulloblastoma patients.



In case of recurrence or residual disease, re-irradiation with (hypofractionated/radiosurgical) stereotactic radiotherapy results in good local control without significant toxicity (40).

In conclusion, craniospinal irradiation (preferably proton-based) is an essential part of the primary treatment of patients with medulloblastomas. The interval between surgery and the start of radiotherapy should preferably be kept within 30 days.

## 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 (30, 41). However, retrospective series of adolescents and adults with medulloblastoma suggest poor tolerance of chemotherapy after craniospinal irradiation (42, 43). In addition, increased and irreversible vincristine-induced neuropathy has been prospectively documented in adults at doses that are common in pediatric protocols (44).

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. Major disadvantage of neoadjuvant chemotherapy is the inevitable delay of initiation of radiotherapy. In children, randomized studies showed a disadvantage for neoadjuvant chemotherapy when an ineffective regimen was used (20), or when radiotherapy was postponed for more than 20 weeks after surgery (45).

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, 18). 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 (46-48). 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 (49), 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.

#### **Addition 2018: Review of recent literature**

In a retrospective analysis of 43 patients with standard risk medulloblastoma, all 15 patients treated with chemotherapy in addition to resection and craniospinal irradiation were alive after a median follow-up of 10 years, whereas 78.6% of those treated without chemotherapy survived 10 years (50). Feasibility of chemotherapy treatment in standard risk adult medulloblastoma patients was demonstrated in the German prospective HIT study, but survival data are difficult to interpret given the absence of a comparative group (51).

Kocakaya et al performed a meta-analysis of studies regarding adult medulloblastoma (52). They found a median overall survival of 65 months; presence of metastases at diagnosis was not a significant prognostic factor. Patients receiving chemotherapy at first-line, however, survived significantly longer (mOS: 108 mo, 95% CI: 68.6–148.4) than patients treated with radiation alone or with chemotherapy only at recurrence (mOS: 57 mo, 95% CI: 39.6–74.4). In this paper it was not possible to differentiate between adjuvant and neo-adjuvant chemotherapy, nor between specific types of chemotherapy. Kann et al used the US National Cancer Database to identify patients aged 18 years and older diagnosed with medulloblastoma between 2004-2012 and underwent resection and craniospinal irradiation. With a median follow-up of 5.0 years, estimated 5-year OS was superior in patients receiving CRT versus RT (86.1% vs 71.6%,  $P < .0001$ ). On multivariable analysis, after controlling for risk factors, CRT was associated with superior OS compared with RT (HR: 0.53; 95%CI: 0.32–0.88,  $P = .01$ ). On planned subgroup analyses, the 5 year OS of patients receiving CRT versus RT was improved for M0 patients ( $P < .0001$ ), for patients receiving 36 Gy CSI ( $P = .0007$ ), and for M0 patients receiving 36 Gy CSI ( $P = 0008$ ) (53).

#### **Rationale for amendment to the current protocol**

Given the above results, improved survival with the addition of chemotherapy to resection and craniospinal irradiation in standard risk medulloblastoma seems likely, although it remains to be seen whether this holds true for all medulloblastoma subgroups (4). Neo-adjuvant chemotherapy may compromise outcome as found by Moots et al in a prospective phase II trial of 11 patients, two of whom progressed while on chemotherapy (54). Overall response after chemo- and radiotherapy was 45%; 5year PFS and OS were only 27% and 55%. Similarly extended treatment time, which may be associated with inferior survival, was found after neo-adjuvant chemotherapy in the German HIT 91 study (45).

#### **Amendment to the current protocol**

Therefore consensus was reached on treating standard risk patients with craniospinal irradiation, concomitant alternate week vincristine and adjuvant chemotherapy. There will be no neo-adjuvant chemotherapy. The chemotherapy schedule, adjuvant carboplatin, vincristine and cyclophosphamide, is identical to that used in high risk medulloblastoma.

## 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) (55-59). Furthermore, recent epidemiologic data suggest similar survival in children and adults, with only infants faring worse (41). 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 (21, 25, 29, 30, 60), although isolated recurrences have been reported after 18 years (25). 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. We propose following scheme: MRI brain to be performed at 3, 6, 9, 12, 16, 20, 24 months after the end of treatment and thereafter twice a year for 3 years and yearly between 5 and 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 (59).

Evaluation of long term toxicity of the treatment should be part of the follow-up. Patients should be screened for endocrine dysfunction yearly and treated with hormone suppletion if necessary.

## **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 and informed consent patients should be notified by email to [neuro-onco-trials@erasmusmc.nl](mailto:neuro-onco-trials@erasmusmc.nl)

At least the following information should be registered for each patient: date of birth, sex, patient hospital registration number, treating physician, date of diagnosis 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 &gt; 1.5 cm<sup>2</sup> consider second look surgery</i>	R0 R1 ≤ 1.5 cm <sup>2</sup> residu	R2 (after second look surgery)
3. History and physical examination	<i>If clinically 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 cm<sup>2</sup>; R2 = residual tumor > 1.5 cm<sup>2</sup>

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 cm<sup>2</sup> 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 radiotherapy and/or chemotherapy.

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  $\beta$ -catenin mutations and MYC amplification status)
- Optional: Electron-microscopy; some small tumor fragments may be fixed for electron-microscopic studies (e.g. in glutaraldehyde)
- Unless central review is needed for clinical purposes the material may be stored locally. In time samples will be transported collectively.

#### • 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 locally. In time samples will be transported collectively.



- **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. Samples should be stored locally and will in time be transported collectively

**Review of histopathological diagnosis**

Because of lack of funding, central review of histopathological diagnosis will not be standard procedure but may be performed on indication or for research purposes.

## 8.4 Radiation therapy

Treatment of the craniospinal axis is a large burden to the patient, necessitating careful medical monitoring and management of toxicities. Furthermore, the technical aspects of radiotherapy planning and delivery of this target are very challenging. It is advisable to concentrate treatment delivery at a center with an experienced radiation team.

Risk group	Regimen
Standard-risk patients	radiotherapy and chemotherapy (concurrent and adjuvant)
High-risk patients	radiotherapy and chemotherapy (neo-adjuvant, concurrent and adjuvant)

### Timing of Radiation Therapy

When no neo-adjuvant chemotherapy is planned, radiotherapy should start within 30 days of surgery. In case of rapid clinical progression due to tumour an even quicker start (whole brain) should be considered. The expected duration of radiotherapy is approximately 6 weeks (30-31 fractions, 5 times per week).

In case of neoadjuvant chemotherapy the radiotherapy should start within 3 weeks of the second course of chemotherapy, depending on bone marrow recovery. Control of neutrophils and platelets should be performed on day 22  $\pm$  3 days and weekly thereafter, starting RT as soon as platelets  $> 100 \times 10^9/l$ , neutrophils  $> 1 \times 10^9/l$

### RT preparation

For accurate dose delivery and reproducibility an individual mask immobilizing head and shoulders is necessary. For accurate target delineation a registration of the post-operative MRI of the cerebrum on the planning CT is mandatory. A recent planning MRI for boost planning is advised.

### Radiation technique

The preferred technique is intensity modulated proton therapy. Due to the limited availability of proton therapy, a quick start of the referral procedure is mandatory. In case proton therapy is not available or achievable the patient will be treated with photon therapy, either 3D CRT or IMRT/VMAT.

Using highly conformal advanced radiation techniques makes image guidance during delivery very important.

### Target volumes

GTV primary tumor (PT): resection cavity and residual macroscopic disease as visible on recent MRI.

GTV metastases: as visible on MRI.

CTV primary tumor/focal boost: GTV primary tumor + 1.5 cm margin adapted to natural borders (ie bone, tentorium).

CTV posterior fossa (PF) boost: cranial extension: tentorium; caudal border: C1-C2; ventral: brainstem including the pre-pontine CSF space; dorsal: tentorium and occipital bone; lateral: tentorium and bone, the sigmoid sinus can be excluded. The internal acoustic canal is not included unless macroscopic disease is present.

CTV focal metastases boost: GTV boost + 0.5-1.0 cm margin adapted.

CTV craniospinal axis (CSA): the entire subarachnoidal space is included. Specific attention should be given to inclusion of the cribiform plate, temporal fossa, optic nerves, Meckel's cave and other

cranial nerve foramina, the lateral extensions of the spinal nerves and the inclusion of the entire thecal sack caudally as visible on MRI.

## Radiation dose and prescription

### Prescription

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

### Dose

	Standard Risk	High Risk
CTV CSA	36 Gy/CGE	36 Gy/CGE
CTV PF	NA	19.8 Gy/CGE (55.8 Gy/CGE cum)
CTV PT	18 Gy/CGE (54 Gy/CGE cum)	NA
M intracranial	NA	19.8 Gy/CGE (55.8 Gy/CGE cum)
M spine diffuse	NA	3.6 Gy/CGE (39.6 Gy/CGE cum)
M spine focal	NA	14.4 Gy/CGE (50.4 Gy/CGE cum)

Aimed overall treatment time  $\leq 45$  days.

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

Interrupt RT or switch to boost 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 radiotherapy should be interrupted and 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. 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 chiasm and nerves to max 55 Gy, the brainstem to max 60 Gy (the volume of the brain stem receiving > 54 Gy should be limited to 10 cc), spinal cord to 54 Gy, to the retina (eye) to less than 45-50 Gy, the cochlea to 30-45 Gy, to the pituitary and hypothalamus < 45 Gy.

### **Image guidance and robustness**

According to institutional policies.

### **Acute toxicity (up to 3 months after treatment)**

The most important acute toxicities of the craniospinal irradiation are bone marrow suppression, headache, nausea, dermatitis, alopecia and fatigue. During radiation, patients should be monitored carefully including weekly blood counts. Toxicity resulting from the higher dose region(s) include temporary focal deficits, which may necessitate treatment with steroids.

In case of photon therapy mucositis of the GI tract can be expected.

### **Late toxicity (months to years after treatment, irreversible)**

Whole brain irradiation can cause long term neurocognitive toxicity. The neurocognitive effects can vary in severity, ranging from mild concentration problems or short term memory loss to apathy and intellectual decline, and are not reported in great detail for the adult population.

Pituitary dysfunction can occur after dosis as low as 20 Gy, and survivors should be screened for endocrine disorders once a year.

Other long term side effects include hearing loss and fibrosis of back musculature.

In case of photon therapy reduced fertility, cardiovascular morbidity can be seen.

## **8.5 Chemotherapy: schedules and management**

### **8.5.1 Chemotherapy for standard risk medulloblastoma**

Adults with standard risk medulloblastoma will receive radiotherapy with concomitant and maintenance chemotherapy, but no neo-adjuvant chemotherapy.

#### **8.5.1.a Treatment overview**

All patients will receive 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. Post-radiotherapy (maintenance) chemotherapy will start after recovery from radiotherapy, preferably 4-6 weeks after the last radiotherapy fraction.

#### **8.5.1 b Dose and administration of vincristine during radiotherapy**

Vincristine 1.5 mg/m<sup>2</sup> 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<sup>2</sup> (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<sup>2</sup> (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<sup>2</sup> (1.5 mg maximum). Escalate to full dosage when symptoms do not recur.

**8.5.1.c 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.

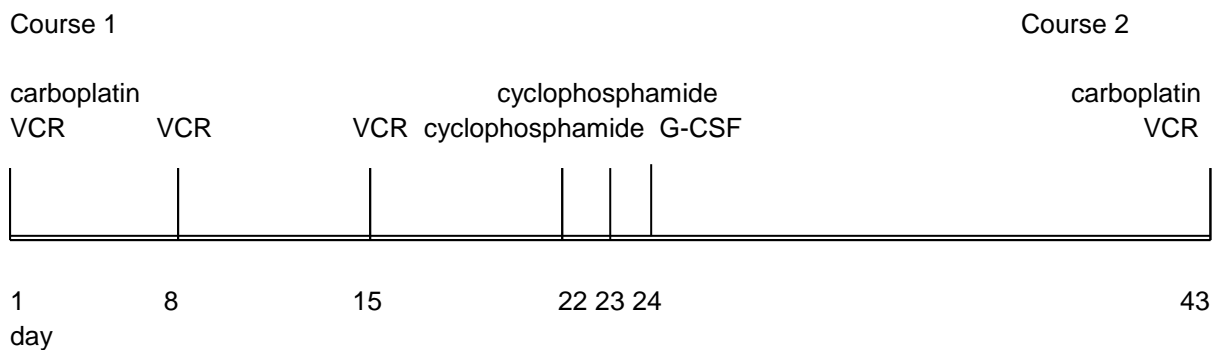
*Doses and overview*

Carboplatin (CBDCA): AUC 6 mg/ml, min d. 1  
 Vincristine (VCR): 1.5 mg/m<sup>2</sup> (maximum dose 2.0 mg) d. 1, 8, 15  
 Cyclophosphamide (CPM): 750 mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> will be administered, either in two doses of 375 mg/m<sup>2</sup> 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  $\geq 2$  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/m<sup>2</sup>) 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/m<sup>2</sup> (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<sup>2</sup> (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/m<sup>2</sup> (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.

## **8.5.2. Chemotherapy for high-risk medulloblastoma**

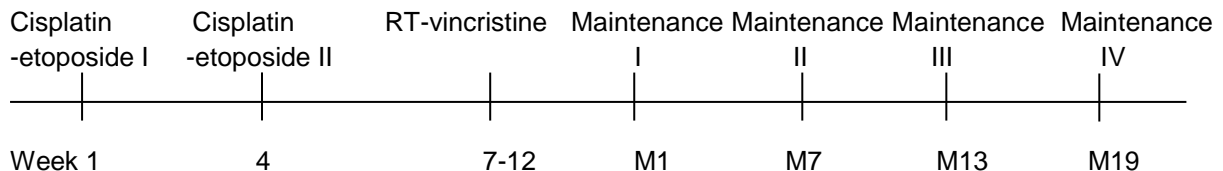
### **8.5.2.a Treatment plan overview**

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.

### **8.5.2.b Neoadjuvant courses**

#### ***Neoadjuvant doses***

Cisplatin 80 mg/m<sup>2</sup> d.1 IV  
Etoposide 100 mg/m<sup>2</sup> 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 orgametril in case of grade 3-4 thrombopenia (i.e. platelets < 50 x 10<sup>9</sup>/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 mg/m<sup>2</sup> 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.

#### **8.5.2.c Chemotherapy during radiotherapy**

see 8.5.1.b

#### **8.5.2.d Maintenance Chemotherapy**

See 8.5.1.c

#### **8.5.2.e Recommended observations during protocol treatment**

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

## **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. Imaging will consist of cranial MRI only unless other localizations were present at presentation or new symptoms prompt additional or more extensive imaging.

## 9 Required clinical observations

Table 1. Required observations

Observation	Post-operatively	Prior to each neo-adjuvant CT*	Prior to RT	During RT (weekly)	During maintenance CT	After maintenance CT <sup>4</sup>	Follow-up <sup>5</sup>
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 <sup>6</sup>	X ≤ 72 hrs of operation		X		Before start [and in case of residual disease after RT: also after 2 <sup>nd</sup> maintenance course]	X	X
MRI – spine <sup>6</sup>	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 <sup>1</sup>	X	X	X		Every 3 weeks	X	o.i.
Renal function <sup>2</sup>	X	X	X		Every 3 weeks	X	o.i.
Electrolytes <sup>3</sup>	X	X	X		Every 3 weeks	X	o.i.
PA review	X						

\*high risk patients only

<sup>1</sup> Bilirubin, ASAT, ALAT, gammaGT and alkaline phosphatase

<sup>2</sup> Creatinine and creatinine clearance calculation (or GFR)

<sup>3</sup> Sodium, potassium

<sup>4</sup> 0-14 days after day 21 of cycle 4

<sup>5</sup> 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

<sup>6</sup> 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**

Patients will be registered prospectively as described above in section 7: Registration.

All further data will be collected retrospectively 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.

All CRF entries must be based on source documents.

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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 punt als de complete zin goed is) .../1

### 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 punt wanneer de zin betekenis heeft en een onderwerp en een lijdend voorwerp heeft)

.../1

**Constructieve praxie**

11. “wilt u deze figuur natekenen?”  
(1 punt wanneer de figuur correct is nagetekend)  
(Er moet een vierkant te zien tussen de twee vijfhoeken)

.../1



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  $\beta$ -catenin mutations and MYC amplification status)
- Optional: Electron-microscopy; some small tumor fragments may be fixed for electron-microscopic studies (e.g. in glutaraldehyde)
- Samples may be stored locally until transported in bulk.

- **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 locally

- **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. Samples may be stored locally at -80C until transported in bulk.