Amendment to Treatment Protocol Medulloblastoma in Adults
Regarding Chemotherapy in Standard Risk Patients

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**Introduction and rationale for the amendment**

In the 2010 and January 2017 versions of the “Medulloblastoma in Adults” treatment protocol it is concluded that the evidence for treating standard risk adult medulloblastoma patients with chemotherapy is insufficient, therefore, chemotherapy was advised only for high-risk patients. More recently a number of papers have addressed this issue and prompted this amendment, even though none were randomized prospective studies. The full protocol will also be updated but since that will take longer, the amendment will function in the mean time.

**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. (Franceschi et al., 2016) 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. (Friedrich et al., 2013)

Kocakaya et al performed a meta-analysis of studies regarding adult medulloblastoma. (Kocakaya et al., 2016) 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). (Kann et al., 2017)

**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. (Taylor et al., 2012) 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. (Moots et al., 2016) 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. (Kortmann et al., 2000)

**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.


