During the last 20 years, pilot studies and randomized trials have been performed in medulloblastoma. Indications of chemotherapy can now be given according to the extension of the disease at diagnosis and also according to the age of the patient.

**Average risk medulloblastoma patients**
The SIOP III trial compared EFS for patients with an average risk medulloblastoma treated with standard (36-56 grays) craniospinal irradiation alone and patients who received vincristine, carboplatin, cyclophosphamide and etoposide before standard craniospinal irradiation. The EFS probability at 5 years for the group that received chemotherapy and radiotherapy was 73% whereas that for the group that received only radiotherapy was 60% (p=0.04).

However, it is admitted that in average risk medulloblastoma patients the dose of irradiation can be reduced at 23.4 grays to the craniospinal axis and 54 grays to the posterior fossa when effective chemotherapy is delivered. A pilot study was performed, delivering weekly vincristine concurrent to reduced-dose irradiation with eight cycles of adjuvant chemotherapy consisting of lomustine, cisplatin, and vincristine delivered after the completion of irradiation. The PFS of 65 patients aged 3 to 10 years was 79% at 5 years. The French M-SFOP 93 study delivered two courses of 8 in 1 chemotherapy and two courses of etoposide and carboplatin before reduced-dose craniospinal irradiation. The 5-year RFS of the 136 included patients was 64% (+/-8%).

The treatment related late complications remain of major concern in these patients and the current SIOP IV study compares the early and late toxicity of hyperfractionated radiotherapy with that of conventional irradiation; in both arms the patients receive a chemotherapy consisting of lomustine, cisplatin, and vincristine.

**High risk medulloblastoma patients**
Historically high-risk medulloblastoma patients treated with craniospinal radiation therapy alone had a 5-year PFS of 20-40%. A variety of chemotherapy regimens have been attempted to improve this outcome.

Fifteen patients with M+ disease treated with radiotherapy and chemotherapy consisting of lomustine, cisplatin, and vincristine had a 5-year PFS probability of 67% (+/-15%). In a CCSG study 188 high risk medulloblastoma patients were randomly assigned to receive either 8/1 chemotherapy before and after standard dose craniospinal irradiation or weekly vincristine during craniospinal irradiation followed by eight cycles of lomustine, vincristine, prednisone. The 5-year PFS of the entire cohort was 54%. It was 63% for the group of patients treated with lomustine, vincristine and prednisone.

In a POG study 94 metastatic medulloblastoma patients were randomly assigned to receive three cycles of cisplatin and etoposide before or after irradiation; all patients subsequently received eight cycles of cyclophosphamide and vincristine. The 5-year EFS was 65%. At St Jude four courses of high dose cyclophosphamide, cisplatin and vincristine followed with stem cell rescue have been delivered after craniospinal irradiation. The 4-year EFS for high risk patients was 74%.

It is likely that more intensive chemotherapy can improve the prognosis of high risk medulloblastoma patients. In the mentioned studies patients with aisolated postoperative local residual or patients with M1, M2, M3 stages are not always clearly identified. Furthermore in these studies the dose of irradiation has often been increased and it is difficult to know the respective rôle of chemotherapy and irradiation. Further investigative studies are mandatory.
Young children

Sequelae from tumor and its treatment, especially craniospinal irradiation, are more severe in young children. For these reasons, different approaches have been explored using prolonged postoperative chemotherapy in order to delay or avoid irradiation in this age group.

In the Baby POG1 protocol, 62 children less than 3 years of age receive postoperative chemotherapy and delayed craniospinal irradiation after the age of 3. The 5-year PFS and OS are 31% and 39% respectively.

It is now clear that the initial extension of the disease is a very strong prognostic factor when the place of radiation therapy is reduced.

It has been shown that irradiation can be avoided in patients who had a complete surgical resection and no metastases. In these new approaches the role of salvage treatment for progressing patients before irradiation is important and in the French study the place of high dose busulfan and thiotepa with stem cell rescue followed by an irradiation restricted to the posterior fossa has been developed. In this study, patients who have a surgical complete resection has a 41% 5-year EFS and a 79% 5-year OS.

For patients with metastatic disease at diagnosis investigative protocols are currently evaluated.

The evaluation of the long term sequelae in these patients is mandatory as they may develop complications related to these new approaches, for instance long term complications of high dose agents or leukoencephalopathies due to intra ventricular methotrexate as it is used in the German protocol.

References

5. SFOP TC 94