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Chemotherapy of Medulloblastoma in Children

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1. Introduction

Medulloblastoma is one of the most common childhood tumour of the central nervous system. During the past years several researchers dealt with its aetiology, pathology and therapy: surgical-, radio- and chemotherapy. The objective of the present chapter is to review the chemotherapy and we shall present our results and the few clinical data about the targeted therapy.

2. Incidence

Tumours of the central nervous system (CNS) are the second most common childhood malignant diseases after hematological malignancies. The incidence is similar in the different developed countries: in Europe is 29.9/million (1978-1997), in USA 30.7/million (1992-2006). However, the highest incidence is registered in Hungary and the Scandinavian countries. In Hungary the incidence was 37.41/million between 1999 and 2008 and 43.9/million in 2009. The cause of this high incidence in Hungary is unknown (Gupta & Banerjee et al, 2004; Hauser et al., 2003; Kaderali et al., 2009; McNeil et al., 2002; Peris-Bonet et al., 2006; Pizzo & Poplack, 2011). Astrocytomas and medulloblastoma are the most frequent among childhood CNS tumours.

3. Prognostic factors

The prognostic factors are especially important in risk group assignment of brain tumours, because the increased intensity of treatment in high risk cases has much more side effects, than the therapy of the average risk patients.
The most frequently used prognostic factors in the past were: the size of the tumour, the metastases including the tumour cells in the spinal fluid 2 weeks after the surgery (Chang (T_{1-4}; M_{0-3}) (Laurent et al., 1985) and the extent of the surgical intervention (Albright et al., 1996). Later the age and the histology of tumour were also introduced (Ellison, 2010; Giangaspero et al., 2006; Packer et al., 1994). According to several publications residual tumour mass greater than 1.5 cm^2 after the surgical intervention, the presence of metastases, age younger than 3 years are unfavourable prognostic factors (Albright et al., 1996; Chang et al., 1969; Eberhart et al., 2002; Jenkin et al., 2000; Klesse & Bowers, 2010) The histology of the tumours (desmoplastic/nodular, classic, large cell/anaplastic) is an important, independent prognostic factor too, which was proved by Rutkowski et al. in a study of 260 young children (Rutkowski et al, 2010).

Several biological factors have prognostic value (ERBB2, TP53, PDGFRA, TRKC, CDK6, α and β-catenin). The prognostic role of the aberrantly expressed miRNAs is yet under investigation (Birks et al., 2011). However, the most reliable and independent prognostic factor is microarray gene expression profile (Aihara et al., 2010; Fernandez-T et al., 2004; Pizzo & Poplack, 2010; Rutkowski et al., 2010; Tabori et al., 2010). Four distinct groups were established by Northcott (Northcott et al., 2010): Wnt, Shh, C and D. Wnt and Shh was previously described as the wingless type and sonic hedgehoge pathway involvement in the tumorproliferation (Wechsler-Reya & Scott, 2001). In Group C and D a clear molecular pathway involvement could not be clearly identified. The new classification does not follow the classical pathological classification (as classic, desmoplastic, large cell/anaplastic subtypes) and it shows some association with age and metastatis production. The separation of these groups by immunohistochemical analysis only was a great step toward the everyday practice in using this classification as prognostic factor. Group Wnt, Shh, C, D are characterized by the presence of CTNNB1, GLI1, NPR3 and KCNA1 proteins. Wnt and Shh groups seem to need less intensive therapy with outstanding survival and less side effects.
Most centres use the following prognostic factors: the young age (<3 years) residual tumour after surgery, the metastases, the histology and in some centres the MYCC/MYCN amplification and the expression of ERBB2 (Pizzo & Poplack, 2010; Rutkowski et al., 2010; Takei et al., 2009).

4. Therapy

The therapy of the malignant tumours is surgical, radio- and chemotherapy, similarly to other childhood tumours. In brain tumours the most important is the surgical therapy and is curative if it is radical ablation and no metastases are found. However, the surgical therapy is hindered by the localisation of the tumour and the difficulty in differentiating the tumour from the normal tissues.
The radiotherapy of medulloblastoma is an important and effective part of therapy. However its use is limited by the irreversible damage caused in children, which is specially serious in young children and infants causing serious neurocognitive damage (Fouladi et al., 2005; Mulhern et al., 2004). Hence it should be avoided in children less than 3 years old in spite of their lower survival rate (Johnston et al., 2009). It is remarkable, that the increased intensity of the chemotherapy enabled the decrease of the craniospinal radiation dose in the average risk cases without the worsening the survival to 23.4Gy along an unchanged focus-dose (55.8Gy) which decreased significantly the late side-effects (Mulhern et al., 1998; Packer et al., 1999, 2006).

4.1 Chemotherapy

It is difficult to compare the different studies to select the optimal treatment protocol due to the non-uniform prognostic factors, the lack of reliable – centrally checked – patho-histological and molecular diagnostics and the often low number of patients and duration of observation. Hoff (von Hoff et al., 2009) and collaborators published the results of a 10 years long follow up. In their patient-group 12% of relapse occurred five years or more after the end of therapy.
An important obstacle of the chemotherapy is the blood-brain barrier despite the fact that the tumour breaks through the barrier when growing. There were several trials for increasing the possibility of passing the barrier but without any provable result. (Kobrinsky et al., 1999; Prados et al., 2003)

The additive curative effect of chemotherapy after surgery and radiotherapy was proved by a prospective, multicentric, randomised trial in 1990 (Evans et al., 1990; Tait et al., 1990). In the beginning vincristine and the nitrosoureas were applied, which are still used in several protocols for the treatment of medulloblastoma. However, the usefulness of vincristine was recently challenged because vincristine could not be detected in the spinal fluid in measurable concentration after 1,5 mg/m² i.v. bolus injection. Later more and more chemotherapeutic drug combinations have been used. The key agents are the nitrosoureas (lomustine, carmustine), cyclophosphamide, vincristine and the later used cisplatin, carboplatin, and etoposide (Mueller & Chang, 2009). Some protocols apply ifosfamide alternating with cyclophosphamide (Park et al., 2010). The application of methotrexate is limited not only because of its potential side effects, but also because it can be used only before radiotherapy, however, some protocols described rather good results in cases when no irradiation was done (Bleyer, 1981; Chi et al., 2004; Fossati-Bellani et al., 1990; Rutkowski et al., 2005). The alkylating oral drug dibromdulcitol was an excellent substance for the treatment of medulloblastomas because its favourable pharmacokinetic properties in the spinal fluid and its tolerable toxicity (Paál et al., 1994; Schuler et al., 1988, 1992). Later in spite of the good clinical results the drug became unavailable. However, this may be partially substituted by temozolomide, but there is no study yet, which proves its efficacy in medulloblastoma.

The increased arsenal of the chemotherapeutics and the higher intensity of the treatment resulted in improved survival. In cases with favourable prognosis the survival rate is already over 80%, and around 70% in cases with unfavourable prognosis (Gottardo & Gajjar, 2008). However, the toxicity of the treatment increased, too. Therefore, besides improving survival rates reducing early and late toxicity are also important. In the future a less toxic treatment is expected thanks to the development of the targeted molecular therapy based on tumour-biological knowledge.

The most important criteria are:

1. the optimal timing of the chemotherapy
2. the most effective combination of cytostatics
3. sufficient intensity and length of the chemotherapy
4. a tolerable toxicity of the drugs used in the protocol.

Some trials proved that the chemotherapy given before and after the irradiation (sandwich therapy) is disadvantageous; the survival is shorter if the radiotherapy is longer than 50 days (von Hoff et al., 2009; Taylor et al., 2003). Hence the radiotherapy should be given as early after the surgery as it is possible (Bailey et al., 1995; Kortmann et al., 2000). During the radiotherapy several protocols contain the administration of vincristine (von Hoff et al., 2009; Packer et al., 1994, 1999) or in one protocol carboplatin (Jakacki et al., 2007). A preoperative chemotherapy is applied in several paediatric tumours, because it decreases the size of the tumour and facilitate the tumour removal. Hence it would be reasonable to introduce it in huge chemosensitive brain tumours, too (Schuler et al., 1993). The preoperative chemotherapy is feasible and safe in children with high risk medulloblastoma according to some pilot trials (Di Rocco et al., 1995; Grill et al., 2005; Schuler et al., 1993). However, it is not applied in the practice up to now.

In most protocols a combination of vincristine, a nitrosourea (lomustine or camustine) and a platinum compound (cisplatin or carboplatin) is used. In several protocols cyclophosphamide is used instead of nitrosourea because of the good antitumour effect and

shorter bone marrow toxicity of cyclophosphamide, (von Hoff et al., 2009; Mueller & Chang, 2009; Packer et al., 1994) and in some treatment protocols etoposide is also added to this combination (Chi et al., 2004; Dhall et al., 2008; Hauser et al., 2009).

Our protocol for average risk cases begins with three intrathecal triplet (methotrexate, ara-C, prednisolone) and VECp-block (vincristine, cyclophosphamide, etoposide) after the surgery. This is followed by radiotherapy (5^{th} - 11^{th} week). During the radiotherapy the patients get weekly vincristine. 2 weeks after the radiotherapy chemotherapy is continued by vincristine — etoposide — cyclophosphamide/ carboplatin; vincristine — cisplatin — etoposide / BCNU blocks until the 73^{nd} postoperative week.

In high risk cases autologous stem cell transplantation is made after the 40^{th} postoperative week instead of maintenance therapy. If a residual tumour is present it is removed by a "second look" surgery before the transplantation.

In children less than 3 years old the therapy is similar to that in high risk cases, except that no radiotherapy is given and the stem cell transplantation is made as soon as no tumour is seen by MRI. Radiotherapy is given only, if the tumour is still present after the age of three years.

The toxicity of our protocol was tolerable; and there was no therapy related mortality. After 31 months the overall survival was 79% in the average risk patients and 63% in high risk patients.

The best therapeutic results in average risk cases were achieved by the multicentre trial HIT'91 (von Hoff et al., 2009). The overall survival in patients without metastasis was 91% after 10 years. After the removal of tumour a combination of radiotherapy and vincristine was applied, which was followed 6 weeks later by 8 cycles with lomustine (CCNU), vincristine and cisplatin. Packer et al., described a 86% survival after 3 years follow up by a similar regime (Packer et al., 1999). A 93% survival was published by Strother et al. (2001) (Strother et al., 2001) with a more aggressive therapy. They administered 4 cycles of high dose chemotherapy after surgery and radiotherapy (cyclophosphamide, cisplatin, and vincristine) followed by auto-transplantation after each cycle.

The results in high risk cases are more consistent ranging from 34 to 40% across studies (Mueller & Chang, 2009). However, Chi et al. achieved 60% overall survival after 3 years by 5 cycles of vincristine, cisplatin, etoposide, cyclophosphamide and methotrexate given after surgery followed by myeloablative chemotherapy with autologous stem cell rescue (Chi et al., 2004). The results of Gajjar et al. (Gajjar et al., 2006) was similar: 83% event free survival in average risk patients and 70% in high risk cases after 5 years.

Good survival was achieved by the COG99701 study (Jakacki et al., 2007). They administered vincristine and carboplatin during the radiotherapy in patients with metastatic medulloblastoma. 6 weeks later the patients received 6 courses of monthly cyclophosphamide and vincristine. The overall survival after 4 years was 81%.

The increased intensity of therapy resulting a longer survival has more late side effect. Hence the stratification of the tumours according to prognostic factors into average or high risk group is important.

In cases of medulloblastomas of children less than 3 years old radiotherapy should avoid. The most favourable approach after surgery is the myeloablative consolidation chemotherapy after conventional induction therapy which may result 60% overall survival after 3 years (Chi et al., 2004). The result of the intensive chemotherapy depends both on the histologic type and the presence of the residual tumour (Dhall et al., 2008). Those trials

which combine the systematic and intraventricular chemotherapy had better results only among children without metastases and residual tumour (Zeltzer et al., 1999)
The survival of relapsed patients is very poor, especially in patients who had already received radiotherapy and/or auto-transplantation (Butturini et al., 2009). However, there are several trials by intensive chemotherapy and transplantations. (Park et al., 2010). The prolongation of the survival with metronomic therapy was possible in some studies. The metronomic therapy is referred to as low-dose chemotherapy or antiangiogenic chemotherapy (Kieran et al., 2005; Privitera et al., 2009; Sterba et al., 2010). Recently, the combination of the alkylating agent temozolomide with etoposide, which is a topoisomerase II inhibitor was found to be efficacious in prologing the survival in relapsed medulloblastoma. (Wang CH et al., 2009; Ruggiero A et al., 2010). However, the study of the application of the metronomic therapy for a longer time after the about 6 months long intensive and maintenance therapy in the primordial therapy of high risk cases may be justified too due to the occurrence of late relapses.
The toxicity of the previously described chemotherapeutic modalities depends on their intensity independent from the well known side effects of the radiotherapy. The most common and most serious ones are the acut myelotoxic effect and infections. Some authors describe yet anorexia, nausea, diarrhoea, pain and hypokalemia.
Better comparability of the different therapeutic modalities, improvement of results and the decrease of side effects are expected from the application of the molecular biologic procedures in the stratification and tailored therapy.

4.2 Targeted treatment

There is still not any new, successful, widely accepted therapeutic approach which can substitute or at least complement the standard treatment of medulloblastoma.
Presently, targeted treatment exists only in SHH group among the four groups described by Northcott et al. (2010). In this group tumor proliferation is attributed to the lack of inhibition of SMO protein by loss of function of inhibitory Patched protein (Ptch1) or activating mutation of SMO. SMO inhibitors, as cyclopamin, IPI-926 and the orally available GDC-0449 inhibit hedgehoge pathway. The latter went through a Phase 1 study, resulting in a 3-month long transient well-defined remission achieved in one 26-year old patient with proven Ptch1 mutation (Rudin et al., 2009).
Before the establishment of the new subgroups of medulloblastoma, there were also other molecularly targeted treatments. In some cases they were administered to some individual patients. Common feature of these treatments was the transient success, which finally turned into progression. The background of the progression could be the mutation of the targeted receptor or other involved proteins.
One of these targets were somatostatin receptors (SSTR), which were recognized in medulloblastoma cell surface in late nineties of the last century (Fruhwald et al., 2004; Guyotat et al., 2001;). Several attempts were to bind radioactive isotope to its agonist octreotide or its derivates, providing localized, targeted radiotherapy, which did not show extra survival advantage above conventional irradiation, (Beutler et al., 2005). Somatostatin analogues themselves through SSTR receptors may inhibit cell proliferation. Medulloblastoma express high amount of SSTR based on Octreoscan examination (Muller et al., 1998). Only one patient was described who received only octreotide without radioactive isotope, and was a long term survivor (Glas et al., 2008).

Receptor tirozin kinases another possible target group. There are several drugs targeting these receptors which are also expressed in a certain part of medulloblastoma (ErbB2, PDGFR). Their increased expression usually results in worse survival and increased metastatic ability (Gilbertson et al., 1995; Gilbertson & Clifford, 2003). The most experience is reported with imatinib, which proved to be effective in vitro, however, in vivo successful human experiences are still missing (Abouantoun & MacDonald, 2009). This may be partially caused by their hindered penetration through blood brain barrier.

Another possible therapeutic approach is the inhibition of histon deacetylases (HDAC). Acetylation of histones' amino terminal tails by histon acetyltransferase relaxes the chromatin for transcription, and removal of acetyl groups by HDAC repress transcription (Roth et al., 2001; de Ruijter et al., 2003). Histon hypoacetylation and inappropriate transcriptional repression are hypothesized to be a key contributor to the development of human cancers (Marks et al, 2001; Marks & Dokmanovic, 2005). HDAC inhibitors have been shown to cause pleiotropic effect on human cancer cells, including apoptosis, cell cycle arrest and differentiation (Su et al., 2011). Valproic acid (VPA), an anticonvulsive drug is one of the recently discovered HDAC inhibitors. There is one published Phase 1 study in pediatric CNS tumors, 2 patients with medulloblastoma were included (Su et al., 2011). The treatment was well-tolerated, however response was not observed among this little cohort of patients with medulloblastoma.

Another promising area in the treatment of medulloblastoma could be the administration of retinoic acid (RA). RA has been shown to have anticancer efficacy in a variety of cancers. Retinoic acid is commonly used in the treatment of certain childhood cancers. It is a drug with protean effects including cytodifferentiation, apoptosis, and inhibition of angiogenesis to name a few (Miller, 1998). RA has been shown in preclinical models to cause apoptotic cell death in medulloblastoma by promoting BMP-2 transcription (Hallahan et al., 2003). This results in production of soluble BMP-2 protein that induces p38 MAP kinase phosphorylation and ultimately apoptosis (Spiller et al., 2008). Recently a phase 3 trial has been opened to treat medulloblastoma with RA.

There are several different approaches to try to kill medulloblastoma cells by means of immunotherapy. Only some of them were introduced in small series of pediatric patients with limited success. In the last decades of the twentieth century application of lymphokine actived killer (LAK) cells directly administered intrathecally with co-administration of human recombinant IL-2 for patients with recurrent disseminated medulloblastoma was published. Some of the limited number of patients showed long term survival (Okamoto et al., 1988; Silvani et al., 1994).

Another method is the adoptive transfer of tumor-specific cytolytic T cells to the tumor bed and cerebrospinal fluid. This is an attractive strategy, but limited in its clinical application owing the paucity of defined antigens consistently expressed by medulloblastoma. So far only two in vitro animal medulloblastoma xenograft models have been published. One is targeting IL13Receptor-alpha2 by genetically modified CD8+ citotoxic T-cells expressing an IL13-zetakine chimeric immunoreceptor (Stastny et al., 2007). The other model is targeting HER2 expression, which is a feature of the malignant phenotype of medulloblastoma (Gilbertson et al., 1995). Recruiting the cellular arm of the immune response to HER2 positive tumor cells, genetically engineered HER2-specific T-cell with antigen binding property and lytic capacity were created. Adoptive transferred HER2-specific T-cells were administered in SCID mouse orthotopic medulloblastoma xenograft, which resulted in sustained regression of HER2 positive medulloblastoma, which might have resulted in a

promising immunotherapeutic approach (Ahmed et al., 2007). Phase 1 study of adoptive transfer of tumor-specific cytolytic T cells exists in patients with recurrent glioblastoma multiforme and neuroblastoma.

Another immunotherapeutic method which is already investigated in human patients with recurrent medulloblastoma is based on dendritic cell-based tumor vaccination. Dendritic cells are the antigen presenting cells, which are present in central nervous system exclusively. Autologous mature dendritic cells loaded with tumor lysates derived from autologous, resected medulloblastomas were injected subcutaneously in 5 patients with medulloblastoma. Although the treatment was safe, no response was observed in any patient (Ardon et al., 2010).

Natural killer (NK) cells display the highest cytolytic activity against tumor cells, and are considered suitable candidates for adoptive immunotherapy to treat cancer patients. Castriconi et al showed that in vitro medulloblastoma cell lines express ligands for activating NK-receptors, which makes medulloblastoma highly susceptible to NK-mediated cytolysis (Castriconi et al., 2007). However, human studies using NK-cells in medulloblastoma are lacking at this moment.

5. Conclusions

The therapy of medulloblastoma has changed during the last few decades which resulted in the improvement of the long-term survival up to almost 80%. This is due to the complex chemotherapy beyond the improved surgical and radiotherapeutical techniques. After cyclophosphamide, nitrosoureas and methotrexate more effective drugs would be applied in the treatment of medulloblastoma: carboplatin, cisplatin, etoposide and ifosfamide. In resistant or relapsed cases several other drugs are used, too, as Temozolomide. The preoperative therapy in spite of the encouraging pilot studies could not become a general practice. The high dose chemotherapy with autologous stem cell rescue seems to be effective to eradicate the remained tumour cells in high risk cases. The prolongation of the chemotherapy with cytostatic drugs in low doses and/or antiproliferative agents (retinoic acid, valproic acid, antiangiogenic agents) seems to be effective to prolong the remission in incurable cases. The chemotherapy is especially important in very young children (less than 3 years old) because of the serious late side effects of radiotherapy. The targeted molecular therapy is promising, however, in spite of the several clinical studies the effectivity of molecular therapy is not proved yet in phase III. studies.

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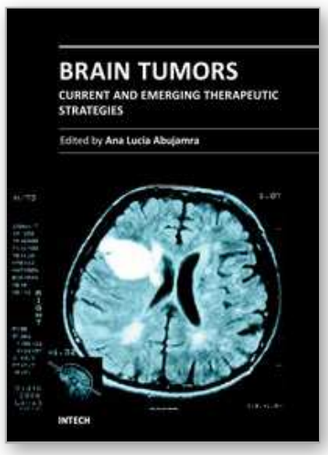
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