Medulloblastoma: Perspectives in therapy with molecular subgroup-specific differences

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SUMMARY: Molecular subgrouping signifies a new era in medulloblastoma treatment. The four molecular variants of medulloblastoma (WNT, SHH, Group 3, Group 4) show distinct characteristics. Studies on large groups of medulloblastoma patients demonstrated the clinical and molecular differences between these groups. These insights have a huge impact on better understanding of medulloblastoma, and provide many possible opportunities in treating this disease. Surgery is still the cornerstone of treatment, but one day it could perhaps become obsolete, if biological therapy evolves in a way where it would be the most cost- and overall effective, and the least toxic modality of treatment. Sonidegib, an inhibitor of a Shh signaling pathway component is the first step in that direction, and is currently undergoing phase III clinical trials. Differences regarding molecular subgroup could also be employed in radiation therapy protocols. This article is a synthesis of recent achievements in medulloblastoma therapy, with special attention devoted to subgroup-specific differences.

KEYWORDS: medulloblastoma, molecular subgroup, treatment, therapy, perspectives

Medulloblastoma is the most common malignant CNS tumor in children and accounts for about 15-20% of pediatric CNS malignancies, with an incidence rate of 0.49 per 100000 person-years. It is less common in the adult population and comprises 2% of adult CNS malignancies. The incidence of medulloblastomas in adults is 0.05 per 100000 person-years.[1]

It is an infratentorial tumor of embryonal origin, classified as grade IV by the WHO, and includes five histological subtypes: classic medulloblastoma, desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, large cell medulloblastoma, and anaplastic medulloblastoma.

Some histologic features (such as presence of nodules/balls and fine fibrillary stroma) signify better 5-year survival rate while others, e.g. necrosis, high rate of anaplasia and prominent nucleoli, indicate a worse prognosis. [2] The Chang staging system for medulloblastoma is based on spreading (T1-T4) and metastases (M0-M4). A risk stratification based on clinical criteria (patient's age, extent of resection and metastasis stage) divides patients into two groups: average-risk and high-risk. The average-risk group involves patients over 3 years of age, without metastatic disease (M0) and with a surgical residue smaller than 1.5 cubic centimeters. All other patients are thought to have high-risk disease. [3]

The histologic and clinical parameters influence the extent of chemotherapy and radiotherapy applied in treating a medulloblastoma patient. It was noted that the correlation of these parameters with the actual severity of the disease is not high enough. The consequence of this disconcordance is that some patients, with a more severe type of medulloblastoma than diagnosed, get under-treated and vice versa, resulting in disease recurrence and unnecessary amount of side effects, respectively.[4]

Due to the need for better severity stratification, additional characteristics of the tumor were explored to identify novel markers. Four molecular subgroups were identified: WNT, SHH, Group 3 and Group 4. The WNT subgroup carries the best, and Group 3 the worst prognosis, while SHH and Group 4 have an intermediate one.[5]

The goal of this article is to analyze recent achievements in the individualization of therapy for medulloblastoma patients, through the implications of the molecular subgroup on surgical treatment, chemotherapy and radiotherapy.

Subgroup-Specific characteristics

In 2012, M. Kool et al. performed a meta-analysis on 550 medulloblastoma patients from seven studies to distinguish age and sex representation, metastatic potential, genetic abberations and prognosis between the four molecular subgroups. [6] Overall, the most common subgroup was Group 4 with 34% of total cases. SHH was slightly more common than Group 3 (28% vs. 27%). The WNT subgroup was represented by 11% of cases. Considering gender distribution, medulloblastoma occured 1.5 times more frequently in males than in females. WNT and SHH subgroups displayed a male:female ratio of 1:1, whereas in Group 3 and Group 4 the ratio was 2:1.

Patients were distributed into three age groups (infants, aged <4 years; children, from 4-16 years; and adults aged >16 years) which showed distinct subgroup distribution, metastasis occurence and overall prognosis. The median age for all patients was 7.3 years, with a range from 0.3 to 52 years. The infant group represented 21% of all cases, 67% of all patients were children and 12% were adults. The WNT subgroup incidence peaked at ages 10-12 and 16-18, without almost any ocurrence in infants. The SHH subgroup had a bimodal distribution, with occurence in infants and adults, bypassing the children group. Group 3 was most common in children under the age of 6, showing a steady decline with the increase in age. Group 4 was mostly represented in the children group.

Metastases were most commonly found in Group 3 and Group 4 (30% and 31% of tumors in these groups, respectively), par-

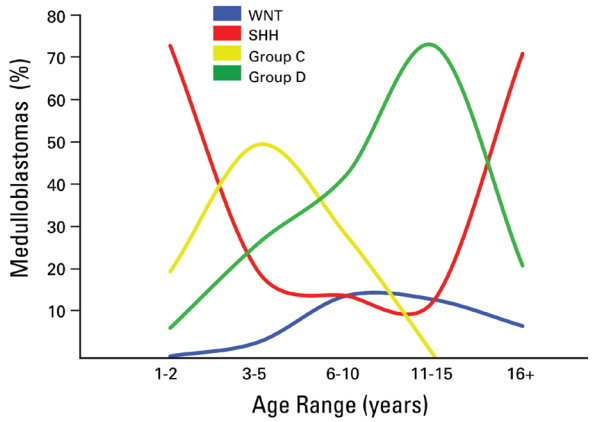

Fig 1. Image from: Nortchcott PA, Korshunov A, Witt H et al. Medulloblastoma Comprises Four Distinct Molecular Variants. J Clin Oncol. 2011; 29:1400-1407 doi:10.1200/jco.2009.27.4324

ticularly in the infant population of these subgroups (47% and 36%). In the SHH subgroup metastases occured in 17% of infants and 22% of children, while none occured in adults. The WNT subgroup was the least likely to develop metastatic disease (9%), and all affected patients were children.

Molecular subgroups also showed differences in overall survival. The WNT subgroup signified the best prognosis, with a 95% 5-year and 10-year overall survival in children and a 100% 5-year overall survival in adults. SHH carried a better prognosis in infants (77% 5-year and 10-year overall survival) than in children (68% 5-year overall survival and 51% 10-year overall survival) and adults (75% 5-year overall survival and 34% 10-year overall survival). Group 3 was associated with the worst outcome, with infants having a 45% 5-year overall survival and 39% 10-year overall survival and children having a slightly better 58% 5-year overall survival and 50% 10-year overall survival. Group 4 showed a homogenous 10-year overall survival around 60 % in all age groups.[6]

Oncogene amplifications were also shown to be subgroup-specific. Nuclear beta-catenin overexpression, which is a characteristic of the WNT subgroup signified an excellent prognosis. MYC amplification was mostly identified in Group 3 tumors and was associated with a dismal prognosis. In Group 4 and the SHH subgroup, the most characteristic oncogene amplification was that of MYCN, and was also an indicator of worse prognosis.[6]

Implications on surgery

Location of medulloblastoma in the brain is also subgroup-specific, because of distinct developmental origins of medulloblastoma cells. A study by P. Gibson et al. analysed the association between the molecular subgroup of medulloblastoma and its location by using magnetic resonance imaging, intra-operative reports and mouse models of human medulloblastoma. The results of the study proved the general belief, that medulloblastomas arise only in the cerebellum, to be wrong. WNT subgroup tumors were shown to emerge from the dorsal brainstem, while SHH subgroup tumors originate from the external granule cell layer of the cerebellum, and are located within the cerebellar hemispheres.[7] The cells of origin of Group 3 tumors are the postnatal cerebellar progenitor cells.8 It is now hypothesized that SHH subgroup tumors may arise from the brainstem as well.[9]

The surgical approach to medulloblastomas is the midline suboccipital craniotomy, with a C1 laminectomy if the tumor spreads inferiorly, which is rare. If the tumor extends superiorly, the inferior part of the cerebellar vermis is resected, whereas if the tumor extends more laterally (to the foramina of Luschka), the resection of the vermis can be avoided by using the telovelar approach. The tumor is excised maximally, with residue under 1.5 cubic centimeters considered to be prognostically equal to total excision, allowing the tumor mass strictly adhered to the brainstem to be left behind. [10]

Implications radiotherapy

After surgical excision of the tumor, all patients receive irradiation of the entire craniospinal axis, with dosage depending on risk group (average-risk group is given 23.4 Gy irradiation, whereas high-risk patients receive 36 Gy), and a boost of 54-56 Gy to the posterior cranial fossa. In children under the age of 3 radiotherapy is postponed or completely omitted, due to its devastating effects on the developing nervous system.[11]

A study of medulloblastoma recurrence, by Ramaswamy et al., has shown that different molecular subgroups display distinct recurrence patterns. It was demonstrated that none of the tumors showed a change in subgroup at the time of recurrence, putting an end to the hypothesis of the subgroup shift, in which SHH and Group 4 tumors were thought to transform into a more aggresive, group 3 tumor. Due to the low recurrence of WNT subgroup tumors leading to a small sample, data collected for this group was not statistically relevant. SHH tumors displayed almost invariably a local recurrence pattern, while Group 3 and Group 4 mostly recurred as metastases. These results imply that in SHH tumors emphasis should be put on local irradiation, with potential sparing of the neuraxis, whereas in Groups 3 and 4 craniospinal irradiation should be intensified. 8 Numerous clinical trials of WNT subgroup tumors have the goal to identify if the irradiation should be de-escalated, and to what extent, to maximally reduce side effects while still achieving remission.

Implications on chemotherapy

Chemotherapeutical management of medulloblastoma varies in different research groups and hospitals. Children under the age of 3 benefit from intensified, radiation-sparing chemotherapy, with or without stem cell rescue therapy. Older children and adults receive chemotherapy concurrently with radiotherapy. The most common protocols include the Children Cancer Group vincristine, lomustine, prednisolone (VCP) protocol, and the Pediatric Oncology Group protocol which utilizes vincristine, cyclophosphamide, etoposide and cisplatin. The

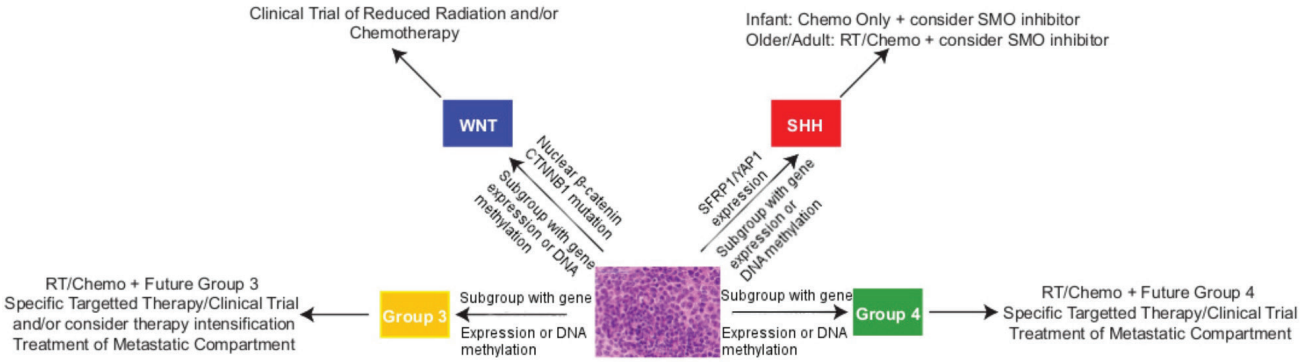

Fig 2. Image from: Adamski J, Ramaswamy V, Huang A, Bouffet E. Advances in managing medulloblastoma and intracranial primitive neuro-ectodermal tumors. F1000Prime Rep. 2014; 6: 56. doi: 10.12703/p6-56

consequences of chemotherapy are many, with endocrinologic defficiencies, hearing loss and neurocognitive deterioration among others.[12] Therefore novel agents are sought after to help decrease these treatment sequelae.

The most advanced steps in achieving effective, molecular subgroup-based therapy, have been taken in the SHH subgroup. Inhibitors of Smoothened, a receptor in the Shh signaling pathway have been synthesized (Vismodegib (GDC-0449) and Sonidegib (LDE225)). Sonidegib is currently in phase III trials.[13] Groups 3, 4 and the WNT subgroup lack specific biological agents that are involved in clinical trials at the moment (no such trials can be found on www.clinicaltrials.gov).

Discussion

Molecular subgrouping of medulloblastoma represents a giant leap in improving the care for medulloblastoma patients. The imminent issue is the fact that further advances in specifying different subgroups inside subgroups will lead to even smaller groups of patients, which will make the design of clinical trials very complicated.

Pharmacological therapy is the treatment modality that is expected to receive most benefits from molecular subgrouping of medulloblastoma. Advances are anticipated in identifying new molecular targets in each of the subgroups, with smoothened currently being the only target whose inhibitor is undergoing clinical trials. By reducing chemo- and radiotherapy side effects, biological therapy should bring substantial improvements in the quality of life of medulloblastoma patients, the same way Gleevec did in chronic myelogenous leukemia patients. The study of medulloblastoma recurrence patterns by Ramaswamy et al. has suggested some important alterations in radiotherapy protocols, which are subgroup specific. Future clinical trials are needed to find an optimal risk/benefit ratio of dosage and location of irradiation. Proton therapy, which employs protons as opposed to standard radiotherapy, which utilizes photons, is becoming widely used as it more precisely delivers radiation to the tumor site, sparing the healthy tissues. [14]

Subgrouping of medulloblastoma did not lead to differences in surgical excision of the tumor. The extent of resection should perhaps be reviewed to see if patients with more favourable prognoses (WNT subgroup) would benefit from less radical surgery if the tumor is located in very sensitive parts of the posterior fossa, such as the dorsal brainstem. New, supplementary methods are being developed, such as intra-operative, tumor-specific fluorescence agents which would increase the precision of surgical resection. The agent already tested in vitro is called hypericin and is derived from Hypericum perforatum (St. John's wort). It accumulates specifically in medulloblastoma cells and increases fluorescence intensity in a superior fashion than 5-aminolevulinic acid (5-ALA), used in high-grade gliomas. It is also photocytotoxic meaning it sensitizes tumor cells to photodynamic therapy which utilizes light of high intensity to destroy them.[15]

Conclusion

Molecular subgrouping of medulloblastoma substantially widened the perspectives in medulloblastoma treatment. It explained the age-specific differences in overall survival and in the potential for tumor recurrence and metastasis. Numerous molecular targets for biological therapy are being elucidated, which could eventually put an end to the use of highly toxic, non-specific chemotherapeutic agents. Subgroup specifics demonstrated implications, albeit minor, on radiotherapy and surgery as well. These new acknowledgements are paving the way for clinical trials whose aim is to eliminate toxicity and further increase overall survival.

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Meduloblastom- mogućnosti liječenja pomoću molekularnog grupiranja

Sažetak: Molekularno grupiranje označava novu eru u liječenju meduloblastoma. Četiri molekularne podgrupe meduloblastoma (WNT, SHH, Grupa 3 i Grupa 4) pokazuju značajne razlike. Studije velikog uzorka pacijenata oboljelih od meduloblastoma demonstrirale su kliničke i molekularne specifičnosti unutar tih podgrupa. Ova saznanja imaju veliki značaj u boljem razumijevanju meduloblastoma, pružajući mnoge potencijalne mogućnosti u liječenju ove bolesti. Kirurško liječenje tu još uvijek ima najznačajniju ulogu, no jednog dana bi moglo postati potpuno zamijenjeno biološkim lijekovima, nastave li se razvijati u smjeru u kojem bi postali ekonomski i medicinski najučinkovitiji, s istovremeno najnižom razinom toksičnosti. Sonidegib, inhibitor komponente signalnog puta Sonic hedgehog, predstavlja prvi korak u tom smjeru i trenutno je u trećoj fazi kliničkih ispitivanja. Razlike u molekularnim podgrupama bi također mogle biti korištene u izradi novih radioterapijskih protokola. Ovaj članak je sinteza nedavnih istraživanja mogućnosti liječenja meduloblastoma, sa posebnim osvrtom na razlike vezane uz molekularne podgrupe.

Ključne riječi: meduloblastom, molekularna podgrupa, liječenje, terapija, perspektive