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Where are we with Targeted Therapies for Medulloblastoma?

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Introduction

Medulloblastoma, the most common pediatric brain cancer, is no longer thought of as a single disease. It is now known to be is a heterogeneous tumor with four distinct molecular subgroups [1] which include wingless (WNT), sonic hedgehog (SHH), group 3 (V-myc avian myelocytomatosis viral oncogene homolog [MYC] amplified), and group 4. Histological characteristics, patient demographics, copy number aberrations, and prognosis differ between the groups. Current risk stratification, based solely on clinical features, defines high risk disease as tumors with dissemination, residual disease greater than 1.5 cm2, and age less than 3 years with the remainder being termed average risk. Five year overall survival rates with high risk medulloblastoma are up to 65%and can be greater than 80% in patients in those with average risk disease [2] using current standard-of-care multimodal therapy that includes surgery, craniospinal radiation and chemotherapy. Those with recurrent/relapsed disease do not have effective salvage treatment options and the prognosis for these patients is poor [3,4].

Medulloblastoma outcomes are better predicted by subgroup analysis rather than current risk stratification based purely on clinical features. Indeed the new molecular data will soon be incorporated into the next WHO classification of CNS tumors as has been recommended by the International Society for Neuropathology-Haarlem consensus guidelines for nervous system tumor classification and grading [5]. Classifying tumors using molecular data reveals that in many cases high risk patients are being overtreated while average risk patients are being undertreated. Additionally, craniospinal irradiation to the developing nervous system results in significant neurocognitive and neuroendocrine sequelae. Targeted therapy according to subgroup analysis has the potential to improve overall survival with less morbidity.

WNT Subtype

The study of turcot's syndrome, a rare heritable disorder, associated with colon cancer, glioblastoma multiforme or medulloblastoma has contributed to further understanding of this tumor [6]. The adenomatous polyposis coli (APC) gene has been shown to be mutated in this syndrome. APC is a component of the wingless (Wnt) pathway, which is involved in proliferation and the fate of neural progenitor cells [7]. The binding of the Wnt ligand signals to its receptor frizzled activates the WNT cascade which includes APC, glycogen synthase kinase 3β, Axin, and β-catenin. The WNT subgroup of medulloblastoma has the best prognosis of all the subtypes with overall survival exceeding 90% [8] thus current interest in is de-escalation of therapy in this group of patients.

A few key unique and highly specific mutations have been identified within the WNT group. More than 90% of WNT tumors harbor somatic mutations in the CTNNB1 gene, which encodes B-catenin. The majority of these tumors display monosomy 6 and this finding has long been associated with excellent prognosis [9-11]. DDX3X mutations are the second most common in this subgroup and are a potential therapeutic target in *in-vitro* studies [12] and TP53 mutations are found in approximately 12% [13]. A preclinical WNT model has been developed with lesions in CTNNB1 and TP53 and several WNT inhibitors are in Phase I/II clinical trials for WNT-activated solid tumors in adults [14]. Expression of poly (ADP-ribose) polymerase (PARP) enzyme has been observed in Wnt tumor samples and is associated with poor prognosis [15]. The majority of Wnt pathway inhibitors target PARP and lead to the destruction B-catenin. The PARP inhibitor rucaparib (AG-014699) enhanced temozolamide-induced tumor growth delay in human MB xenografts [16]. Also the PARP1 inhibitor Olaparib, has been shown to enhance radiation sensitivity of medulloblastoma cells *in vitro* [17]. CARP-1/ CCAR1 is a peri-nuclear phospho-protein that is a co-activator of the cell cycle regulatory anaphase promoting complex/ cyclosome (APC/C) E3 ligase. CARP-1 functional mimetics (CFMs) are a novel class of small molecule compounds that interfere with CARP-1 binding with APC/C subunit APC-2, and suppress growth of a variety of cancer cells in part by promoting apoptosis. CFMs activate multiple cell growth inhibitory and apoptosis pathways to suppress MB cell growth, survival and metastasis processes, and underscore their potential as novel class of anti-MB agents [18]. Due to their interaction with the B catenin pathway this molecule would be an interesting one to study particularly for the WNT pathway.

SHH Subtype

This group is characterized by constitutive activation of the SHH pathway. The hedgehog (Hh) pathway was first identified to be involved in medulloblastoma when mutations in patched (PTCH) were detected in patients with Gorlin syndrome, a rare autosomal dominant condition which is associated with increased risk of medulloblastoma and basal cell carcinoma development. During normal development PTCH is able to interact with SHH which releases smoothened protein (SMO) from PTCH-mediated repression. Activated SMO initiated release of Gli transcription factors from suppressor of fused (SUFU), which is a negative regulator of the pathway. This allows Gli to translocate to the nucleus and induce expression of Hh pathway target genes [19]. SHH pathway mutations include mutations in PTCH1, SMO, SUFU and amplifications of GLI1, GLI2 and MYCN. Children also frequently harbor TP53 mutations in this subgroup [20]. Prognosis for the SHH subgroup varies. Multivariate analysis revealed that TP53 status, enriched in approximately 20% of SHH tumors, was the most important risk factor for SHH medulloblastoma. Interestingly, poor outcomes of those with TP53 mutations is restricted to those with SHH medulloblastomas only and risk is not increased in those with WNT medulloblastomas carrying the same TP53 mutation [13]. The worst indicator of poor prognosis in SHH medulloblastomas is a subset with amplification of GLI2 expresion independent of the SHH pathway, with survival of 20% to 35% at 5 years [21]. These high risk patients

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are ideally suited for targeted therapy. Smoothened inhibitors have been of interest in treating these tumors. However those tumors with alteration in downstream SHH pathway genes such as SUFU, GLI2, or MYCN may have primary resistance to SMO inhibition [22]. Also treatment of these tumors in both humans and mice has shown rapid acquisition of secondary resistance [23-25]. Mechanism of inhibitor resistance include activated Smo mutations, phosphatidylinositol 3-kinase upregulation, and GLI2 amplification [26]. Vismodegib (GDC-0449), a smoothened inhibitor, became the first US Food and Drug Administration (FDA) approved Hh pathway inhibitor based on a phase II study in participants with advanced basal cell carcinoma [27]. A phase I trial has been completed for those with medulloblastoma [28] and there are four clinical trials underway for medulloblastoma patients [29]. Oral sodinegib (LDE225) is the only other SMO inhibitor that has been shown to have a response on medulloblastoma. Complete and partial responses have been observed in patients with medulloblastoma a phase I study with BCC and SHH-MB patients [30]. There is also a phase II/III study ongoing with sodinegib study in both adult and pediatric patients with Hh-pathway activated, relapsed MB (NCT01708174). A five gene SHH signature developed by Amakye et al. is being used to identify participants for this trial [31]. This signature has been shown to have an association with tumor response in three other independent trials [32].

As discussed, GLI activation independent of smoothened can occur from recurrent mutations affecting the PI3K/AKT/mTOR pathway in SHH medulloblastomas, particularly in adult patients. This suggests that combination therapy of SMO inhibitors with PI3K/AKT/mTOR inhibition may benefit this subgroup of patients [20]. Also arsenic trioxide which promotes Gli transcription factor degradation or itraconazole which acts on SMO have been suggested in preclinical experiments for use with SMO antagonists [33] and both agents may be of use in tumors that develop resistance to SMO antagonists because secondary resistance is mainly caused by GLI2 amplifications. Other molecules that have potential to be used in combination therapy include Active8, which has activity against wild type and mutant SMO [34], and GANT58 or GANT 61 which primarily target nuclear GLI [35]. Combination therapies with smoothened antagonists would allow the avoidance or delay of the development of resistance to these drugs.

Group 3 and 4

Group 3 medulloblastoma is mostly found in infants and children and has the worst prognosis with a 5-year survival of about 50% and a high rate of dissemination upon diagnosis. As such, these tumors are the most in need of effective therapy. Unfortunately, the lack of definitive molecular pathways in this tumor's pathogenesis make targeted therapy challenging.. Myc amplification is by far the major mutagenic characteristic of this group [36]. MYC is an interesting gene, as it not only has the ability to serve as a transcription factor but can also recruit histone acetyltransferases, allowing it to also regulate global chromatin structure [37]. TGF-b signaling components and the transcription factor OTX2 (a possible target of the TGF-b pathway) are also frequently amplified in group 3 tumors [38]. MYC inhibition is the key strategy for targeting this tumor. It has been shown that transcription of MYC and MYCN and subsequent activation of their downstream transcriptional programs can be targeted by bromodomain and extraterminal (BET) bromodomain protein inhibition [39]. JQ1, a potent inhibitor of BET bromodomain proteins has been shown to reduce cell proliferation and cause prominent apoptosis *in vitro* models of MYC-amplified medulloblastoma [40]. This study also showed responsiveness in a MYCN-driven murine medulloblastoma model so this therapy may be useful in SHH and some group 4 tumors. Group 4 tumors are the most common and the most poorly understood. Expression and methylation profile studies suggest that further subgroups exist within this group [41]. Almost two thirds of group 4 medulloblastomas have an isochromosome 17q and occasionally isolated 17p deletions are seen [36,41]. MYC amplifications are found in this subgroup however intragroup prognostic analysis failed to show any association of MYCN status with prognosis in this subgroup [21]. Group 3 and 4 medulloblastomas have been shown to have EXH2 and KDM6A alterations, which are involved in histone methylation. HDAC5 is another histone acetylase which is overexpressed in medulloblastoma and interestingly the gene locus is located on chromosome 17q [42]. There may be some role for histone deacetylase inhibitors in group 4 since the amplification of HDAC5 may be associated with i17q but this has not been looked into specifically in tumors divided by subgroup [43]. High-throughput screening protocols in addition to advanced pharmacokinetic modeling have lead to the discovery of 2 potential agents for Group 3 and 4 medulloblastomas. Pemetrexed, an FDA approved antimetabolite that inhibits multiple enzymes in the folate pathway is active against multiple solid tumors [44]. Gemcitabine disrupts DNA synthesis and leads to apoptosis. Both agents are highly active against the MYC gene and both have shown inhibition of tumor growth in both *in vitro* and *in vivo* and prolonged survival in a mouse model.

Conclusion

Although once thought to be a single disease, medulloblastoma is now better described as multiple, molecularly unique subgroups that can be differentiated through gene expression profiling. Each tumor is unique in its origin, pathogenesis, prognosis and potential therapeutic options. This cytogenetic analysis can be used to identify those at higher risk as well as those with substantially lower risk who may benefit from dose de-escalation. The identification of numerous novel therapeutic targets gives hope of targeted therapies that may be less toxic than the current standard of care treatment, which includes craniospinal radiation.

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