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An early foray with targeted therapy and inspiring novel approaches to combat adult medulloblastoma

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See article by Frappaz et al. pp 1949–1960.

Advancements in treatment of adult medulloblastoma (MB) are hampered by low disease prevalence and the ease of extrapolating practice from pediatric trials. However, identification of multiple molecular subgroups of MB with distinct differences between adult and pediatric populations indicates the clear need for adult-directed investigations.[1,2] The most common adult subgroup defined by sonic hedgehog (SHH) pathway activation is the subject of a trial by Frappaz and colleagues[3] in this issue. Adults with recurrent or refractory SHH subgroup medulloblastoma (rrSHH-MB) were treated with a novel approach of combined targeted SHH pathway inhibitor and an alkylating agent. To better appreciate, this effort requires an appreciation of the field to date.

Under normal conditions, SHH protein binding to transmembrane protein PTCH1 releases inhibition of protein smoothen (SMO). Activated SMO translocates to the cell membrane and activates a cascade of regulatory signals that lead to GLI proteins mediating transcription of target genes leading to deregulated cell proliferation.[4] In SHH-MB, SHH pathway activation most commonly occurs with mutation or other alteration at *PTCH1* or *SMO*.[4] In the presence of a SMO inhibitor, the downstream GLI protein-facilitated transcription is inhibited. The clinical impact has been reflected with early successful responses of treating rrSHH-MB with SMO inhibitors; however, these responses are consistently short-lived.[5]

Vismodegib is the first FDA-approved SMO inhibitor with demonstrated activity primarily in advanced or metastatic basal cell carcinoma and increasingly with reports of activity in rrSHH-MB.[6] It is noteworthy that the reverse is never seen. Non-SHH MB patients treated with SMO inhibitor have never shown activity that is congruent with our understanding of the molecular mechanism. The primary limitation of vismodegib in clinical trials has been lack of durable response beyond a few months with speculation that a multiagent approach may be more effective.[5,7]

As reviewed in the discussion by Frappaz et al,[3] another approach to treating recurrent MB has been with alkylating agent temozolomide. Like SMO inhibitor-directed therapy, response has been unfortunately transient. Nonetheless, with temozolomide demonstrating some objective response, with known modest toxicity profile, and with great clinical familiarity, it was an obvious candidate drug to trial in a multiagent approach on rrSHH-MB.[8]

With these findings, Frappaz and colleagues conducted a phase I/II study to assess the efficacy of combining vismodegib and temozolomide. Patients were randomized 2:1 to temozolomide alone. After a 3-month safety run-in, the study transitioned into a phase II minimax Simon's 2-stage design to assess progression-free survival at 6 months (PFS-6). A preset threshold of PFS-6 of 55% was set for minimum clinical efficacy. Because of concerns of poor accrual for a rare disease, no stipulation was placed on a number of prior failed therapies so long as patients were naïve to the study drugs. A clever third arm was created to enable patients who had already been tried on temozolomide to receive single-agent vismodegib. This maximized both the opportunity to study the efficacy and toxicity of vismodegib and to offer an additional option of therapy to these patients. The stage I data analysis of PFS-6 of 20% among patients, receiving vismodegib and temozolomide (arm A), fell short of the predefined rules and resulted in study closure. However, the objective response rate (ORR) of 40% is nontrivial, and the short median duration of response (DOR) of just 3.17 months informs on the biology of this disease that readily acquires drug resistance.

The outcomes of this study were disappointing, yet they are important and revealing. Such trials both measure our success and provide feedback on our limitations. Immediately we can begin to speculate, was it the wrong combination of multi-targeted therapy? Was the approach with vismodegib alone to downregulate the SHH pathway too simple? The reliably swift acquisition of drug resistance would suggest so. Many other mechanisms of SHH pathway activation can occur by disruption along any point of the downstream pathway and these alterations would all be impervious to upstream SMO-targeted inhibition. Specifically, points of disruption entirely unaffected by SMO inhibition include *SUFU* or any of

the many *GLI* genes. Beyond the SHH pathway, disruption of *TERT*, deregulation of the PI3K/AKT pathway, or even *IDH1* mutations have also been identified in SHH-MB.[2,4] In fact, targeting a complex signaling pathway with just one drug of vismodegib (recognizing temozolomide was addressing another mechanism) may drive selection pressures for other deregulated tumor variants to dominate. As suggested by the authors, perhaps the wide inclusion criteria permissive of heavily treated patients unwittingly selected for patients with inherently more resistant tumors.

Next-generation sequencing (NGS) was performed in the study by Frappaz et al in effort to predict subpopulations of rrSHH-MB responsive to therapy, but modest success was achieved in predicting responders vs nonresponders to therapy, indicating the need for more effective profiling for tumor susceptibility to direct best therapy. For example, already we know there are *SMO* alterations such as D473H that inhibit the binding of vismodegib to SMO. However, in response, there is already novel SMO inhibitor L-4 developed and demonstrating excellent preclinical activity.[9] For assessing SHH pathway integrity, rather than testing for a few known alterations, whole-genome sequencing or whole-transcriptome sequencing will be more informative. To integrate into routine patient care, these advanced and costly technologies would need to be readily available and affordable along with availability of the growing array of targeted drug therapies.

Optimal new drugs should have both durable activity on the disease and maintenance of quality of life. Although vismodegib has a relatively low toxicity profile acutely,[6,7] the 11% grade 3-4 dose-limiting toxicity is nontrivial. In addition, the persistence of chronic symptoms that frequently lead to treatment discontinuation by patient choice heralds the need for parallel advancements to preserve quality of life.[7] Consider current inefficiency in pharmacokinetics. Over 99% of vismodegib is protein bound. With <1% of vismodegib unbound in plasma and with half as much unbound drug accessing the CSF (cerebrospinal fluid) space, perhaps the convergence of nanoparticle technology to enhance CNS bioavailability will help to win this war on SHH-MB. In fact, vismodegib formulated into polyoxazoline block copolymer micelles (POx-vismo) to increase bioavailability has already been accomplished with promising results in mice with SHH-MB.[10] The story of SHH pathway modulation to overcome SHH-MB has only just begun.

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