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From blunt tools to bullseyes: The impact of targeted therapy in pediatric neuro-oncology

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Central nervous system (CNS) tumors are the 2nd most common type of tumor found in children and account for the highest rate of cancer-related death in pediatrics.[1] Historically, treatment for CNS tumors employed multimodal therapy, including surgery, chemotherapy, and/or radiation. While these treatments were life-saving for many patients, they were biologically indiscriminate and could be associated with long-term toxicity.[2] Over the past 15 years, there have been extraordinary advances made in understanding tumor biology for pediatric CNS tumors, which has opened a new therapeutic era of precision medicine.

This shift began with observations in patients with germline cancer predisposition syndromes. In tuberous sclerosis complex, patients with subependymal giant cell astrocytoma are at risk of developing obstructive hydrocephalus. Treatment with mTOR inhibitors offered rapid and remarkable reduction in tumor size, allowing avoidance of surgery and radiation and providing initial evidence of the significant impact of targeted therapy.[3] Following this, there was identification of recurrent RAS/MAPK alterations in pediatric low-grade glioma. Involvement of this pathway in gliomagenesis had been recognized for many years, as patients with neurofibromatosis type 1 were at risk for developing optic pathway glioma, but additional alterations involving *BRAF* and *FGFR* were subsequently discovered.[4–6] This has been followed by other rare alterations in glioma, including *NTRK* fusions, *ALK* rearrangements, recurrent histone mutations in high-grade glioma, and hypermutation in patients with underlying mismatch repair deficiency.[7–10] Each one of these alterations identified an area of tumor vulnerability, where targeted therapy could inhibit a specific cell pathway or cellular interaction, leading to more precise tumor-specific therapies. In many cases, targeted therapy has been nothing short of revolutionary, moving from hope for stable disease to unprecedented radiologic and clinical responses.

While these exciting treatment advances have changed treatment paradigms, many open questions remain. Durability of response is emerging as a potential issue, with uncertainty regarding the optimal duration of therapy.[11] Long-term effects of targeted therapies are currently unknown, with unusual and unique short-term toxicities seen with different classes of drugs, ranging from rash (BRAF and MEK inhibitors) and growth delay (RAF inhibitors) to concerns about bone health (NTRK and FGFR inhibitors) and beyond.[12–14] Functional outcomes have not been studied in a comprehensive manner, and it is uncertain what the long-term benefit of targeted therapy will be, including metrics such as vision, school/work performance, and endocrine and neurocognitive outcomes. For higher-grade tumors, targeted therapy may only offer temporary benefit, with further investigation needed to understand resistance mechanisms and identify biomarkers to better risk stratify patients.[15]To date, most targeted therapies have been offered as a single agent, and the role of combination therapy is still very limited.[16] Within neuro-oncology, patients with glioma have benefited the most from targeted therapy, and the role of targeted therapy in other CNS tumors such as medulloblastoma, ependymoma, and other embryonal and rare tumors is still being explored.[17,18]

Unfortunately, these paradigm-changing advances have only benefited select populations. Most patients that could benefit from targeted therapy live in areas of the world without access to comprehensive molecular analysis or access to relevant drugs. Certain alterations, such as *FGFR* alterations and histone mutations, do not have highly effective medications available at this time, highlighting a need for ongoing drug development. Lastly, clinical trials have been done in pediatric populations, where these tumors are concentrated. While this is a logical approach, there is limited data on outcomes and toxicities in the adolescent and young adult (AYA) population. It is known that pediatric-type tumors transcend institutionally defined age cut-offs, which may lead to drug access issues if drugs are only approved up to a certain age.[19]

This is an exciting new frontier in pediatric neuro-oncology, one in which there is hope for better disease control and improved long-term outcomes. As a community, we need to ensure there is long-term monitoring of patients, ongoing basic science and translational research to better understand tumor evolution with targeted therapy, and equitable access to testing and drugs for all populations globally. Within the current issue of *Neuro-Oncology Advances*, the current evidence and controversies in targeted therapies are further explored, with a focus on glioma. This includes treatment for common alterations (*BRAF* or *NF1* alterations), rare alterations (*FGFR* and *NTRK*), tumors with poor outcomes (diffuse midline glioma), and marginalized populations (those living in low/middle-income countries and AYAs). We believe this gives a comprehensive overview of the current landscape of targeted therapy options for CNS

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tumors. While more work remains to be done in this field, the outcomes seen to date demonstrate the promise of targeted therapy, with the hope that the bullseye we hit today will pave the road for improved precision medicine in the future.

Conflict of interest statement

J.B. served on advisory boards for Servier Canada, Alexion Canada and Rhythm Pharmaceuticals. E.B. is a member of advisory boards with Novartis, Servier, Alexion, and Fore.

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Supplement Article