Essay

Access to new drugs in paediatric oncology: can we learn from the ongoing ONC201 saga?

New drugs are the cornerstone to improving survival among children with cancer. For high-grade glioma, only four drugs have been licensed in the past four decades; of which three are still in production (bevacizumab, lomustine, and carmustine). All were selected to overcome both the blood–brain barrier and resistance to chemotherapy and targeted therapies. Only one of these drugs, temozolomide, is licensed for paediatric high-grade glioma in some countries, despite few trials supporting its activity.[1] The situation is even worse in paediatric diffuse intrinsic pontine glioma (DIPG). Preclinical research on DIPG has identified several compounds with potential activity;[2] however, these agents need to be evaluated rigorously using state-of-the-art methods and, if proven valuable, made available to all patients worldwide.

DIPG in children and young people

DIPG accounts for 10–20% of childhood brain tumours and the mortality rate is 100%, with a median overall survival of 9–11 months.[3,4] Timely diagnosis and treatment are essential when a child is diagnosed with DIPG. The most clinically effective treatment is radiotherapy, which is always offered palliatively.[3] Over the past 50 years, despite many clinical trials of chemotherapy, biological therapies, and various radiotherapy regimens, there have been almost no signs of improvement in survival.[4] More than 80% of diffuse midline gliomas, including DIPG cases, harbour a H3K27M mutation in histone H3-encoding genes. This observation is a not only a clue to the developmental mechanisms of DIPG, but might also offer a target for treatment.

ONC201: a new drug

ONC201 is an antagonist of the dopamine receptor D2 and a potent stimulant of the mitochondrial caseinolytic protease P enzyme[5–7] that impairs oxidative phosphorylation to induce cell death (figure). The preliminary evidence of its anticancer effect triggered its commercial development, which has been quite eventful.[8–11] When its original structure was replicated by other researchers, ONC201 was found to have no anticancer activity.[8] This second structure was an isomer of the original active drug, and the isomeric structure of ONC201 was shown to be crucial to its activity.[8–10] Consequently, the drug was initially patented with an incorrect chemical structure.[8] 2–3 years later, one of the scientists who identified the chemical structure error applied for a new patent for the correct active isomer compound and licensed it to a different company, leading to an intellectual property disagreement.[9] Preclinical studies support the therapeutic potential of ONC201 and phase 1/2 trials established the safety profile and recommended phase 2 dose of ONC201.[12,13] Further case studies and expanded access programmes have reported clinical responses and long-term survival in children diagnosed with diffuse midline gliomas.[14] These results encouraged the development of new clinical trials to test ONC201 in paediatric patients diagnosed with H3K27M-positive diffuse midline gliomas, including DIPG (NCT03416530). More than 20 active trials involving ONC201 are listed on ClinicalTrials.gov.

Accessing ONC201 outside trials

After the publication of the preliminary clinical results in adults with high-grade glioma, news about the potential activity of ONC201 spread via social media throughout the international DIPG community. However, access to paediatric ONC201 trials was restricted almost exclusively to patients in the USA or Japan, and the company (Oncoceutics/Chimerix) did not provide a wide international compassionate access route. Innovation and new drugs are useless if not accessible to children with cancer.

The German ONC201

Making use of the unique German regulatory framework, a German oncologist filled the void created by restricted international access and synthesised and provided ONC201 to interested parties, once a diagnosis of H3K27M-positive diffuse midline glioma had been confirmed.[7] Indeed, the individual healing attempt (*individueller Heilversuch*) is a medical treatment option in Germany that deviates from the medical standard, aimed at treating a specific patient.[15] It is an expression of medical freedom of therapy and is different from compassionate use, which is overseen by the German health authorities. The oncologist started prescribing ONC201 to patients outside of Germany who were willing to receive a consultation, and found a pharmacy that would make and deliver the drug.[7] According to parents, the treatment costs (including shipping) could exceed €3000 per month depending on the weight of the child (confidential personal communication). This German commercial alternative was offered worldwide at a time when ONC201 was not available from the license applicant and international travel was restricted because of the COVID-19 pandemic.

An Australian research team analysed the German ONC201 capsules from eight families who had bought the

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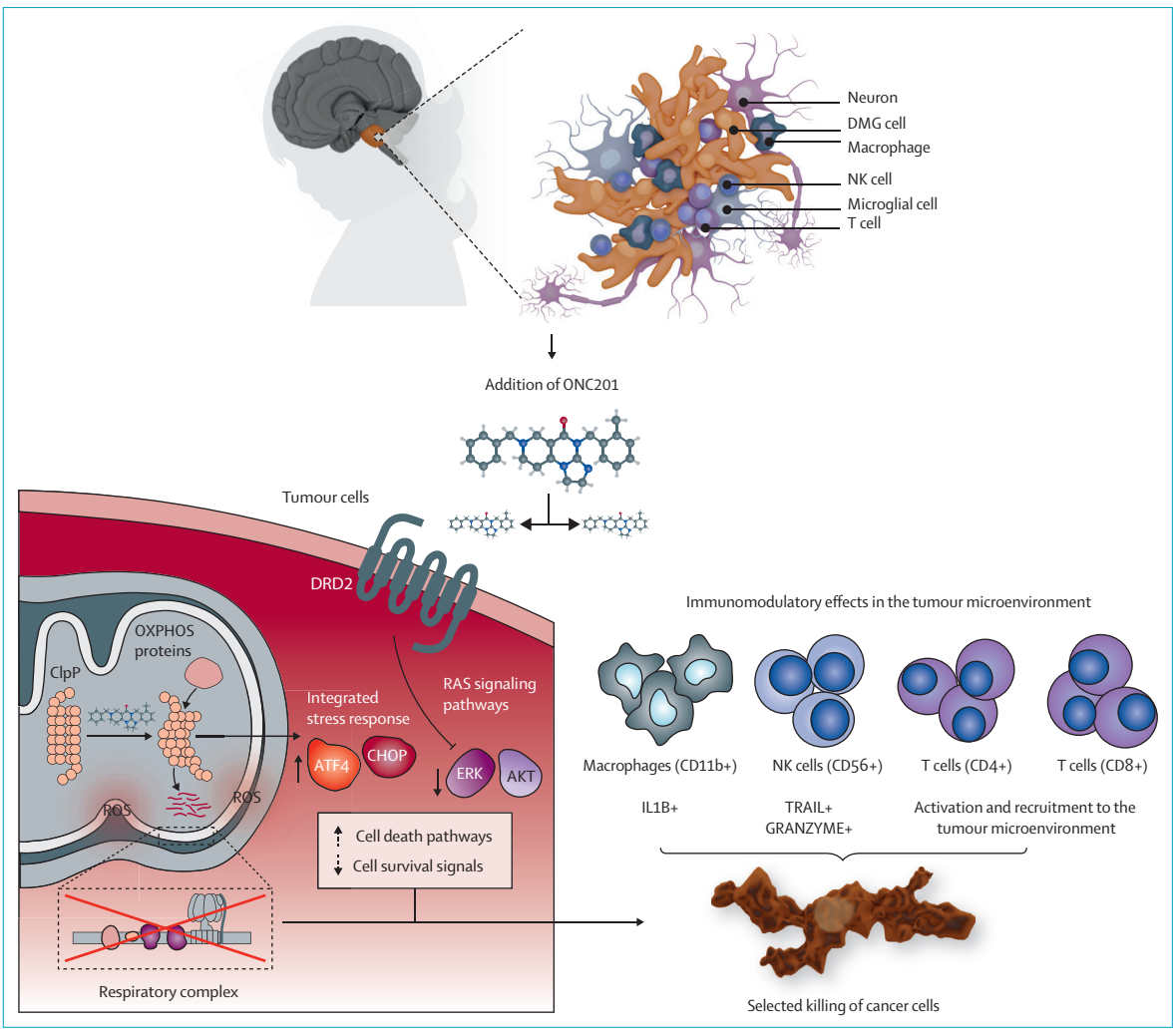

***Figure*: Mechanism of action of ONC201**
AKT=serine/threonine-protein kinase. ATF4=activating transcription factor 4. CHOP=C/EBP-homologous protein. ClpP=caseinolytic protease P enzyme. DMG=diffuse midline glioma. NK=natural killer. OXPHOS=mitochondrial oxidative phosphorylation. TRAIL=TNF-related apoposis-inducing ligand.

compound and confirmed it was an active conformation of the molecule.[7] Preclinical testing demonstrated activity in DIPG cell lines with similar results to the ONC201 formulation being used in the trials from the license applicants. Patients receiving German ONC201 alone or in combination had a median overall survival of 18 months.[7]

The French initiative

The unusual saga was taken a step further by the father of a French patient with DIPG and French associations. They asked French authorities (Agence Nationale de Sécurité du Médicament et des produits de santé [known as ANSM]) to make ONC201 available in France for patients with H3K27M-positive diffuse midline gliomas so that patients would not have to travel abroad to access a compassionate programme or to purchase the German ONC201 at their own expense (confidential personal communication). Similar situations have also been reported in other countries, such as France and the UK.[16,17] A national procedure was established and validated by competent authorities to provide ONC201 to both adult and paediatric patients with H3K27M-mutant diffuse midline gliomas at relapse after radiotherapy. The drug is prepared at the Gustave Roussy Institute (Villejuif, France) and, after validation by a national molecular board, is sent to treating centres in France that request it for patients at relapse to avoid conflicts with an upcoming official trial investigating the same drug (BIOMEDE 2; NCT02233049). This initiative is articulated with the SACHA trial (NCT04477681), which prospectively collects data of paediatric patients receiving new drugs on a compassionate basis.

What can we learn from these initiatives?

The public and parents' attitudes are showing that the inability to access drugs that they believe can help their

children is unacceptable in our modern society. But should we view these experiences as an achievement, highlighting an unexpected flexibility of an otherwise rigid drug development system?

The unique solutions adopted to work within the regulatory environment have offered worried families the opportunity to try a drug for their child to ensure that they have exhausted all options to save them. A novel therapy could be seen in such a setting by parents as risky; however, it is primarily perceived as a reason for hope. Many families believe that not achieving cure is an institutional or national issue because it is the government's responsibility to provide appropriate drugs, and so they frequently seek second opinions elsewhere. Social media and the internet offer limitless opportunities and mechanisms for sharing experiences with an international parent community. They can also tempt anxious parents to engage with practitioners seeking financial reward for scientifically unjustifiable treatments or toxic treatments at outrageous expenses without acceptable reporting of outcomes.[18] For many parents, the German ONC201 was seen as a unique opportunity. The families that were brave enough to put their faith in the German oncologist felt this was the best option and better than doing nothing, despite the paucity of proof and the unethical costs. But were they fully aware of the risks when they decided to pay to access this drug?

From a physician's perspective, the uncertainty surrounding its regulatory provenance and the quality control of production or legal cover for post-treatment safety made it unacceptable to take clinical responsibility for the prescription of ONC201. Young and disabled children must be protected and cannot formally consent to treatments of this nature. Parental consent is proxy consent and can be linked to their priorities rather than the child's. However, in the past three decades, many clinical trials of innovative drug therapies have consistently failed to improve survival. Explaining this complexity to worried parents is an unbelievably hard task. The impossibility of accessing drugs and the need to wait for official results is not acceptable for many parents.

Notably, more than 4 years after the opening of these ONC201 trials, there has yet to be a peer-review publication of the results. Considering that clinical trials of DIPG require only 30–50 patients to show a clinical benefit, this absence of publications raises questions regarding the complexity of trial design or limitations in eligibility to access them. This delay in publication might be partly because the pharmaceutical company developing ONC201 had very little experience in paediatric oncology, further strengthening the importance of collaboration with academic experts. The small number of approved anticancer drugs in paediatric oncology highlights the specific difficulties of drug development in this setting. It is the stakeholders' responsibility to monitor the soundness of a clinical trial because clinical development of a new drug often remains too driven by commercial strategies. DIPG or diffuse midline gliomas are a unique clinical and neuroscientific challenge that requires a streamlined approach to develop innovative treatments. A complete treatment programme needs to be developed by combining the most promising approaches, seeking synergies. Any accelerated initiative needs to accommodate international access via cross-border trials and multicentre technical networks.

The German and French approaches of making ONC201 available conflict with the standard regulatory pathways for drug testing and licensing, and there is a risk that, despite the absence of solid evidence, parents believe the drug works and so are willing to obtain it for their children. The many drawbacks and risks associated with the German initiative make it unacceptable (appendix). We believe that such initiatives must not be replicated. In the UK, there was substantial discussion surrounding access to novel therapies and the protection of practitioners from litigation in the approved Access to Medical Treatment Act.[19] A database was to be established in which such innovative drug use would be recorded for open access to share learning; however, the database was never created, and this act has remained dormant. Moreover, the Medical Research Council raised concerns about the database.[20]

See Online for appendix

The French initiative supported medical prescribing of ONC201 as a second-line treatment, supervised by trained oncology teams and linked to data collection as part of a national trial (SACHA study; NCT00213473). Such an initiative clearly seems like a step in the right direction. However, it still collides with state-of-the-art development and regulatory standard patent issues, and therefore compromises between stakeholders must be found.

Next steps?

ONC201 harbours unique characteristics because it is administered orally, has a good toxicity profile, crosses the blood–brain barrier, and has a unique mechanism of action, which differs from standard or previous treatments that have failed to increase survival. These features led to an overall very good risk–benefit balance in a disease for which the certainty of death outweighs all the potential risks. The use of ONC201, with its high solubility suitable for oral formulation and low systemic toxicity profile, compares favourably with other drugs introduced for cancer treatments.

A simple way to avoid most of the caveats of these initiatives would be to have more centres participating in early-phase trials, especially when solid signals of activity are observed. This would increase access to new promising drugs and help execute well designed trials or programmes. The French initiative seems to be a good model to increase safe access to new drugs. However, the main issues—how

to provide the drug or how to make the drug from the initial chemical, which clearly conflicts commercially with the pharmaceutical drug development pipeline—would remain. This initiative would also come at a cost, but new incentives could be generated so that pharmaceutical companies could simply provide the drug and get the data gained from the compassionate experience of programmes such as the SACHA study. These data might diverge from the data obtained from the drug development programme, representing real-world data from a less selected patient population and providing opportunities for a better description of adverse events and measurement of efficacy. Moreover, additional partnerships and funding could be provided by non-profit organisations and charities.

If, or when, a pharmaceutical company refuses to provide a drug, competent authorities could be allowed to develop or synthesise the drug to ensure compassionate access is secured for all patients until regulatory filings are completed, with drug development stopped to ensure the validity of the indication and collection of data. It is important to keep in mind that, in paediatric oncology, consecutive improvements have been primarily achieved through clinical trials conducted with international academic consortia interacting with pharmaceutical companies to incorporate or test new anticancer agents. From this perspective, the multi-stakeholder international platform ACCELERATE stands as one of the forums to identify bottlenecks in children's cancer drug development and address these complex and intertwined issues in a methodical manner. Stakeholders should all work together to reach solutions through innovative tools. Ultimately, innovation for the sake of innovation is not enough; innovation can only lead to substantial improvement in survival if clinical trials allows regulatory filings and reimbursement approvals.

Conclusion

This story of development of a drug is a fascinating example of the expanding range of stakeholders' actions driving drug development. The parental impact in this story confirms the evidence that children's needs must be given higher priority in cancer drug development than they already receive, but can this be achieved with current systems? The complex intertwined processes of drug development should not compromise safe access to treatment and state-of-the-art evaluation of activity and toxicity. We offer our view in an attempt to weigh up the risks and benefits of such approaches. New innovative incentives need be developed collectively. Meanwhile, the story is being repeated with ONC206, another new candidate treatment for DMG.[21]

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