Translating preclinical hopes into clinical reality for children with ependymoma

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See the article by Wright et al, on pages 1620–1627.

Standard of care for pediatric ependymoma comprises maximal surgery and focal radiotherapy. This is, however, not sufficient to cure all patients, and approximately one third will eventually relapse. With the exception of a study with a gamma-secretase inhibitor,1 most of the phase I/II trials performed to date in children with ependymoma have not been driven by a strong preclinical background, and not unexpectedly, only limited responses have been documented.2,3 Usually, only a limited number of children with ependymoma are enrolled in these early drug development trials, making a definitive statement about efficacy difficult and imprecise. Accordingly, none of these agents have been incorporated in the therapeutic armamentarium against this disease.

With the advent of large-scale genomic studies, new therapeutic targets have been discovered based on recurrent alterations.4–7 The lack of relevant models, however, has impaired the preclinical studies necessary to justify the implementation of early therapeutic trials. In an attempt to address simultaneously the issue of new drug development and the question of preclinical models, Wright et al in this issue report on the development of a strong program to identify key molecular events for ependymoma oncogenesis and create relevant transgenic models.8–10 Their first model, based on a genetic alteration found in one subtype of supratentorial pediatric ependymoma involving EphB2 amplification together with an Ink4/ARF deletion, was used for an extended drug screen of almost 8000 compounds and identified 5-fluorouracil (5FU) as an effective drug both in vitro and in vivo.9 Consequently, a phase I trial was initiated in order to define the maximal tolerated dose and to search for signal of efficacy in children and young adults with ependymoma (Wright et al, Neuro Oncol this issue). As concluded by the authors, the results were not as good as anticipated based on the preclinical data, and the authors have proposed to test the drug in a phase II trial in combination with another agent.

This valuable albeit disappointing endeavor to translate an interesting finding from bench to the clinic highlights some of the specific problems hampering the therapeutic development for ependymoma. Indeed, ependymoma is a disease that has been difficult to model in vitro and in vivo with only a few models available. The limited number of recurrent genomic alterations, especially in posterior fossa ependymoma, which accounts for the majority of tumors in children, has precluded the generation of models driven by genomic changes (mutation, amplification). While models driven by alterations found in clinical samples such as that driven by EphB2 are important, the rarity of this pathway limits the utility of these findings to most patients with ependymoma. Alternative strategies by direct in vivo screening with the introduction of selected oncogenes and/or tumor suppressor genes in neural stem cells sorted by enhanced green fluorescent protein expression under the fatty acid binding protein promoter of radial glial cells10 will generate new models that may recapitulate other subtypes of ependymomas. Patient-derived xenografts represent another way to generate models. Only a few have been published so far, and their growth is frequently quite slow, complicating the evaluation of the effect of new therapeutic agents.11,12 Finally, models corresponding to recurrent tumors, which have usually substantial biological modifications compared with the tumors at diagnosis,13 are important because they may better represent the tumors susceptible to treatment with new agents at relapse. If a new drug is developed to treat ependymomas irrespective of their biological background, assessment on multiple preclinical models should be used to confirm activity, extending beyond short-term cell cultures. Conversely, if a new drug is targeted to treat a specific ependymoma subtype(s), the preclinical work should focus on finding the determinant of tumor response in that model. This can be quite straightforward for targeted drugs already tested in adult cancers but more time and resource consuming with less targeted drugs such as histone deacetylase inhibitors or conventional chemotherapy such as 5-FU. All therapeutic agents have limitations and will not be effective for the treatment of all tumor types even with the same molecular profile. It is a
matter of debate whether screening for efficacy should be performed in a small number of patients immediately after the first hints of activity in preclinical models or whether preclinical testing should be extended in order to improve the delineation of the target population for phase II trials. Precision medicine is making a plea for the latter option. Considering the relative rarity of the disease, one could consider that optimization of the early clinical trials by extended preclinical testing could be extremely valuable. The patients can typically be treated only once or twice, while their biological avatars can be treated with more agents. In this case, it would be of paramount importance to organize consortia that bring biological resources in common to test and validate drugs more extensively before translating these results to the clinic, similar to the recent transatlantic endeavor for diffuse intrinsic pontine glioma.  

In the context of a disease against which really effective medications are still lacking, it would be unfortunate to discard a drug like 5-FU based on an unsuccessful phase I trial, if we consider that the preclinical studies suggested that this agent may be suitable only for a given ependymoma subtype. Interestingly, while the preclinical data suggested activity in supratentorial EphB2-positive tumors, the presence of a few responders in posterior fossa ependymomas suggests that the actual mechanisms of action of 5-FU in ependymoma should be further elucidated. Going back to the bench to explain the results of this phase I trial could be extremely valuable in evaluating this drug further, both alone and in combination.

References