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Editorial Comment

# PDGFR inhibition in brain tumours – Oft expectation fails where most it promises ☆

*Eric Raymond**

*Department of Medical Oncology (INSERM U728 – Paris 7), Beaujon University Hospital, Assistance Publique – Hôpitaux de Paris, 100 boulevard du Général Leclerc, 92110 Clichy, France*

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Brain tumours, including malignant gliomas, are associated with a strikingly pitiable prognosis notwithstanding the current efficacy of surgery, radiotherapy, and chemotherapy. Targeted therapies have opened new avenues in the treatment of several diseases and the tyrosine kinase platelet derived growth factor receptors and the vascular endothelial growth factor receptors (PDGFRs/VEGFRs) are currently recognised as the most promising targets for therapeutic interventions in tumours arising in the central nervous system.[1] Despite recent progresses made in several other tumour types with novel targeted therapies, the overall outcome of patients with gliomas remains desperately limited, thus leading to the frantic screening of several anticancer agents with multiple mechanisms of action[2]. So far, temozolomide, a cytotoxic drug that acts as a methylating agent, remains the only recently registered anticancer agent that has demonstrated reliable, but still humble, benefit either alone or in combination with radiation therapy in glioma.[3] Unmet medical needs made glioma a potential niche for the development of experimental therapeutics for academia and industry. Carcinogenesis and angiogenesis in gliomas were shown to be dependent – at least in part – upon VEGF/VEGFR and/or PDGF/PDGFR activation, triggering downstream PI3kinase/AKT/mTOR cell signalling pathways. Recent drugs targeting angiogenesis at the level of VEGF (bevacizumab), VEGFR (sunitinib, sorafenib, and valatinib), PDGFR (imatinib), and mTOR (temsirolimus, everolimus, and deforolimus) have been tested in patients with malignant gliomas, offering hope of benefits.[1,2]

PDGF and PDGFR were among the first oncogenic targets tested in clinical trials for malignant gliomas.[4] PDGFs belong to a family of structurally and functionally related growth factors also including VEGFs.[5] PDGF and VEGF are highly genetically conserved growth factors and are part of a large superfamily of cystine containing proteins.[6] Autocrine PDGF and PDGFR loops have been proposed to play a role in the survival of glioma cells. Nearly all tested human glioma cell lines and fresh tumour isolates express PDGFs and PDGFRs at various levels.[7–9] In several laboratory studies, overexpression of PDGFs caused the formation of glioma-like tumours[10,11] and inhibition of PDGF/PDGFRs induced a slowdown in glioma cell proliferation.[9,12,13] Mechanisms by which PDGF expression is activated in gliomas remain poorly understood. Several years ago, authors suggested that PDGF might be involved in the response to transforming growth factor β (TGFβ) in gliomas.[14] In the search for understanding the mechanisms associated with PDGF/PDGFR activation, TGFβ signalling was found capable of activating the transcription of PDGF-B and its secretion through Smad2/3/4, further illustrating that effects of TGFβ

☆ From: 'Oft expectation fails, and most oft there Where most it promises; and oft it hits Where hope is coldest, and despair most fits.' William Shakespeare, All's Well That Ends Well (II, i, 145–147).

* Tel.: +33 1 4087 5614; fax: +33 1 4087 5487.
E-mail address: eric.raymond@bjn.aphp.fr


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on glioma cell proliferation depend on PDGF-B/PDGFR signalling.[15] The proliferative response to TGFβ in human glioma and the poor prognosis associated with TGFβ pathway activation in gliomas is mediated by the absence of epigenetic silencing of PDGF-B expression. Adult neural stem cells capable of generating both oligodendrocytes and neurons were shown to express PDGFR-β and respond to PDGF by proliferation, leading to the formation of glioma-like hyperplasias. It has been proposed that PDGFR-β-positive stem cells constitute the cellular origin of gliomas and that the autocrine PDGF/PDGFR loops operating in such tumours reflect a normal role for PDGFs in regulating self-renewal and differentiation in tumour stem cells.[16] Imatinib is an efficient PDGF/PDGFR pathway inhibitor that has been tested in the search for novel agents in a variety of tumours of the central nervous system. When imatinib demonstrated outstanding clinical efficacy in gastro-intestinal stromal tumours by blocking KIT, a tyrosine kinase receptor closely related to PDGFR, imatinib was seen as an excellent research tool for efficient screening of putative PDGF-dependent tumours in animals and clinical trials. Animal models evaluating the effects of imatinib in brain tumours demonstrated activity[17], supporting further clinical evaluations of this drug in patients with tumours of the central nervous system. At that time, launching clinical trials in adults and children was considered the ultimate opportunity for evidencing which human brain tumours were really dependent of PDGF/PDGFR signalling for survival with the promise of clinical activity for diseases with unmet medical needs.

In this issue, Geoerger et al.[18] and Baruchel et al.[19] evaluate the antitumour effects of imatinib in paediatric patients with a variety of advanced central nervous tumours in two separate trials performed in European and Canadian consortiums, respectively. They both found that imatinib can be given safely to paediatric patients but efficacy data were rather disappointing despite evidences showing that PDGFR was expressed in several brain tumour malignancies. Similar data have been previously reported in an EORTC phase II study performed in adult patients with gliomas.[4] In that trial, sustained tumour stabilisation and sporadic responses, as measured by computerised tomography (CT) scan or magnetic resonance imaging (MRI), were reported but imatinib was unable to convincingly provide a disease-free survival advantage in any of the patients tested. Objective responses, as evaluated by CT-scan and MRI under imatinib therapy, have been subject to criticisms since they may not reflect the intrinsic antitumour effects of the drug but rather changes in tumour vessel permeability and thereby the uptake of contrast enhancing macromolecules such as iodine and gadolinium.[4] In none of the above trials were PDGFR expression and/or PDGFR mutations in glioma cells associated with imatinib activity. Overall, despite a strong preclinical rationale, imatinib does not seem to be an active drug in patients with tumours of the central nervous system. Based on these data it is clear that there is no longer a rationale to support the use of off-label single agent imatinib in patients with central nervous system tumours. Furthermore, current results showing the absence of activity of imatinib as a single agent do not support the use of imatinib in combination with other anticancer agents outside the frame of clinical trials.

There are several examples in oncology where expression of receptor tyrosine kinases in cancer cells may not have been sufficient enough to translate into efficacy using inhibitors in clinical trials, but why do such discrepancies between preclinical data and clinical results exist in the case of brain tumours? Data generated from both paediatric and adult trials with imatinib do not suggest any trivial reason related to dosing, scheduling, and/or pharmacokinetic interactions. Obviously, reasons may rather lie in our current lack-of-knowledge with regards to the tumour biology of established human malignant tumours of the central nervous system. Clearly, clinical data in paediatric and adult populations strongly suggest that while the PDGF/PDGFR autocrine/paracrine loop may play an important role in survival and differentiation of stem cells in brain tumours, this pathway may not be relevant in established tumours in which differentiated tumour cells deriving from stem cells enter into contact with tumour stroma. Based on clinical data showing no antiproliferative effects of imatinib, it is likely that those brain tumour cells may develop PDGF/PDGFR-independent pathways for survival and migration. As we learn from our mistakes, the search for more relevant molecular targets than PDGF/PDGFR remains urgently warranted. Hopefully, deciphering mechanisms of brain tumour growth, invasion, and angiogenesis may help in identifying novel targets and developing new anticancer agents for the treatment of brain tumours in the near future.

## Conflict of interest statement

Eric Raymond is a consultant for Pfizer, GSK.

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