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αvβ3 Integrin and Fibroblast growth factor receptor 1 (FGFR1): Prognostic factors in a phase I–II clinical trial associating continuous administration of Tipifarnib with radiotherapy for patients with newly diagnosed glioblastoma

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Abstract ***Background:*** Based on our previous results showing the involvement of the farnesylated form of RhoB in glioblastoma radioresistance, we designed a phase II trial associating the farnesyltransferase inhibitor Tipifarnib with radiotherapy in patients with glioblastoma and studied the prognostic values of the proteins which we have previously shown control this pathway.

Patients and methods: Patients were treated with 200 mg Tipifarnib (recommended dose (RD)) given continuously during radiotherapy. Twenty-seven patients were included in the phase II whose primary end-point was time to progression (TTP). Overall survival (OS) and biomarker analysis were secondary end-points. Expressions of αvβ3, αvβ5 integrins, FAK, ILK,

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fibroblast growth factor 2 (FGF2) and fibroblast growth factor receptor 1 (FGFR1) were studied by immuno-histochemistry in the tumour of the nine patients treated at the RD during the previously performed phase I and on those of the phase II patients. We evaluated the correlation of the expressions of these proteins with the clinical outcome.

Results: For the phase II patients median TTP was 23.1 weeks (95%CI = [15.4; 28.2]) while the median OS was 80.3 weeks (95%CI = [57.8; 102.7]). In the pooled phase I and II population, median OS was 60.4w (95%CI = [47.3; 97.6]) while median TTP was 18.1w (95%CI = [16.9; 25.6]). FGFR1 over-expression (HR = 4.65; 95%CI = [1.02; 21.21], $p = 0.047$) was correlated with shorter TTP while FGFR1 (HR = 4.1 (95% CI = [1.09–15.4]; $p = 0.036$)) and αvβ3 (HR = 10.38 (95%CI = [2.70; 39.87], $p = 0.001$)) over-expressions were associated with reduced OS.

Conclusion: Association of 200 mg Tipifarnib with radiotherapy shows promising OS but no increase in TTP compared to historical data. FGFR1 and αvβ3 integrin are independent bad prognostic factors of OS and TTP.

1. Introduction

Despite post-operative combination of radiotherapy and temozolomide,[1] the prognosis of the patients with a glioblastoma (GBM) remains poor because of a local recurrence mainly due to resistance of the GBM cells to radiotherapy.

Our team has been involved for several years in the deciphering of molecular pathways involved in the regulation of tumour micro-environment and radioresistance. We have shown that fibroblast growth factor 2 (FGF)-2 controls radioresistance through RhoB, whose farnesylated form modulates GBM cell radioresistance *in vitro* but also controls hypoxia *in vitro* and *in vivo* in GBM models.[2–5] Furthermore inhibition of farnesylation of RhoB led to radiosensitisation, vascularisation normalisation and oxygenation in GBM xenografts.[3,6] We recently demonstrated that upstream of RhoB, αvβ3 and αvβ5 integrins control GBM radioresistance via the integrin linked kinase (ILK) and RhoB.[7] Moreover, we showed *in vitro* and *in vivo* that these integrins control a major factor of radio and chemoresistance, hypoxia, inhibition of this pathway leading to oxygenation and normalisation of the vascularisation.[8,9]

Because of the pivotal role of the farnesylated form of RhoB in the GBM radioresistance, we developed a phase I/II trial combining the farnesyltransferase inhibitor (FTI) Tipifarnib in continuous administration with radiotherapy in patients with GBM, allowing us to define the recommended dose (RD) of 100 mg bid with encouraging results at this treatment dose.[10] In this article, we report the results from the bicentric, open-label, single arm, phase II trial of 100 mg bid Tipifarnib given concurrently with conformational radiotherapy in adults with newly diagnosed GBM. Moreover, due to our previous results, we studied on the pre-treatment tumour specimens from the patients enrolled in the phase I/II study, the expression of the proteins we previously demonstrated to be involved in RhoB-mediated GBM radioresistance and hypoxia.

2. Patients and methods

2.1. Patient eligibility

This phase I/II trial was approved by the local ethics committee (n°1-02-54), the institutional review board, and by the French Agency for Health Products (n°030201). All patients provided a written informed consent. Thirteen patients were included in the phase I component of this clinical trial.[10] The phase II started on December 2005 in the two French comprehensive cancer centres Claudius Regaud Institute in Toulouse and Jean Perrin Institute in Clermont Ferrand.

Patients with newly diagnosed, histologically confirmed GBM multiforme (Grade IV astrocytoma) according to the World Health Organization criteria,[11] previously untreated except for biopsy or surgery, were eligible. No prior chemotherapy or prior cranial irradiation was allowed. Other inclusion criteria including age, biology and imaging criteria were described in the phase I related article.[10]

2.1.1. Treatment plan

According to the result of the phase I,[10] Tipifarnib ((R115777; Zarnestra), Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium), a potent and selective non-peptidomimetic FTI was orally administered daily at the RD of 100 mg bid every 12 h starting one week before and until the end of the radiotherapy, continuously 7 days/week. No temozolomide treatment was administered because the initiation date of this phase I–II study was anterior to the date at which Temozolomide became part of the GBM standard treatment.

Radiotherapy was administered with a total dose of 60 Gy in 2 Gy daily fractions delivered 5 d per week over 6 weeks.[12] No dose reduction was allowed.

At progression, all patients were treated with Temozolomide.