Decrease in tumor cell oxygen consumption after treatment by vandetanib (ZD6474), an inhibitor of VEGFR-2, EGFR and RET tyrosine kinases, and its effect on responses to radiotherapy

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Introduction:

The evolution of the tumor micro-environment at the early phase of an anti-angiogenic treatment is complex. The concept of a transient normalization has emerged as a working hypothesis. A transient increase in perfusion has been described with some agents, such as thalidomide (1). Besides this effect, another drug (SU5416) induced a tumor reoxygenation by another mechanism: a long term effect on tumor oxygen respiration (2). A key question is whether this mechanism of reoxygenation (inhibition of oxygen consumption vs transient "normalization") is common to other anti-angiogenic agents that target VEGFR-2.

Objectives

We investigated the early effects of vandetanib (ZACTIMA™; ZD6474), an inhibitor of VEGFR-dependent angiogenesis, on tumor oxygenation and the possible consequences for combining vandetanib with radiotherapy.

Materials and Methods:

Tumor oxygenation, perfusion, oxygen cell consumption and radiation sensitivity were studied in transplantable liver tumors after daily doses of vandetanib ($25 mg \cdot kg^{-1}$ ip). Measurements of oxygenation (pO_2) and tumor cell oxygen consumption were carried out using Electron Paramagnetic Resonance (EPR) and perfusion assessed by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) using P-792 as contrast agent. Regrowth delay assays were measured after treatment with vandetanib alone, RX irradiation alone or a combination of both treatments.

Results:

Vandetanib induced an early increase in tumor oxygenation (Fig1) that did not correlate with remodeling of the tumor vasculature or with changes in tumor perfusion , as Vp, Ktrans, and the number of perfused voxels were unchanged after the treatment (Fig.2). A decrease in tumor cell oxygen consumption was observed (Fig.3), which could have been responsible for this increase in tumor oxygenation. Consistent with this increase in tumor oxygenation, we found that vandetanib potentiated the antitumor effects of radiotherapy (Fig.4).

Discussion :

The observation that vandetanib causes an early increase in tumor oxygenation has implications for the timing and sequencing of VEGF signaling inhibitors in combination with radiation.

References :

(1): R. Ansiaux et al, Clin. Cancer Res. 11, 743-750, **2005**

(2): R. Ansiaux et al, Cancer Res. 66, 9698-9704, **2006**

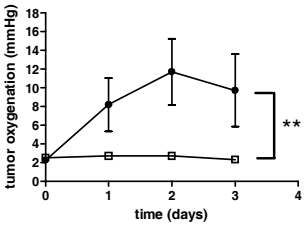

Fig.1

Evolution of the tumor oxygenation. Note the early reoxygenation of the tumor after vandenatib treatment.

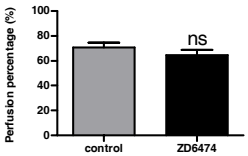

Fig.2

Number of perfused voxels as measured by DCE-MRI.

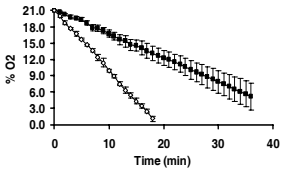

Fig.3

Influence of the treatment on the oxygen consumption by tumor cells.

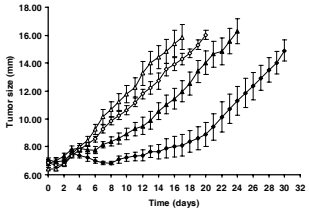

Fig.4

Tumor growth. From left to right: control, vandenatib alone, X-Rays alone, X-Rays after two days of vandenatib treatment.