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Annals of Oncology Advance Access published online on August 12, 2008

Annals of Oncology, doi:10.1093/annonc/mdn543

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Gemcitabine uptake in glioblastoma multiforme: potential as a radiosensitizer

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Glioblastoma multiforme (GBM), the most frequent malignant brain tumor, has a poor prognosis, but is relatively sensitive to radiation. Both gemcitabine and its metabolite difluorodeoxyuridine (dFdU) are potent radiosensitizers. The aim of this phase 0 study was to investigate whether gemcitabine passes the blood–tumor barrier, and is phosphorylated in the tumor by deoxycytidine kinase (dCK) to gemcitabine nucleotides in order to enable radiosensitization, and whether it is deaminated by deoxycytidine deaminase (dCDA) to dFdU. Gemcitabine was administered at 500 or 1000 mg/m² just before surgery to 10 GBM patients, who were biopsied after 1–4 h. Plasma gemcitabine and

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dFdU levels varied between 0.9 and 9.2 μM and 24.9 and 72.6 μM , respectively. Tumor gemcitabine and dFdU levels varied from 60 to 3580 pmol/g tissue and from 29 to 72 nmol/g tissue, respectively. The gene expression of dCK (β -actin ratio) varied between 0.44 and 2.56. The dCK and dCDA activities varied from 1.06 to 2.32 nmol/h/mg protein and from 1.51 to 5.50 nmol/h/mg protein, respectively. These enzyme levels were sufficient to enable gemcitabine phosphorylation, leading to 130–3083 pmol gemcitabine nucleotides/g tissue. These data demonstrate for the first time that gemcitabine passes the blood–tumor barrier in GBM patients. In tumor samples, both gemcitabine and dFdU concentrations are high enough to enable radiosensitization, which warrants clinical studies using gemcitabine in combination with radiation.

gemcitabine, glioblastoma multiforme, radiosensitizer

Received for publication February 26, 2008. Revision received June 1, 2008. Accepted for publication June 2, 2008.

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Online ISSN 1569-8041 - Print ISSN 0923-7534

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