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LIPOSOMIATED DOXORUBYCYN (LD) AND HYPERTHERMIA ON GLIOBLASTOMA RELAPSING AFTER SURGERY, RADIOTHERAPY AND TWO CHEMOTHERAPY LINES: A CASE REPORT

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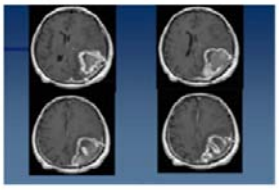
Rationale for using liposomal doxorubicin.

Temozolomide is an imido-tetrazine readily absorbed orally and able to cross the blood brain barrier. TMZ has demonstrated activity against Glioblastoma and astrocytoma in various degrees, and in brain metastases (Reardon DA 2006, Addeo R 2011). Although TMZ has become the drug of choice in association with radiotherapy for Glioblastoma, many Glioblastoma patients develop resistance to the drug and become incurable. The complete reasons for why this resistance takes place is at the moment not completely understood, but seems linked to the presence of certain subpopulations of cancer-stem cells inside the tumor mass (Joannensen TC. 2012). This possible and eventual resistance to treatment has forced our group to look for other drugs active on GBM. We have chosen liposomal doxorubicin for various reasons that we will now describe. Liposomal doxorubicin (Caelyx®), is a formulation of hydrochloride doxorubicin wrapped in a film composed by phospholipids and polymers of methoxypolyethylene (mPEG) embedded in the lipid surface (Green AE. 2006). This association provides a favorable pharmacokinetic profile characterized by an extended circulation time, a reduced volume of distribution, thereby promoting an increased tumor uptake (Gabizon A. 2012; Holloway RW. 2010). Tumor abnormal microcirculation and permeability is responsible for the increased uptake and retention of liposomal drugs (Maeda H. 2006). This phenomenon of increased permeability is greatly increased by HT, as demonstrated by Ponce (Ponce AM.2006) and Dvorak (DvorakJ. 2004). Dvorak was one of the first to use the combination of Caelyx® and HT on hepatocellular carcinoma, reporting that the combination of HT and doxorubicin itself may be supra-additive, resulting in enhanced anti-tumor efficacy in the heated region and in decreased toxicity (DvorakJ. 2004). Caelyx® has been investigated by Koukoukaris (Koukourakis MI. 2000) in glioblastoma and in metastatic brain tumours. These authors are in agreement with the Chua and Lesniak group, who have concluded that Caelyx® selectively overcomes the blood brain barrier and accumulates 13-19 times higher in Glioblastoma tissue (Koukoukaris MI.2000; Chua SL. 2004; LesniakMS. 2005). Furthermore, Chua (Chua SL. 2004) has demonstrated the possibilities of using Caelyx® in association with TMZ in recurrent Glioblastoma. Liposomal doxorubicin has been associated with disease stabilization and a modest haematologic toxicity. These studies have convinced our group to test the use of pegylated doxorubicin in recurrent cases of GBM in our clinic. Our initial cases are thus briefly described hereafter.

Case of patient treated with Caelyx. The patient (a right handed man) was first surgically treated (December 2005) for left posterior parietal Glioblastoma. The patient then underwent RT (45 Gy CFRT in 18 fractions) followed by a boost CFRT to reduced target (20 Gy in 4 fractions). He then started and continued Temodar (10 cycles) until progression (January 2007). This was followed by 2 cycles of ACNU, until progression (March 2007) (Fig.1). He was then started on Ionidamine and RadiofrequencyHyperthermia(HT). The initial cycles were done at 45 day intervals, then after an initial good response and apparent stabilisation, the GBL progressed the treatment was done at larger intervals of up to 9 CT+HT (the last treatment was done in Nov 2007).

Fig.1



The treatment was as follows: 12 mg/m^2 IV + steroids in glucose solution and on day 1200 mg of Quercetin p.o. one hour before HT, and repeated at least four hours later. From days 2 to 5 the patient underwent 4 consecutive days of more HT and quercetin treatment (100 mg before and after completion of HT).
HT was delivered by means of a 13.56 MHz radiofrequency capacitive device (Synchrotherm Duer) via two opposite plates at the maximum tolerated power for at least one hour for five consecutive days. Due to progression we decided to begin 20 mg of Caelyx® i.v. + HT, with the following schedule: after i.v. injection of Caelyx® an HT application lasting 1 h was done. Following a HT every day were applied for 10 times and a partial regression and stabilization was obtained (Fig..2) .

Fig.2