Effects of Trabectedine on tumour growth and metabolism in preclinical models of HER-2 overexpressing ovarian cancer

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Target audience: All oncologists and radiologists involved in new therapeutic strategies in ovarian cancer.

Introduction – Epithelial ovarian cancer (EOC) is a heterogeneous disease with a poor prognosis. Evaluation of metabolic effects of anticancer therapies would enhance the capability of non invasive imaging approaches to monitor molecular mechanisms underlying tumour responsiveness. Magnetic Resonance Spectroscopy (MRS) offers powerful tools to detect metabolic alterations occurring in tumour cells following drug treatment and to identify novel endpoints of tumour response[1].
Trabectedin (ET-743) is a new marine-derived antitumor agent, which has shown in vitro and in vivo activity in multiple tumor types, including soft tissue sarcoma and ovarian cancer [2-4]. Its activity is based on interference with DNA repair mechanisms resulting in cell cycle perturbation and apoptosis. The drug is particularly indicated in platinum-sensitive ovarian cancer patients.

Aims – Purpose of this work was to investigate the role of Trabectedine as a possible new therapeutic approach in a xenograft model of the HER2-overexpressing SKOV3.ip EOC cells in immunodeficient mice.

Methods – Xenografts derived from s.c. implantation of in vitro cultured SKOV3.ip cells (1x 10^6) in the dorsum of SCID mice were treated weekly with trabectedine (0.2 mg/kg, n= 8) or saline (n=5) per three weeks, starting from day 13 post injection (dpi) and their growth was monitored twice a week by caliper.
In vivo MRI/MRS measurements were performed on a Varian/Agilent Inova system, operating at 4.7 T by using a combination of volume and surface coil (RAPID Biomedical). MRI evaluation was performed by T1W (TR/TE=500/20ms) and T2W (TR/TE=3000/70ms) multislice spin echo images. ADC measurements were performed by acquiring DW images (TR/TE=2000/50 ms, b ranging from 0 to 1105 s/mm^2). The different contributions of ADCslow and ADCfast for diffusion and perfusion estimation in tumours have been performed by two separate fits for b values higher or smaller than 100 s/mm^2, respectively. Quantitative ^{1}H MRS analyses were performed according to a protocol described by Canese et al [5] by using a PRESS sequence (TR/TE =4000/23 ms). LCModel was used for spectral fitting. Ex vivo MRS analyses were performed on tissue extracts at 9.4 and 16.4 T by using high resolution Bruker Avance spectrometers as described by Pisanu et al [6]. Histological analysis of xenograft sections following hematoxylin/eosin, Ki67 and HER2 staining was performed on biopsies during and at the end of treatment.

Results - In vivo experiments showed significant differences in tumor growth of trabectedine vs. saline treated SKOV3.ip xenografts (ANOVA, P<0.05) (see Figure 1A). Preliminary results of in vivo and ex vivo MRS showed a decrease in the tCho level and increases in the Lac content as shown in the spectra in Figure 1B and Figure 2A and in the histograms Figure 2B. ADCslow distributions showed the presence of necrosis in the treated tumour which was absent in the saline treated xenografts as indicated by the presence of high value of ADCslow (the right wing of Figure 1C). Increase in the ADC perfusion component is also observed (Figure 1D).

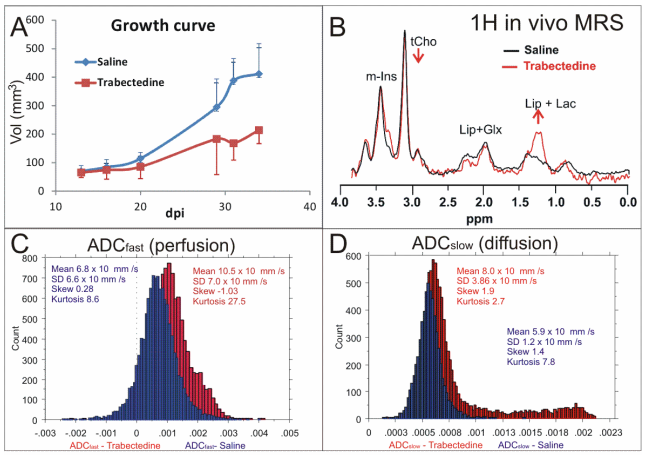

Figura 1 - In vivo 1H MRI/MRS

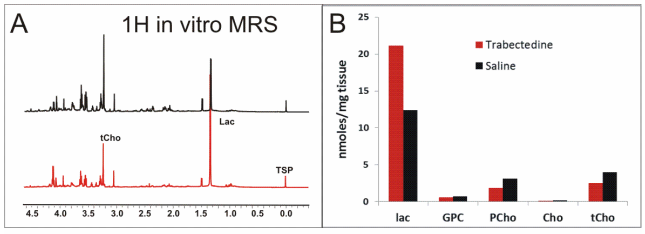

Figure 2 - In vitro 1H HR-MRS

Discussion and conclusions - MRI/MRS represents a power tool for the detection of the cytotoxic response of a new anticancer treatment in experimental EOC models, showing previously unexplored trabectedine-induced metabolic and morphofunctional changes. These alterations are peculiar for cytotoxic effects while no changes in tCho and Lactate content were found in this SKOV3.ip model after a conventional cytostatic treatment [6]. The tCho reduction (mainly due to PCho) suggests that this signal could be a potential biomarker of trabectedine response, while the Lac increase likely reflects the activation of lactic dehydrogenate (LDH) as a consequence of the cytotoxic insult to the cancer lesion cells. Furthermore, the increase in Lac is in agreement with previous findings in serum of patients treated with trabectedine. [7]

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