

METASTATIC BREAST CANCER PATIENTS TREATED WITH LOW-DOSE METRONOMIC CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE AND CELECOXIB: CLINICAL OUTCOMES AND BIOMARKERS OF RESPONSE

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Background: Preclinical results showing therapeutic effect and low toxicity of metronomic chemotherapy (MCT) with cyclophosphamide (Cy) + celecoxib (Cel) for mammary tumors, encouraged its translation to the clinic for treating advanced breast cancer patients (ABCP).

Patients and methods: Study design: Single arm, mono-institutional, nonrandomized, phase II, two steps clinical trial (Approved by Bioethics Committee and Argentine Regulatory Authority). Treatment plan: Cy (50 mg po.d) + Cel (200 mg p.o.bid). Patient eligibility criteria: ABCP progressed to anthracyclines, taxanes and capecitabine, ≤ 4 chemotherapy schemes, with good performance status. Biomarkers assessment: Several pro- and anti-angiogenic molecules and cells were determined as biomarkers. Informed consent signed. Primary endpoint: clinical benefit (CB).

Results: Twenty patients were enrolled. Main clinical outcomes were prolonged disease stabilization and partial remission in 10/20 and 1/20 patients, respectively. CB=55%, Time to Progression (TTP)=21.1 weeks. Median TTP in patients who achieved CB=35.6

weeks, mean Overall Survival=44.20 weeks. There were no grade 3/4 toxicities associated to treatment. Circulating endothelial cells (CECs) increased at the time of progression in patients who showed CB ($P=0.014$). Baseline CECs and Circulating Endothelial Progenitor cells showed marginal associations with TTP. Serum VEGF decreased ($P=0.050$), sVEGFR-2 increased ($P=0.005$) and VEGF/sVEGFR-2 ratio decreased, during treatment ($P=0.041$); baseline VEGF and VEGF/sVEGFR-2 were associated with TTP ($P=0.035$ and $P=0.030$, respectively), while sVEGFR-2 did not.

Conclusions: Treatment was effective, showed low toxicity profile and excellent tolerability. The combination had anti-angiogenic effect. Increased levels of CEC could be useful for detecting progression. Baseline VEGF and VEGF/sVEGFR-2 values could be useful as early predictors of response. Trial registration: ANMAT#4596/09.

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