Meet the Expert: Session 2 Oncology

4. Advances in the Application of Metronomic Chemotherapy for the Treatment of Breast Cancer or Ovarian Cancer

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A new concept for cancer treatment, especially breast and ovarian cancer, is "metronomic" chemotherapy – the prolonged use of close, regular administration of relatively low minimally or non-toxic doses of chemotherapy with no long break periods. It is thought the main targets for this type of therapy are endothelial cells in the tumor neovasculature, and circulating endothelial progenitor cells, although there are other possible targets as well including tumor cells. Combination with a targeted antiangiogenic drug such as antibodies to VEGF or VEGF receptor-2 significantly improves the efficacy of metronomic chemotherapy regimens. The first clinical trials of metronomic chemotherapy involved daily treatment of metastatic breast cancer (MBC) patients, using oral drugs such as cyclophosphamide (CTX) and methotrexate. Subsequent phase II clinical trials in MBC suggest combination of this or similar metronomic regimens with an aromatase inhibitors (letrozole), trastuzumab, or bevacizumab can improve clinical benefit, with minimal toxicity.

With the goal of improving clinical metronomic chemotherapy for advanced malignancies, we have developed new and unique models of advanced visceral metastatic disease using the human breast, ovarian, hepatocellular carcinoma or melanoma cell lines. Highly metastatic variants are generated by isolating lung metastases emerging in mice four months after surgical resection of a primary orthotopic transplant, in the case of breast cancer or melanoma. These metastases are developed into cell lines, which are then used in a second round of selection involving orthotopic transplantation, and recovery of large modular lung metastases which arise within six weeks of resection. Cell lines from such metastases were developed and used for subsequent therapy experiments, in which treatments are initiated once visceral metastatic disease is firmly established in multiple organ sites. Using this model in our breast cancer studies, we found that the long-term daily all oral metronomic combination of CTX and tegafur + uracil (UFT) caused remarkable prolongation of survival with no overt toxicity, in contrast to metronomic UFT or CTX alone (R Munoz et al., Cancer Res 66: 3386–91, 2006). This result helped stimulate a phase II clinical trial in MBC patients using CTX with an oral 5-FU prodrug plus bevacizumab in which unusually encouraging results were reported, both in terms of efficacy and favourable toxicity (Dellapasqua et al. J Clin Oncol 26: 4899–905, 2008). More recently we have developed a model of advanced human ovarian cancer in immune-deficient mice, using intraperitoneally injected luciferase-positive OVCAR-3 cells. Metronomic administration of CPT-11 has shown highly significant anti-tumor activity in this model, with minimal toxicity. In addition, recent phase II clinical trial results by Garcia et al. (J Clin Oncol 26: 76–82, 2008) have shown promise of daily oral low-dose cyclophosphamide combined
with bevacizumab (Avastin®) for the treatment of advanced, recurrent ovarian carcinoma. Studies are ongoing in my laboratory investigating the efficacy and toxicity of various promising metronomic chemotherapy regimens combined with a targeted antiangiogenic drug that might be considered for clinical trial testing in women with recurrent ovarian carcinoma.