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Invited Abstract (Plenary Session): Determination of Clinically Effective Dose and Schedule

Using a Novel Computer Technology for Tailoring Targeted and Chemotherapeutic Drug Schedules to the Individual Patient

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Abstract

Introduction: Over the last three decades, mathematical approaches have been employed in the attempt to improve the pharmaco-therapeutic rationale in oncology (e.g., Agur, Arnon, Schechter, 1988, 1992; Ubezio, Tagliabue, Schechter, Agur, 1994). To aid in tailoring drug treatments to individual patients, a predictive biosimulation technology was constructed, comprising computer-implemented mathematical models of physiological, pathological and pharmacological processes in a patient's body (denoted *Virtual Cancer Patient*, or *VCP*). The VCP was validated by accurately retrieving clinical outcomes in chemotherapy-treated breast cancer patients. Using this tool, *in vivo* effects of targeted drug therapy on tumor progression were predicted, such as the low efficacy of long-term monotherapy that inhibits the vascular endothelial growth factor (VEGF) receptor, and the higher prospects of a combined therapy, inhibiting both VEGF and the platelet-derived growth factor (PDGF; Arakelyan, Vainstein, Agur, 2002a,b). The validated VCP served for identifying a new regimen involving a once weekly application of low docetaxel doses, which is expected to significantly improve efficacy/toxicity ratio in breast cancer patients. The aim of the present work was to test the efficacy of the suggested regimen in a mesenchymal chondrosarcoma (MCS) disease model, validated in xenografts, and to put forward improved regimens of chemotherapy and targeted drug combinations for a specific MCS patient.

Materials & Methods: The validated disease model was calibrated by growth curves and histopathological results of untreated human tumor xenografts, derived from a lung metastasis of a MCS patient. The xenograft model was then scaled to a human MCS model, based on a gene expression analysis. Published data and *in vitro* proliferation assays of the patient's tumor cells served for modeling pharmacokinetics and

pharmacodynamics in the mice-xenografted human tumor, of targeted therapies (bevacizumab, sunitinib, sorafenib) and of chemotherapeutics, e.g., docetaxel, gemcitabine, doxorubicin, irinotecan. Tumor growth dynamics were then simulated under different mono- and combination treatment schedules and compared to the corresponding experimental growth curves of treated and untreated xenografted tumors. Subsequently, the validated xenograft model was scaled to portray the human patient's characteristics and used to predict treatment outcomes of the above mentioned drugs, as well as of perifosine and bortezomib. Improved regimens were selected, based on the expected changes in size of the patient's lung metastasis, whose initial diameter is 57 mm.

Results: A combination of bevacizumab and docetaxel and a sunitinib monotherapy were predicted to be significantly superior to all other tested therapies, most notably gemcitabine, in inhibiting the MCS patient's tumors, xenografted in mice. The average accuracy of the VCP's predictions in MCS xenografts was 82%.Over a 60 day treatment period, the combination doxorubicin+sorafenib, bevacizumab +docetaxel, bevacizumab +irinotecan, perifosine+sorafenib, and high-dose bortezomib monotherapy, were predicted to be most efficacious for the MCS patient himself. In particular, a combination of bevacizumab and either docetaxel, or irinotecan, applied once weekly, is predicted to be more successful in suppressing the MCS tumor growth than the standard bevacizumab therapy, applied in combinations with docetaxel or irinotecan. However, none of the simulated schedules is expected to yield complete or partial response. Based on Arakelyan, Vainstein, Agur (2002a,b), long-term efficacy of several bevacizumab+docetaxel combinations was tested with or without sorafenib, sorafenib being an inhibitor of both PDGF and VEGF receptors. Thus, several 120 days treatment schedules were simulated and efficacy was estimated 28 days post treatment, according to the RECIST protocol, as well as 120 days post treatment. Based on the simulation results it is predicted that the most efficacious bevacizumab +docetaxel schedule, over a four months treatment period is Bevacizumab 15 mg/kg Ivinf 90 min q14d9′ + docetaxel 43 mg/m2 IVinf 90 min (q8d6+14′d rest)2′. However, even though this regimen yields significantly smaller tumors than other bevacizumab+docetaxel combinations, it is still expected to lead to progressive disease. In contrast, the addition to the latter bevacizumab+docetaxel regimen of Sorafenib (400 - 500 mg/m^2, PO, b.i.d 120 ′) is predicted to result in a stable disease.

Conclusions: Our results suggest that treatments involving a cytotoxic agent and an anti-angiogenic agent better suppress tumor growth than chemotherapy alone. Regimens that involve bevacizumab dosings and a weekly application of docetaxel, or irinotecan, are predicted to be the most efficacious among the tested treatment combinations, thus confirming earlier VCP predictions. Yet, it is predicted that even these schedules, applied over 120 days, will result in a progressive disease. In contrast, a stable disease is expected to be achieved during a similar treatment period of a weekly chemotherapy, combined with both a VEGF inhibitor and a PDGF receptor inhibitor. Further clinical research is warranted for confirming the superiority of the suggested schedule. The xenograft experiments, validating the model predictions, support the use of the VCP as a powerful tool for personalizing patients' treatment, especially when the application of new drugs is anticipated.

References:

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