Wednesday, 21 March 2012 12:00–13:15

POSTER SESSION

Targeted Therapy

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Anti-tumor and Anti-cancer Stem Cell Activity of a Poly ADP-ribose Polymerase Inhibitor Olaparib in Breast Cancer Cells

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Purpose: Although the poly ADP-ribose polymerase (PARP) inhibitor olaparib is known to have a potent anti-tumor activity in BRCA-related breast cancer cells, a limited number of preclinical studies have shown anti-tumor activity of olaparib in BRCA-naïve breast cancer cell lines. We have investigated the anti-tumor activity of olaparib in breast cancer cell lines derived from patients with non-familial sporadic breast cancer.

Methods: Effects of olaparib (AstraZeneca) alone or in combination with five different chemotherapeutic agents (cisplatin, doxorubicin, etoposide, paclitaxel and SN38) on cell growth, cell cycle progression, apoptosis and proportion of cancer stem cells using the mammosphere assay and CD44/CD24/ESA cell surface marker assay were investigated in a panel of six sporadic breast cancer cell lines. The ERK phosphorylation was also investigated to elucidate mechanisms of action of olaparib.

Results: Olaparib significantly inhibited the growth of two estrogen receptor (ER)-positive and HER2-negative breast cancer cell lines and two ER−negative and HER2-negative breast cancer cell lines (the 50% growth inhibitory concentrations were 1.3-3.0μM) associated with the G2/M accumulation and induction of apoptosis. In contrast, two HER2-positive cell lines were resistant to olaparib. Interestingly, olaparib significantly decreased the proportion of putative cancer stem cells in either sensitive or resistant cell lines. In addition, olaparib increased the expression of p-ERK. Combined treatments of olaparib with a MEK inhibitor U0126 completely suppressed the expression of p-ERK. These treatments also inhibited the G2/M accumulation and apoptosis induction by olaparib. Among five chemotherapeutic agents commonly used for breast cancer treatment, only an irinotecan metabolite SN38 showed an additive anti-tumor activity with olaparib. Importantly, the combined treatment enhanced an increase in the G2/M accumulation and apoptosis induction as well as a decrease in the proportion of cancer stem cells.

Conclusions: This study confirms that the PARP inhibitor olaparib has substantial anti-tumor and anti-cancer stem cell activity in breast cancer cell lines of a non-familial origin. Up-regulation of p-ERK might explain, at least in part, anti-tumor and anti-cancer stem cell activity of olaparib. A combined treatment of olaparib with irinotecan might be effective in the treatment of non-BRCA-related breast cancer.

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An Italian Cost-effectiveness Analysis of Paclitaxel Albumin (nab Paclitaxel) Vs Solvent-based Paclitaxel for Metastatic Breast Cancer Patients − the CONSTANZA Study

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Background: Paclitaxel albumin is a nanoparticle albumin-bound paclitaxel formulated with the aim to increase therapeutic index in metastatic breast cancer (MBC).

When compared to sb-paclitaxel, paclitaxel-albumin has reported slower time to progression, higher response and overall survival, lower incidence of neutropenia, no need for premedication and shorter time of administration.

This study investigates paclitaxel albumin's cost-effectiveness vs sb-paclitaxel for MBC patients in Italy.

Material and Methods: A Markov model with progression-free, progressed, and dead health states was developed to estimate costs, outcomes and quality-adjusted life-years (QALYs) over 5 years from the Italian National Health Service (INHS) viewpoint.

Weibull extrapolations of trial-based survival data generated transition probabilities to Markov-model states.

On the grounds of the existing literature, patients were assumed to receive paclitaxel albumin 260 mg/m^2 q3w or sb-paclitaxel 175 mg/m^2 q3w as a 2nd line treatment. Health care resource consumption for supportive care, patients' assessment and end of life care were obtained from published sources, whereas for premedication, chemotherapy administration, postmedication and adverse events management was collected from a survey performed on a sample of five Italian oncological centres active in MBC treatment. Health care resources were costed at Euro (€) 2011 via literature. Published utility weights were applied to health states to estimate the impact of response, disease progression and adverse events on QALYs. Two sensitivity analyses (SAs) tested the robustness of the base case Incremental Cost-Effectiveness Ratio (ICER).

Results: Paclitaxel albumin reached an ICER of €16,903.73 for each QALY gained (95% CI:€13,202.50;€37,230.14).

One-way SA showed ICER to be mainly driven by taxanes cost.

Probabilistic SA highlighted that paclitaxel albumin has a 0.98 probability to be cost-effective for a threshold-value of €40,000 and is the optimal alternative from a threshold-value of €18,318 onwards.

Conclusions: Paclitaxel albumin prolongs time to progression, provides higher response rates and overall survival, gains more QALYs than sb-paclitaxel in MBC treatment. Base case analysis and SAs show its high cost-effectiveness for INHS when compared to the current Italian informal acceptability range for ICER (€25,000; €40,000).

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Neurotensin-polyplex as a Potential Tool in Gene Therapy for Human Breast Cancer

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The expression of neurotensin (NTS) receptor subtype 1 (NTSR1) is produced in the cells of invasive breast-ductal carcinoma, which is the most common subtype of breast cancer worldwide. Recently, our group has shown the potential of the NTS-polyplex to transfect therapeutic genes into NTSR1-expressing cells (Mexican patents #264932 and #287089; Rubio-Zapata et al., Cancer Gene Ther, 2009, 16:573−84). Our work aims to demonstrate that the NTS-polyplex is able to transfect a suicide gene and cause cell death in the human-adenocarcinoma MDA-MB-231 cells xenografted in athymic mice.

First, we showed the specificity of NTS-polyplex-mediated gene delivery to cultured MDA-MB-231 cells by using internalization and expression assays together with pharmacological blockade studies. The suicide effect of the HSVTK-gene transfection and ganciclovir (GCV) treatment was evaluated by using cell viability and annexin-V assays. For the experiments in vivo, 3 x 10^6 MDA-MB-231 cells were subcutaneously xenografted in Nu-Nu female mice, age 4 weeks. When tumors reached a 100-mm^3 volume, the mice were split into an experimental group (n = 3) and control (n = 3). The former group was transfected with an HSVTK gene and treated daily with GCV (100 mg/kg body weight) to activate the suicide system. At the end of study, the mice under deep anesthesia were intracardially perfused with 50 mL of PBS followed by 50 mL of 4% paraformaldehyde to dissect out the tumors for histopathological analysis.

Both RT-PCR and immunofluorescence studies confirmed the presence of the NTSR1 in the MDA-MB-231 cells, which were able to specifically internalize and express reporter genes delivered by the NTS-polyplex. In these cells, the transfection of the HSVTK gene decreased cell viability by 60%. This specific therapeutic effect was reproduced in vivo. The NTS-polyplex transfection of the HSVTK gene and GCV treatment significantly decreased the volume, growing rate, and weight of the MDA-MB-231 tumors over time as compared with the controls.

In conclusion, our results in vitro and in vivo clearly show the ability of NTS-polyplex to transfect the HSVTK gene and kill the MDA-MB-231 cells of human breast adenocarcinoma after GCV administration. Our gene therapy model using NTS-polyplex holds great promise in the treatment of breast adenocarcinoma.

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