available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Abstracts

Genitourinary cancer

SUNITINIB IN ADVANCED CLEAR CELL RENAL CANCER: A SINGLE CENTRE EXPERIENCE

G.S. Bruni, G. Facchini, V.R. Iaffaioli, C. Pisano, S. Pignata. *Uro-Gynecologic Department, National Cancer Institute of Naples, Italy*

Renal cell carcinoma represents 2–3% of all cancer. New systemic therapies have reached the market in the last 2 years. Sunitinib was found to be superior to IFN-a in a phase III trial in metastatic renal cancer patients (mRC). Fatigue, gastrointestinal and skin are the most frequently reported toxicities. Most of them are easily solved with medical intervention or dose changes. In our center we evaluated the sunitinib compliance and activity in an unselected series of consecutive patients. In the first year after sunitinib availability in Italy, 17 consecutive patients (13 male, 4 female, median age 62 years, range 40–81) with intermediate/poor risk mRC were treated in our institution. Most frequent metastatic sites were lung, pleura, bone, nodes and liver. Six out of 17 patients were pretreated with cytokines. Overall 68 cycles of sunitinib were given (range 1–11). Objective responses were observed in 5 patients (29%), while stable disease was observed in 4 patients (23%) (overall clinical benefit 52%). Toxicity was as follows:

	G1–2 (%)	G3 (%)
Gastrointestinal	75	0
Skin	29	11
Mucositis	17	23
Hypotirodism	23	0
Anemia	11	0
Leukopenia	11	0
Hearth	6	6
Fatigue	35	6

Results: Dose reductions were done in 9/17 patients (skin 1, mucositis 4, hearth 2, fatigue 1, anemia 1), and in 3 cases treatment was temporaneously interrupted due to toxicity. In conclusions, sunitinib was confirmed to have significant activity in mRC. G3 toxicities are unfrequent, but often require dose modifications. Self-training and internal guidelines in side effects medical treatment and dose reduction rules seems crucial for an optimal use of sunitinib in unselected patients out of clinical trials.

doi:10.1016/j.ejcsup.2008.06.046

CYR61 DOWN-MODULATION SENSITIZES PROSTATE CANCER CELLS TO ZOLEDRONIC ACID AND DOCETAXEL: A NEW ANTI-CANCER STRATEGY

M. Caraglia [a], M. Marra [a], G. Meo [a], S. Zappavigna [a], B. Vincenzi [b], A. Baldi [c], M. Rosolowski [d], M. Loeffler [d], G. Tonini [b], D. Santini [b], A. Budillon [a]. [a] *Department of Research, Experimental Pharmacology Unit, National Institute of Tumours Pascale, Naples, Italy.* [b] *Medical Oncology, University Campus Bio-Medico, Rome, Italy.* [c] *Second University of Naples, Italy.* [d] *Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Germany*

We have analysed the gene modulation induced by zoledronic acid (ZOL) in androgen-resistant prostate cancer PC3 cells with cDNA microarray platform to identify new molecular targets of ZOL in prostate cancer. The gene coding for cysteine-rich, angiogenic inducer, 61 (CYR61), often over-expressed in tumour cells, resulted highly down-regulated with a fold-change of 5.58. Therefore, we have studied the effects of different concentrations of ZOL on CYR61 protein product and we have found that CYR61 protein expression was significantly decreased after exposure to ZOL. The effect of ZOL on CYR61 expression was dose and time-dependent and was due to a reduced transcriptional activity of CYR61 promoter as demonstrated by transfection with a plasmid encoding for luc-CYR61 promoter. Interestingly, other signal transduction inhibitors or cytotoxic agents did not induce or induced less effect on CYR61 modulation if compared to ZOL. Moreover, ZOL reduced CYR61 expression through decreased activation of ras-raf-1-dependent pathway that was dependent from isoprenylation inhibition since they were antagonized by the addition of either farnesol or geranilgeraniol. Finally, we have investigated the role of CYR61 in the regulation of growth inhibition and invasion/motility of PC3 cells using a shRNA for CYR61 in order to down-regulate the expression of CYR61 protein. We have found that shCYR61 enhanced inhibition of proliferation and motility/invasion induced by ZOL by S-phase accumulation. In the same experimental conditions, CYR61 protein down-regulation potentiated the inactivation of the ras-dependent proliferation pathway. Since CYR61 was reported to be involved in the resistance to taxanes we have evaluated if ZOL could sensitize PC3 cells to Docetaxel (DTX). We have found a sequence-dependent synergism induced by the combination between ZOL and

doi:10.1016/S1359-6349(08)00111-0

DTX on PC3 cell growth inhibition and similar results were recorded after transfection of PC3 cells with shCYR61. In conclusion, it is possible to design new molecular rationale-based therapeutic strategies in androgen-independent prostate cancer.

doi:10.1016/j.ejcsup.2008.06.047

DOCETAXEL AND ZOLEDRONIC ACID COMBINATION ADMINISTERED IN TWO DIFFERENT SEQUENCES IN HORMONE REFRACTORY PROSTATE CANCER PATIENTS: PHASE I CLINICAL STUDY – ZANTE

G. Facchini [a], M. Caraglia [c], A. Morabito [f], S.G. Bruni [a], G. Nasti [e], P. Maiolino [d], S. Striano [b], A. Budillon [c], A. Di Napoli [a], M. Marra [c], C. Pisano [a], S. Pignata [a], F. Perrone [f], R.V. Iaffaioli [e]. [a] *Medical Oncology Unit, Uro-Gynaecologic Department, Naples, Italy.* [b] *Urologic Unit, Uro-Gynaecologic Department, Italy.* [c] *Experimental Pharmacology, Italy.* [d] *Pharmacy Unit, National Cancer Institute, Naples, Italy.* [e] *Colo-Rectal Unit, National Cancer Institute, Naples, Italy.* [f] *Clinical Trial Unit, National Cancer Institute, Naples, Italy.*

Background: Docetaxel (DTX) is effective in the treatment of hormone-refractory prostate carcinoma patients (HRPC). *In vitro* data suggest that zoledronic acid (ZOL) and DTX have a synergistic effect on the growth inhibition of prostate cancer cells and that such synergism is sequence-dependent. Therefore, prostate cancer is a suitable target for a pharmacological combination between DTX and ZOL. On the basis of these considerations, a phase I trial on the combination of ZOL and DTX was designed in the treatment of HRPC.

Materials: A dose-escalation of DTX was planned in combination with a fixed dose of ZOL (2 mg), both administered every 14 days. The following two different sequences of the two drugs were explored: Sequence A: DTX at day 1 followed by ZOL at day 2. Sequence B: ZOL at day 1 followed by DTX at day 2. The first dose level of DTX was 30 mg/m^2 with a planned dose escalation of 10 mg/m^2 for each level until 50 mg/m^2. Serum cytokines and PBMC were also collected prior and after the different treatments at each cycle.

Results: Up to now, we have enrolled 22 patients. Six patients at third level (Sequence B) were required due a case of vascular toxicity of grade III (deep thrombo-phlebitis). A different pattern of circulating sangiogenic factors (interleukin 8 and 12, VEGF, PDGF), cytokines (TNF-a, IFN-c, interleukin 6 and 4) and gamma/delta T lymphocyte subpopulation was recorded in the two different sequences. The study is still ongoing and further results will be presented at GOIM meeting.

doi:10.1016/j.ejcsup.2008.06.048

INTRAVESCICAL GEMCITABINE VERSUS MITOMYCIN FOR RECURRENT SUPERFICIAL BLADDER TUMOURS (STAGES PTA AND PT1): A RANDOMIZED PROSPECTIVE STUDY

Vincenzo Faiola [a], Liliana Montella [a], Raffaele Addeo [a], Sergio Bellini [b], Antonio Miragliulo [b], Gregorio Cennamo [a], Rosario Guarrasi [a], Raffaele Gargiulo [a], Michele Lanna [b], Bruno Vincenzi [d], Michele Caraglia [c], Salvatore Del Prete [a]. [a] *U.O. Oncologia, Ospedale SanGiovanni Di Dio ASLNA3, Frattamaggiore (NA), Italy.* [b] *U.O. Urologia, Ospedale "Santa Maria Delle Grazie", Casoria (NA), Italy.* [c] *U.O. Frarmacologia Sperimentale, INT Pascale, Napoli, Italy.* [d] *U.O. Oncologia, Campus Biomedico, Roma, Italy*

Background: Approximately, 30–40% of patients with a superficial bladder cancer treated with Bacille Calmette-Guerin(BCG) or epirubicin do not respond and other 35% of initial responders have a relapse within 5 years. We compare the therapeutic efficacy and toxicity of intravescical instillations of Gemcitabine (GEM) with mitomycin C (MMC) in patients with a recurrent superficial bladder cancer.

Methods: Patients with a history of a recurrent Ta-T1, G1-G2 bladder transitional cell carcinoma, previously treated were enrolled in the study. The patients received a 6-week course of GEM instillations or 4-week course of MMC. In both arms, for the initial responders who remained free of recurrences, maintenance therapy consisted of a 10 monthly treatment during the first year. All patients were followed every 6 months by cystourethroscopy.

Results: A total of 120 patients were enrolled and randomly assigned to either the MMC treatment arm or Gemcitabine treatment arm. The remaining 109 patients (55 in MMC arm and 54 in Gemcitabine arm) were evaluable. The median duration of follow-up was (identical for both groups) 34 months.

Of the 54 patients in the Gemcitabine group 42(78%) remained free of recurrence compared to 37 (67%) of the 55 patients treated with MMC ($p = 0.05$). Among patients with recurrences, 10 in the MMC arm and 6 in the Gemcitabine group had progressive disease by stage: either local urothelial spread, or muscle infiltration, in 5 and 3, respectively. Local toxicity in both treatment groups was acceptable. The incidence of. chemical cystitis in MMC arm was statisticantly different from that in GEM group ($p = 0{,}012$).

Conclusions: Gemcitabine for its better clinical activity and favourable toxicity profile than MMC, is a logical candidate for intravescical therapy in refractory transitional cell patients. Final results will be presented at 2008 ASCO Meeting.

doi:10.1016/j.ejcsup.2008.06.049

HIGH-DOSE CHEMOTHERAPY AS INITIAL SALVAGE TREATMENT IN RELAPSED TESTICULAR CANCER PATIENTS

F. Morelli, A. Piano, A. Capotorto, L. Tozzi, S. Ronga, V.M. Valori, E. Maiello. *Oncology Unit, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy*

Background: In the last few years, high dose chemotherapy (HDCT) with haematopoietic stem cell transplantation (HSCT) has been increasingly investigated as a therapeutic option for early or late intensification in patients with poor prognosis germ cell tumor (GCT) or in pats who relapse or who have a partial response after a first line chemotherapy.

Methods: Eleven patients were treated with three cycles of VeIP (ifosfamide 1200 mg/m^2, mesna 1200 mg/m^2, cisplatin 20 mg/m^2, days 1–5 and vinblastine 0.11 mg/kg, days 1–2) and one course of HDCT: Carbo-PEC (carboplatin 400–550 mg/m^2/day on day 1, etoposide 450 mg/m^2/day, cyclophosphamide 1600 mg/m^2/day and mesna 3600 mg/m^2 on days 1–4) followed on day 7 by HSCT.