4520 POSTER

Sunitinib plus interferon-alfa in the first-line treatment for metastatic renal cell carcinoma (mRCC): results of a dose-finding study

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Background: Sunitinib malate (SUTENT®) is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3 with demonstrated antitumor activity in two, multicenter phase II trials of pts with cytokine-refractory mRCC [Motzer et al., JAMA 2006; 295: 2516–24] and an international, phase III randomized trial in which sunintinib showed statistically superior efficacy over interferon (IFN)-alfa as first-line mRCC therapy ($P < 0.001$) [Motzer et al., NEJM 2007; 356: 115−24]. Here we report the safety and efficacy results of a phase I trial for sunitinib in combination with IFN-alfa.
Methods: Treatment-naive pts with clear-cell mRCC received sunitinib 50 or 37.5 mg PO QD in 6-wk cycles (4 wks on TX, 2 wks off) plus IFN-alfa (Intron-A®) at a starting dose of 3 MU SC TWI with weekly intrapatient dose escalation to a maximum of 9 MU as tolerated. Pts who did not tolerate the dose combination received lower doses of sunitinib or IFN-alfa or had dose interruptions. Doses of sunitinib plus IFN-alfa were deemed tolerable if $\geqslant$4/6 pts completed 2 cycles without dose reduction or interruption.
Results: Of 25 pts enrolled, 19 (16 males, 3 females) were evaluable for safety and response; data were premature for 6 pts treated with sunitinib 37.5 mg and IFN-alfa 3 MU. The median age (n = 19) was 63 years (range, 45–77) and, according to MSKCC risk group categories [Motzer et al., JCO 2002; 20: 289–96], 37% were classified with a good prognosis and 63% with an intermediate prognosis. Twelve pts who started treatment with sunitinib 50 mg dose escalated to IFN-alfa 6 or 9 MU compared with 13 pts who started with 37.5 mg and dose escalated to IFN-alfa 3 or 6 MU. Four of 19 pts tolerated 2 cycles, whereas 68% and 90% had dose interruptions of sunitinib and IFN-alfa, respectively. Grade 3 toxicity was reported in 15 pts, and grade 4 toxicity (hypertension) and grade 5 toxicity (myocardial infarction) were each reported in 1 pt. The most common grade 3 toxicities were neutropenia (26%), fatigue (26%), and hand–foot syndrome (16%). After a median of 3 cycles, there were 2 pts with partial response, 14 with stable disease, and 2 with progressive disease (1 pt was not evaluable).
Conclusions: Adverse events with sunitinib plus IFN-alfa, neutropenia and fatigue, were similar to those associated with single-agent use of both agents, and resulted in frequent dose modifications and interruptions. The safety and efficacy of sunitinib 37.5 mg and IFN-alfa 3 MU are being assessed.

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Sequential high dose chemotherapy with paclitaxel and etoposide, carboplatin, melphalan and autologous stem cell support in patients with germ cell tumors; a phase II study

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Background: To determine the activity, TTP and OS of sequential high dose chemotherapy incorporating paclitaxel, in patients with resistant germ cell tumors.
Materials and Methods: Sixteen patients (15M/1F), mean aged 28.5 years (range 16 to 50) with resistant germ cell tumors were enrolled. Following standard premedication paclitaxel (400 mg/m^2 to 560 mg/m^2) was infused over 24 hours. About 1/3 of previously collected and cryopreserved PBSC's were transfused after 72 hours. Following hematologic reconstitution second high dose chemotherapy was infused, consisting of carboplatin 1200 mg/m^2, etoposide 1200 mg/m^2 and melphalan 120 mg/m^2 over 72 hours. Remaining 2/3 of cryopreserved PBSC's were transfused 72 hours after megatherapy.
Results: Overall response rate was 87.6% (7 CR, 7 PR) whereas 1 SD and 1 PD were observed. Of 7 non-responding to conventional treatment patients 1 converted to CR, 5 to PR and 1 showed PD. Two patients who were in CR at transplantation remained in CR and of 7 patients in PR after conventional treatment 4 showed CR, 2 PR, and 1 SD. Main non-hematologic grade III−IV toxicities consisted of neuropathy (12.5%), mucositis (6.3%) and febrile neutropenia (12.5%) after paclitaxel and mucositis (31.3%), nausea and vomiting (12.5%) and febrile neutropenia (50%) after carboplatin, etoposide and melphalan. Mean TTP was 15.09 months (SE 3.57) and mean OS was 24.22 months (SE 3.5).
Conclusions: Incorporation of high-dose paclitaxel chemotherapy in sequential double graft programs appears to benefit patients with resistant germ cell tumors and bears manageable toxicity.

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Serum levels of angiogenin, EAN-78 and GRO chemokines in patients with renal carcinoma in the course of the treatment

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Objective: The progression and development of malignant tumour metastases require a vascular supply. Our present knowledge is not sufficient enough so that we can understand, in detail, the role of chemokines and chemokine receptors in the progression and development of metastases of renal cell carcinoma (RCC).
Methods and Patients: We identified serum levels of angiogenin, panGRO (CXCL 1, 2, 3) and ENA-78 (CXCL5) in serum of 32 patients with RCC (dividing was based on TNM classification) and 14 healthy blood donors by means of multiparametric protein array method of the RayBiotech Company (USA), RayBio Human Angiogenesis Antibody Array I. The resulting concentration of individual proteins was expressed as relative value of spot colouring in comparison to controls.
Results: We found significant differences between the blood donors and patients with RCC both in pre-operative and post-operative levels of angiogenin, panGRO and ENA-78 (on day 7 and week 8). The increase in angiogenic factors lasted in patients even without metastases 2 months after surgery. None of the patients showed sings of other inflammatory processes. We found no correlation between the levels of angiogenin and stages I+II, III and IV RCC. Patients with advanced carcinoma (stage III) had pre-operatively higher serum levels of ENA-78 than those with stages I+II ($p = 0.009$) and IV ($p < 0.001$). Eight weeks after surgery, patients with RCC stages I+II had significantly higher levels of panGRO than patients with stage IV.
Conclusion: The selected method is sufficiently sensitive for the identification of serum angiogenin, panGRO and ENA-78. Chemokines are quickly degradated at the site of inflammation and the resulting reaction is often compartmentalized. Only detailed analysis of the microenvironment, which determines the resulting immune response, can help us fully clarify the cellular interactions of the immune system and the tumour.

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Retroperitoneal lymphadenectomy (RPLA) or primary cisplatin (CCDP) – based chemotherapy (CHT) in clinical stage (CS) B1/B2 nonseminomatous testicular tumors (NSTT): long term results of the prospective non-randomized study

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Background: In order to reduce therapy related morbidity in patients (pts) with NSTT in CS-B1/B2, we performed a prospective non-randomized study comparing the RPLA with 2−4 cycles of adjunctive CHT (Arm A) vs 3−4 cycles of primary CDDP-based CHT and selective RPLA in pts with incomplete response (IR) (Arm B).
Materials and Methods: From 03.80 to 12.04 we managed 203 pts in CS – B1/B2: 43 underwent primary RPLA (unilateral 26) (1980–1996) (Arm A) and 160 received induction CDDP-based CHT +/− RPLA (1996–2004) (Arm B). 3 different CHT regimens were applied (VB, PVB and PEB) as adjunctive or inductive treatment. 130 pts (64%) had raised serum tumor markers (STM) post-orchiectomy.
Results: In Arm A, 5% had pathologic stage (PS) A, 85% PS-B1/B2 and 15% PS-B3 (initially CS-A occurred in 58% pts). 1 pt died after RPLA from pulmonary embolism and is not available for relapse. 1 pt (4.8%) in PS-B1 relapsed in RPLN at 108 months (mo) and achieved CR with RPLA and 5/19 pts (26.3%) in PS-B2 relapsed within median free interval (MFI) of 42 mo (lung 2, only elevated STM 2, RPLN 1) with CR following applied therapy in 1 pt (20%) ($p < 0.005$). After median follow-up (MFU) of 16.3 years (y) overall relapse rate (RR) was 15% with disease specific survival (DSS) in 90.5% pts. In Arm B, 123 (77%) achieved CR with CHT alone, whereas 37 pts (23%) with IR underwent RPLA [histology: fibrosis 9 (24.3%), teratoma 23 (62.2%), carcinoma 5 (13.5%)]. Recurrence/progression occurred in 13 pts (8.1%) (only elevated STM 4, RPLN 6, lung 1, RPLN+lung 1, liver 1) within MFI of 27 mo, with CR following