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.

4522 POSTER

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.

4523 POSTER

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

salvage treatment in 7 pts (53.8%) (CHT 2, RPLA 3, CHT+RPLA 2). DSS is achieved in 154 pts (96.25%) at MFU of 10.9 y. There were no CHT related toxic deaths. Statistical analysis failed to demonstrate any difference regarding RR (15% vs 8.1%) and DFS (90.2% vs 96.25%) between 2 analyzed groups of pts. Postoperative complications occurred more frequently in Arm A (21 vs 4 events) ($p < 0.001$). In Arm A ejaculatory potency was preserved in 62.8% vs 37.2% in favor of unilateral RPLA ($p < 0.001$), whereas overall ejaculatory potency was superior in Arm B (60.5% vs 86.5%) ($p < 0.001$).
Conclusions: Our experience with primary CDDP-based CHT and selective RPLA in CS-B1/B2 NSTT is superior to primary RPLA followed by adjunctive CHT since it 's resulted in high survival rate, low RR, acceptable toxicity and post-operative complications necessitating RPLA in only 23% of cases.

4524 POSTER

Renal cell carcinoma: surgical excision and adjuvant radiotherapy for renal bed recurrence

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Background: The use of postoperative radiotherapy (PORT) in the management of renal cell carcinoma (RCC) is controversial and has previously been associated with unacceptable toxicity. We report the toxicity and outcomes of patients undergoing this treatment after excision of locoregional recurrence.
Methods: From a prospective database 35 patients had RCC recurrence excised between 1999–2006. 10 patients received PORT. CT planned 3D PORT was utilised where possible to deliver $\geqslant$50 Gy in 1.8–2.25 Gy daily fractions. Parallel opposed para-aortic PORT was given for isolated lymph node (LN) recurrence to 45 Gy in 25 fractions. Case records were reviewed for acute and late RT toxicity (RTOG CTC grading) and outcomes.
Results: The median (mean, range) interval from primary nephrectomy to recurrence excision was 2.91 years (3.72, 0.51−10.7) and median interval from surgery to PORT was 90.5 days (321, 24–1995). 7 cases received PORT immediately post-surgery: 4 isolated renal bed recurrences, 2 renal bed and LN recurrences, 1 LN recurrence. 3 cases had deferred PORT – 2 further renal bed recurrences, 1 LN disease. The median total dose was 50 Gy (49.9, 45−60). Treatment was well tolerated in all cases with no unplanned gaps or grade 3 or 4 toxicity. Prophylactic antiemetics were given with nausea and vomiting limited to grade 1 in 5 cases, grade 2 in 2 cases. Grade 1 diarrhoea occurred in 1 case. Haematological and hepatic blood indices were unaffected. 1 case had an increase in serum creatinine and nephrotic syndrome due to paraneoplastic phenomenon. After a median follow up of 19.1 months (24.9, 7.4−86), 6 patients remain alive of whom 4 are disease free, 2 have developed distant metastases. Only one patient relapsed with local failure following incomplete resection. The median time to development of distant metastases was 9.7 months (20.1, 2.2−70.1). For patients who received surgery alone ($n = 24$), after a median follow up of 20.7 months, 9 are alive of whom 4 are disease free, 3 have recurrent local disease, and 2 have metastatic disease. The median time to development of local failure from surgery was 2.3 months (5.3, 0−13.1) and metastatic disease 5.1 months (8.9, 2.2−24.8).
Conclusion: PORT following surgical excision of locoregional recurrence is achievable without significant toxicity and may prevent further local relapse. Patients remain at high risk of metastatic disease and systemic treatment should also be considered in this selected group.

4525 POSTER

Self evaluation of side-effects of patients treated sequentially with sunitinib and sorafenib in kidney cancer

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Introduction: Sunitinib (SU) and sorafenib (SO), 2 tyrosine kinase inhibitors (TKIs) are currently standard treatment of metastatic renal cell cancer (MRCC). Toxicity profile of these drugs are different, but fatigue, diarrhea, skin reactions are common side effects. The severity of these side effects is commonly reported through NCTI scale. However, patient's own evaluation might be different from physician's one, and self evaluation might be more accurate to evaluate overall toxicity. The aim of this study was to assess through simple questionnaires, comparative toxicity of SO and SU in patients who received both drugs sequentially.
Methods: A simple autoquestionnaire was given to patients who were treated by either SU or SO after previous SO or SU treatment., after at least 2 cycles. This questionnaire included 7 items: fatigue, diarrhea, stomatitis, anorexia, hand foot syndrom, general feeling and overall QoL. All the items were scored from 0 to 10 through an analogic scale. Analysis was done for each item separately.
Results: from october 2006 to mars 2007, 27 patients with MRCC filled out the questionnaire. 17 patients had received SO first (duration 2−27 months) followed by SU (2−11 months) and 10 had opposite sequence (duration 2−15 mths for SU and 2−11 mths for SO). Fatigue was more important with SU than SO, whatever the order of administration (75% in first line, and 66% in second line). Diarrhea was significantly more common with SO, scaled >5 in 82% of the pts. Stomatitis was more common with SU in both sequence order (75% first line, 80% second line). Hand foot syndrom was more common when given after SU (83%) than before (50%). Anorexia was similar between both drugs. Overall evaluation of QoL was similar with both drugs, but SO was considered as more difficult to handle in 63% of the pts who received SO first and in 57% of the pts who received SU first.
Conclusion: self evaluation in patients who received sequentially SO and SU demonstrated that fatigue, stomatitis were more severe with SU, while diarrhea, hand foot syndrom were more common with SO. Overall, treatment with SU was better accepted by the pts than with SO.

4526 POSTER

Safety profile of single-agent sunitinib malate from the French Temporary Authorization for Use program (Cohort ATU) in metastatic renal cell carcinoma (MRCC) after failure of treatment with cytokines and gastrointestinal stromal tumor (GIST) patients after failure of imatinib mesylate treatment

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Background: Sunitinib malate (Sutent®) is an oral multitargeted tyrosine kinase inhibitor. Its targets include vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), KIT, RET and FLT3.
Sutent showed significant clinical activity in MRCC patients, in first line and after failure of cytokine therapy as well as in GIST patients following initial treatment with imatinib.
We report the safety of a French ATU program (Temporary Authorization for Use) initiated on March, 27, 2006. This program included patients with advanced or metastatic RCC who failed treatment with cytokines and patients with unresectable or metastatic GIST refractory or intolerant to imatinib.
Methods: From March 27 to September 22, 2006, 589 patients with advanced and/or MRCC and unresectable and/or metastatic malignant GIST in 147 French centers were treated with a schedule of 50 mg oral dose of Sutent daily for 4 weeks, then 2 weeks rest, until disease progression or intolerance. The data cutoff date for this planned interim analysis was December 31, 2006. This abstract provides the results of this analysis.
Results: The median age of the 544 RCC and 45 GIST patients was 62 years (range 24−84). Performance status (available for 322 patients) was 0−1 in 82%, 2 in 14% and 3−4 in 4% of the patients. At the time of data cut-off, a total of 343 patients received at least 1 cycle of treatment with Sutent with a median of 2 cycles (range 1−6). For the 199 patients evaluable for safety, the most common toxicities (all grades; CTCAE version 3) were asthenia (25%), stomatitis (17%), hand–foot syndrome (16%), thrombocytopenia (13%), diarrhea (11%) and hypertension (9%). The overall incidence of grade 3−4 hematological toxicity was 12% including thrombocytopenia (5%) and neutropenia (4%). Grade 3−4 non-hematological toxicity included asthenia (9%) and gastrointestinal toxicity (6%). Most Sutent-related adverse events improved by interruption of dosing or dose modification. Of the 190 patients who received more than one cycle of Sutent, dose modifications were reported in 63 patients (33%) and cycle delays in 28 patients (15%). Treatment was discontinued in 37 of the 343 patients (11%). Two treatment-related deaths were observed; one MRCC patient experienced diarrhea and septicemia and the other MRCC patient experienced exacerbation of a colonic fistula.
Conclusion: Sutent treatment of patients with advanced or metastatic RCC and GIST was associated with an acceptable safety profile.