Poster presentations (Tue, 25 Sep, 09:00−12:00)
Genitourinary malignancies – other

4508 POSTER

Protodynamic therapy – a novel anti-cancer concept for treatment of urinary bladder carcinoma

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Background: Protodynamic therapy comprises the inhibition of cancer cell proliferation by intracellular acidification that leads to apoptosis. cis-Urocanic acid (cis-UCA), a natural compound found in the mammalian skin, acts as a protodynamic drug capable of transporting protons into the cell cytosol at a mildly acidic extracellular pH. We investigated the activity of cis-UCA and other anti-cancer drugs against human urinary bladder cancer cell lines in vitro.
Methods: The 5637 and T24 bladder carcinoma cells were cultured in DMEM medium with supplements at pH 6.5 and treated with cis-UCA for 15 min to 2 h, or with other anti-cancer drugs for 2 h, washed, and cultured for 40–42 h in drug-free medium. The assay protocol was to simulate the drug exposure of bladder carcinomas upon intravesical instillation. Cell viability was measured by using a colorimetric assay.
Results: The number of viable 5637 cells decreased by 95% after treatment with 2% cis-UCA for 2 h in comparison to vehicle-treated cells ($p < 0.001$). The four other drugs tested at their clinically relevant concentrations had clearly lower anti-cancer activity (Table 1). Decreased viability and proliferation activity was always accompanied by distinct morphological changes (cell shrinkage and loosening) observed in light microscopy.

Table 1. Inhibition of 5637 cell viability after 2-hour treatment with anti-cancer drugs

Drug	Concentration	Inhibition[a]
Cisplatin	10 μM	3.5±0.3%
Paclitaxel	10 μg/ml	64±1.3%
Doxorubicin	10 μg/ml	69±1.4%
Epirubicin	2 mg/ml	89±2.4%
Cis-UCA	2%	95±3.6%

[a]Mean % decrease in the number of viable cells ± SD.

Cis-UCA showed an anti-cancer effect proportional to both duration and concentration of the treatment. A complete loss (99–100%) of viable cells was observed with 4% and 6% cis-UCA after a 2-hour treatment of both the 5637 and T24 cells, and 6% cis-UCA decreased the cell viability by 89–90% only after a 15-min treatment.
Conclusions: The results indicate that cis-UCA may possess therapeutic potential in the treatment of bladder cancer. Non-clinical safety and toxicity studies have demonstrated that cis-UCA is well tolerated both locally and systemically. Therefore, intravesical instillation with cis-UCA could provide the basis for a novel protodynamic therapy of superficial bladder carcinomas.

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Sunitinib versus interferon (IFN)-alfa as first-line treatment of metastatic renal cell carcinoma (mRCC): updated efficacy and safety results and further analysis of prognostic factors

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Background: In an international, randomized phase III trial, sunitinib demonstrated statistically superior progression-free survival (PFS) and objective response rate (ORR) compared to IFN-alfa as first-line therapy in mRCC pts ($P < 0.001$) [Motzer et al., NEJM 2007; 356: 115–24]. We present updated efficacy and safety results from this trial and further assess prognostic factors for PFS.
Methods: Treatment-naive patients with mRCC were randomized 1:1 to receive sunitinib 50 mg po qd in 6-wk cycles (4 wks on, 2 wks off) or IFN-alfa (9 MU sc tiw). The primary endpoint was PFS.
Results: 750 pts were randomized: 375 pts to sunitinib and 375 to IFN-alfa. At the time of analysis, the median duration of treatment was 11 mo (range: <1–31) for sunitinib vs 4 mo (range: <1–28) for IFN-alfa. 56 pts (15%) on sunitinib had discontinued due to AEs vs 84 pts (22%) on IFN-alfa. The updated investigator-assessed ORR was 46% (95% CI: 41, 52) for sunitinib vs 12% (95% CI: 9, 16) for IFN-alfa ($P < 0.000001$), including 5 complete responses for sunitinib and 4 for IFN-alfa. Median PFS was 11 mo (95% CI: 10, 13) for sunitinib vs 4 mo (95% CI: 4, 5) for IFN-alfa and favored sunitinib across all MSKCC risk factor groups; pts with 0 risk factors had a median PFS of 14 mo (95% CI: 11, 17) for sunitinib vs 8 mo (95% CI: 7, 10) for IFN-alfa; pts with 1–2 risk factors had a median PFS of 10 mo (95% CI: 8, 11) vs 4 mo (95% CI: 4, 4), respectively; and pts with ⩾3 risk factors had a median PFS of 4 mo (95% CI: 2, 10) vs 1 mo (95% CI: 1, 2), respectively. In the sunitinib group, baseline features predictive of longer investigator-assessed PFS were hemoglobin ⩾LLN ($P = 0.0043$); corrected calcium ⩽10 mg/dL ($P = 0.001$); an ECOG score of 0 ($P = 0.0005$); 0 or 1 metastatic sites ($P = 0.0064$); and ⩾1 yr from diagnosis to treatment ($P = 0.0002$). The most common treatment-related AEs for the sunitinib group were diarrhea, fatigue, and nausea and, for IFN-alfa, fatigue, nausea, and pyrexia.
Conclusions: Sunitinib is a reference standard for first-line treatment of mRCC, with significantly superior efficacy compared to IFN-alfa. The benefits of sunitinib extend across all subgroups of mRCC pts, and previously-defined MSKCC risk factors predict longer PFS with sunitinib.

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A phase 2 trial of sunitinib in bevacizumab-refractory metastatic renal cell carcinoma (mRCC): updated results and analysis of circulating biomarkers

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Background: Sunitinib malate is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3 with antiangiogenic and antitumor activity. This phase 2 study evaluated the efficacy and safety of sunitinib in mRCC patients (pts) refractory to bevacizumab, an anti-VEGF antibody. Plasma levels of angiogenic biomarkers, including VEGF and soluble VEGFR-3 (sVEGFR-3), were assessed for predictive significance with clinical response.
Methods: Eligibility criteria included RECIST-defined disease progression following bevacizumab-based therapy, ⩽2 prior systemic treatment regimens, ECOG performance status of 0 or 1 and adequate organ function. Pts received oral sunitinib at 50 mg/day on a 4 wks on/2 wks off treatment schedule (6-wk cycles). The primary endpoint was objective response rate (ORR) according to RECIST. Plasma VEGF and sVEGFR-3 levels were measured before treatment and at multiple timepoints on study.
Results: Sixty-one pts were enrolled. Median age was 59 yrs (range: 39–80). The ORR was 23% (95% CI: 13%, 36%) and 36 pts (59%) achieved stable disease. Median duration of response was 44 wks (95% CI: 25, NA) and median progression-free survival was 30 wks (95% CI: 18, 36). The most common treatment-related adverse events were fatigue, diarrhea, and nausea. Plasma VEGF levels increased from baseline (3-fold mean elevation), while plasma sVEGFR-3 levels decreased (40% mean reduction). Pts ($n = 34$) with <10 wks between cessation of bevacizumab and start of sunitinib exhibited significantly higher pre-treatment VEGF levels ($p < 0.001$). Based on ELISA specificity, detected VEGF was not bevacizumab-bound. Responding pts had significantly lower pre-treatment sVEGFR-3 levels than non-responding pts ($p < 0.0318$). Responding pts exhibited a greater reduction in sVEGFR-3 levels than non-responding pts ($p < 0.10$). Pre-treatment levels of VEGF and VEGF fold-changes did not differ by clinical response.
Conclusions: Sunitinib has significant antitumor activity in bevacizumab-refractory mRCC pts, suggesting absence of cross-resistance and supporting the hypothesis that continued sunitinib-mediated inhibition of VEGF and additional signaling pathways may be clinically beneficial in the setting of disease progression. Biomarkers, including plasma VEGF and sVEGFR-3, may predict clinical response in sunitinib-treated pts.