7018 POSTER

Alpha-emitting Radium-223: two years follow up from a randomized phase II study in patients with bone metastases from hormone refractory prostate cancer

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Background: The bone-seeking pharmaceutical Alpharadin® ($^{223}RaCl_2$) is under clinical development as a novel treatment for patients with skeletal metastases. Clinical studies have shown that toxicity is low, repeated dosing is feasible and seems to improve overall survival. [1] A pivotal phase-3 trial in patients with hormone refractory prostate cancer (HRPC) is currently recruiting.
Material and Method: In a randomized phase 2 trial 64 HRPC patients with painful bone metastases received 4 monthly injections of Alpharadin (A) or placebo (P) as an adjuvant to external beam radiotherapy (EBRT). A 4.5 months difference in survival was observed at 18 months follow up. Here we report 24 months follow up data on survival, long term toxicity, subgroup analyses based on disease status at inclusion and pre-treatment EBRT.
Results: At 24 months, ten patients (30%) that received A were alive and four (13%) in the P-group. Median survival was 65 weeks compared with 46 weeks, respectively (ITT). Hazard ratio adjusted for baseline covariates was 2.10 (95% CI; 1.140−3.88; p = 0.017, Cox regression). The median survival was more than 40% longer in the A group at all levels of extent of disease (EOD = number of "hot-spots": 20; super-scan). The largest absolute difference occurred in patients with lowest EOD; 107 weeks for A and 68 weeks for P. For all patients who received four injections (28 patients in A, 21 in P), the median survival was 93 and 49 weeks (p = 0.043, Log-rank). In a composite analysis of patients with Hb > 110, bone-ALP
Conclusions: The therapeutic benefit seems to be greater for more fit patients than for those with extensive skeletal involvement. However, the relative improvement in survival was maintained irrespective of extent of disease at baseline. A benign side effect profile was documented following repeated Alpharadin® treatment.

References

[1] Nilsson S, et al., Lancet Oncology 2007

7019 POSTER

Vaccination with Survivin and PSMA-derived peptides: results of a pilot study in prostate cancer patients failing radiotherapy or surgery

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Background: A significant number of patients (pts) progress after prostate cancer (PCa) first line treatments. Among the new experimental approaches utilized to reduce the risk of recurrence anti-tumor vaccines (vax) might be a promising strategy. Preliminary results of a multiple peptide-based pilot study are here presented.
Methods: A phase I-II vax trial with HLA-A·0201-restricted peptides from PSMA and Survivin was carried out in 20 pts with b-failure after radiotherapy (RT) or surgery (8 radical RT, 8 salvage RT and 4 prostatectomy). Mean pre-vax PSA was 1.83 ng/ml, mean pre-vax PSA doubling-time was 1yr (range 1mo−2.5yrs). Vax consisted of two peptides from PSMA (PSMA4−12 and PSMA711−719) and one from Survivin (SVV96−104/97M) emulsified in Montanide ISA 51 and given by 4 fortnightly (priming) and 4 monthly administrations (boosting). To selectively eliminate regulatory T cells (Treg) and possibly enhance immunization, peptides were preceded by low dose cyclophosphamide (CTX, 300 mg/mq, i.v.). Extensive monitoring of antigen-specific T cell responses in peripheral blood (by IFNγ Elispot, HLA-A·0201/peptide multimer staining and short-term in vitro cultures) and analysis of CTX effect on CD4+CD25+Foxp3+ Treg frequency were performed. PSA trends were also analysed.
Results: Vax was well tolerated. According to Elispot more than 90% treated pts developed a statistically significant increase in the frequency of CD8+ T cells recognizing PSMA711−719 (8±11 in pre-vax vs 79±28 in post-vax) or SVV96−104/97M (pre:11±12 vs post:160±42) peptides, while poor immunogenicity was observed with PSMA4−12. No effect of CTX on Treg frequency was instead observed. 6/20 pts showed no biochemical response to vax and were switched to hormonal therapy, while 14/20 exhibited a significant, though transient PSA decrease during vax (11 in the priming and 3 in boosting phase).
Conclusions: Peptide vax seems to rapidly enhance specific immune responses in most pts, resulting in a significant decrease of PSA levels in 70% pts. However the antigenic stimulus provided by immunization is suboptimal, causing a transient effect on PSA and requiring continuous vaccinations to be maintained. Vax might help to postpone the prescription of hormonal therapy in the absence of major side effects, but immunization protocols inducing efficient tumor cell killing still need to be identified.

7020 POSTER

Performance status and interval from first-line docetaxel-based chemotherapy to progression are significant prognostic factors in patients with castration-resistant prostate cancer receiving second-line chemotherapy

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Background: No established second-line chemotherapy is currently validated in patients with metastatic castration-resistant prostate cancer (CRPC) previously treated with docetaxel. However, a number of these patients commonly receive second-line chemotherapy. We investigated the influence of clinico-pathologic factors on the survival of 61 patients with CRPC who received second-line chemotherapy.
Methods: Between January 2004 and December 2006, 61 patients with CRPC were given second-line chemotherapy after failure of docetaxel-based chemotherapy. This study analyzes the correlation between clinical factors evaluated at the time of second-line and the overall survival in these patients using univariate and multivariate analysis.
Results: Sixty-one patients with CRPC were given second-line chemotherapy after first-line docetaxel-based chemotherapy. Second-line chemotherapy consisted of carboplatin-etoposide (n = 42), docetaxel (n = 8), mitoxantrone (n = 4), doxorubicin (n = 3), oral etoposide (n = 2), vinorelbine (n = 1) and cyclophosphamide (n = 1). In univariate analysis prognostic factors for overall survival included performance status (PS) (p < 0.001), interval from first-line chemotherapy to progression (p < 0.001) and median serum PSA (p = 0.1). Multivariate analysis identified PS (hazard ratio (HR), 0.26; 95% CI, 0.09−0.81; P < 0.02) and PFS to first-line chemotherapy (HR, 2.45; 95% CI, 1.2−4.8; P < 0.01) as the independent prognostic factors for overall survival.
Conclusions: Both PS and interval from the first-line docetaxel-based chemotherapy to progression are independent prognostic factors for overall survival in patients with CRPC treated with second-line chemotherapy. This analysis suggests that some easily available clinical factors may help to select patients with CRPC who may benefit from second-line chemotherapy. These both factors should be used as stratifications factors in future clinical trials.

7021 POSTER

Leptin receptor genetic variants are associated with prostate cancer development, aggressiveness and the time to biochemical relapse

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Background: Leptin is a hormone synthesized in fat cells with a relevant role in cell proliferation and angiogenesis. Its receptor (LEPR) was found in human normal prostate and prostate cancer cells (PC), while recent *in* vitro and *in vivo* studies demonstrated a role of leptin/LEPR pathway in androgen-independence mechanism. Our purpose is to understand the role of 3 non-synonymous *LEPR* polymorphisms (Gln223Arg, Lys656Asn and Lys109Arg) in PC risk, aggressiveness and in biochemical relapse.
Methods: We genotyped the *LEPR* polymorphisms in biopsy confirmed PC patients (n = 602) and controls with absent malignant neoplasia (n = 209) by PCR-RFLP and Real-time PCR.