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Analysis of acute and late morbidity and biochemical control for intermediate to high risk prostrate cancer treated with androgen deprivation, HDR and 3D/IMRT: update of a phase I-II dose escalation trial

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Background: Prostate tumors exhibit a high sensitivity to fractionation due to low alpha/beta ratios and may be radioresitant to convention fractionation. HDR regimens may provide superior or equal tumor control over other approaches with possibly lower late sequelae.

Purpose: To evaluate GU and GI morbidity and biochemical control (bNED) of intermediate-high risk prostate cancer patients treated with androgen deprivation (AD), transrectal ultrasound assisted High Dose Rate (HDR) brachytherapy and conformal external radiotherapy as part of an HDR dose escalation trial.

Material and Methods: from April 1999 to October 2002, a total of 127 patients with intermediate or high-risk prostate cancer were enrolled on a dose escalation trial. Criteria included one or more of the following: PSA > 10, Gleason > 6, Bulky T2-T3 clinical stage, 4-6 core biopsies with bilobar disease. Patients with intermediate risk disease received 4-6 months of AD, and 9-12 months for high-risk disease. Patients underwent a single TRUS implant followed by 3 divided fractions of HDR Iridium-192 delivered over 24 hours, followed by 3D-CRT or IMRT to the prostate and/or lymph nodes to doses between 50-54 Gy. Patients were divided into 4 dose arms of HDR including 16.5 Gy (N= 38), 18 Gy (N= 48), 19.5 Gy (N=30) and 21 Gy (N=11). Dose constraints were placed on the urethra (125% of prescription) and anterior rectal wall (70% of prescription) with point dose calculations. 112 patients in Groups 1-3 with a minimum follow-up time of 6 months were analyzed. Pre and post treatment IPSS score were obtained in all patients. Scoring for GU and GI symptoms was based on the current RTOG morbidity scale. Biochemical failure was defined by the ASTRO consensus statement. Kaplan Meier methodology was used to estimate actuarial bNED.

Results: The overall median age was 68. The overall median follow-up for evaluable patients was 24 months, with a median follow-up for each HDR dose arm of 41 mos, 23 mos, and 10 mos, respectively. Overall Pre- and post treatment median PSA levels were 9 and 0.2 ng/mL at last follow-up. The median PSA value decreased from 9 to 0.2 in Arm 1 (med f/u 39 mos), from 9 to 0.3 in Arm 2 (med f/u 21 mos) and from 10 to 0.1 in Arm 3 (med f/u 12 mos). The 4- year actuarial biochemical control rate for all patients was 96%. The crude biochemical control for Arms 1 through 3 was 97%, 94%, and 100% respectively (p = NS). No difference in bNED has been observed to date in pts (17%) treated to LN bearing regions or by dose levels. Overall pre-and post median IPSS scores were 5 and 5 respectively, with no difference observed (p=. 42) Pre- IPSS median scores for Arm 1, 2 and 3 were 3, 8, and 7.5 (p = 0.005) with a difference seen in group 1 vs. 2and 3. However, the Post-IPSS median scores for Arms 1-3 were 6, 4, and 5 with no difference seen. (p = 0.42) The GU grade 2 morbidity at 12 months for arms 1 through 3 were 10%, 6% and 30% (p = 0.05) and the Grade 2 GI morbidity at 12 months for Arms 1-3 were 3%, 0% and 0% respectively (p = 0.10) Within Arm 1, with median follow-up of 41 mos, the Grade 2 Gu and GI morbidity is 9% and 0%. For Arm 2, with a median follow-up of 23 mos, the Grade 2 GU and GI morbidity is 7% and 0%. 3 out of 112 (3%) have developed urethral strictures to date. The 4 year-actuarial risk of a urethral stricture is 14%. All 3 occurred in arm 1 at 13 mos, 36, mos and 48 mos respectively. In multivariate analysis to determine patient and dosimetric risk factors at 12 mos predictive for Grade 2 or higher GU and GI morbidity, no one factor was predictive.

Conclusion: With longer follow-up time and clinical experience, dose escalation with HDR Ir-192 fractionated brachytherapy using a single implant resulted in acceptable Grade 2-3 GU morbidity. Minimal Grade 2 GI sequelae was observed overall (3%) and was only seen in Arm 1. We have not seen an increase of urethral strictures to date in Arms 2 and 3. Overall crude and actuarial biochemical control is excellent. Delayed failures in Arm 1 with addition of short course AD have yet to be realized (med f/u 41 mos) which is encouraging. Accrual to Arm 4 is completed.

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What to do with asymptomatic prostate cancer patients with rising PSA after curative treatment with external beam radiotherapy (RT)?

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Purpose: To describe the characteristics and outcomes of hormonally treated and non-treated asymptomatic prostate cancer patients with biochemical relapse (BR) post-RT

Material and methods: There were 528 prostate cancer patients staged as T1-3N0M0 treated in our institution between January 92 and February 99 with RT (no surgery). A total of 207 patients (39%) had BR defined as 3 consecutive PSA rises separated by at least 3 months (date of BR was considered the 1st of the 3 rises). Of these 207 patients, 140 (68%) were asymptomatic and had either no CT or bone scans or had negative scans. 62 of them (44%) received hormonal treatment and the remaining 78 (56%) were followed without further treatment. We compared the baseline characteristics and outcomes of these two groups using χ^2 or Mann-Whitney test as appropriate.

Results: The Table below shows the characteristics and outcome of the two groups along with p values. At a median follow-up time of almost 7 years for both groups, no patient has died from prostate cancer.

Patient Characteristics	Treated N = 62	Not treated N = 78	P values
Median age (years)	70	70	0.82
Median total dose of RT	65 Gy	67 Gy	0.08
Median Gleason Score	6	6	0.21
Median initial PSA (ng/ml)	17	14	0.69
Most common stage	T2b	T2b	0.86*
Neoadjuvant hormones (yes)	40%	45%	0.59
Median nadir PSA after RT	1.1	0.5	<0.0001
Median PSA at BR	2.2	1.2	<0.0001
Deaths (undue to prostate ca)	2/62	7/78	
Median total follow-up time	81 months	77 months	0.36
Median time for BR (month)	23	31	0.003
Median time post BR(month)	60	43	
Median PSA at last follow-up	1.8	3.4	

*Mann-Whitney test; all others were $\chi 2$

Conclusions: 1.) Asymptomatic patients with rising PSA after radiotherapy may not develop clinically progressive disease for a long time. It is not clear when they should start hormonal therapy. 2) The definition of BR as 3 consecutive PSA rises may be inappropriate to use in the growing number of patients treated with neoadjuvant hormonal therapy. 3) Some prognostic factors that could be considered in future studies are the median nadir PSA after RT, median PSA at BR and median time for BR as suggested by the univariable analysis; 4) Randomized trials of immediate versus delayed hormonal therapy are urgently needed in this population of asymptomatic patients with rising PSA post-RT.

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Disease presentation and development in bladder cancer is related to outcome following radical cystectomy

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Background: Approximately 75% of patients with bladder tumours present with non-invasive (Ta) or superficial invasive disease in lamina propria (T1). The recurrence rate is high, but only a minority will progress and become muscle invasive. In 25% of the patients with bladder tumours the first appearance is a muscle invasive tumour. Disease course was related to outcome following radical cystectomy.

Patients and methods: From 1/92 to 12/98, 208 consecutive patients with muscle invasive bladder cancer undergoing radical cystectomy was retrospectively followed from the time of diagnosis until death. Median follow up was 6.4 years (range, 3.4-10.4). The primary diagnosis, clinical and pathological T classification made it possible to separate the patients into 2 groups of tumour presentation and development. I: patients with de novo muscle invasive tumour (n=136) and II: patients with initial superficial bladder tumour progressing to muscle invasive bladder cancer (n=72).

Results: In univariate analyses T classification (organ confined vs. non-organ confined), N classification (N0 vs. N+) and tumour presentation and development showed to be significant predictors for survival. The 5-year

disease specific survival for the patients with de novo muscle invasive tumour was 60%, whereas it was 38% for patients with initially superficial tumour progressing to muscle invasive disease (p=0.003). The median time from the initial diagnosis until cystectomy varied significantly with minimal delay in group I with 52 days (range, 5 days 8.4 years) and maximum delay in group II with 1 year (range, 8 months - 23.6 years) (p<0.001). However, the median time from the first muscle invasive diagnosis until cystectomy was 52 days for group I and 39 days (range, 0-6.8 years) for group II.

Multivariate analyses, including all patients, revealed that patients with N+, non-organ confined tumour and with initial superficial disease progressing to muscle invasive tumour were independent poor predictors of death of bladder cancer.

Conclusion: These data showed that the proportion of patients with superficial tumours, which progressed despite of close follow up and intravesical therapy had a significant poorer outcome following radical cystectomy compared to patients with de novo muscle invasive tumours. Therefore early identification and early cystectomy of patients with high-risk superficial tumours are suggested.

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Phase III study of neovastat in metastatic renal cell carcinoma patients refractory to immunotherapy

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Cytokines remain the first-line treatment for renal cell carcinoma (RCC). For patients with progressive disease following initial therapy, no standard treatment is available, and new approaches are needed. Neovastat is a naturally occurring antiangiogenic oral drug with pleiotropic properties. No dose-limiting toxicity was observed in pre-clinical and Phase I/II clinical studies. In addition, a phase II trial in RCC patients showed a statistically longer median survival time in patients receiving 240 ml/day vs. 60 ml/day (16.3 months vs. 7.1 months, p = 0.01) (Batist et al., *Ann Oncol 2002;13:1259-63*). Based on these results, a prospective, randomized, double-blind, placebo-controlled phase III trial was conducted to determine the efficacy of Neovastat as monotherapy in metastatic RCC patients who had progressed following a first-line of immunotherapy.

Protocol: Eligibility criteria consisted of unresectable metastatic RCC, measurable disease, progressive disease after immunotherapy, and adequate bone marrow, hepatic and renal functions. Patients were stratified according to ECOG performance status (0 vs. 1) and number of metastatic sites (1 vs. >1) and were randomized in a double-blind fashion to Neovastat (120 ml B.I.D.) or placebo (ratio 1:1). The primary endpoint was median survival time and statistical hypothesis was improvement from 8 to 12+ months. Time to progression, one-year survival rate, quality of life, overall tumor response rate and duration of response were secondary endpoints.

Preliminary results: From May 2000 to January 2002, 302 patients were recruited in 46 centers (Argentina, Canada, Europe and USA). Median age was 61 years (25 to 81) with 75% (222) males and 25% (80) females. Fifty-two percent (52%) of the patients had ECOG 0. Seventy-five (75) patients had metastases restricted to one site. 227 patients had more than one metastatic site (lung, 70%; liver, 25%; bone, 29%). The safety profile of Neovastat appears acceptable and demonstrated no severe toxicity in either arm according to an independent Data Safety Monitoring Board review.

Conclusion: This study will provide key data on survival of patients with refractory RCC and will provide insights on the clinical activity of Neovastat. Mature data will be presented at the meeting.

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A phase II study of ABR-214936 (anatumomab mafenatox) tumour targeted superantigen (TTS) therapy in patients with advanced renal cell carcinoma (RCC)

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Tumour Targeted Superantigen (TTS) therapy is a novel form of cancer therapy. The principle involves targeting of the superantigen with strong activation of cytotoxic T cells in the tumour tissue. ABR-214936 (anatumomab mafenatox) is a recombinant fusion protein of a mutated Staphylococcal enterotoxin A (SEA) and a Fab moiety recognising the oncofetal antigen, 5T4, which is expressed in the majority of patients with RCC.

In this open non-controlled phase II study patients with confirmed RCC, measurable disease and good performance status are treated with a daily 3-hour infusion of ABR-214936 for 4 consecutive days. Pre-formed circulating anti-SEA antibodies neutralise the effects of ABR-214936 and therefore dosing is adapted to the pre-existing antibody-titre. Each patient is treated with an individual dose based on the pre-treatment anti-SEA antibody concentration and adjusted to body weight. A second cycle is given 4-6 weeks later at which the dose is adjusted to the new anti-SEA titre. Patients are evaluated by means of a pre-treatment CT scan with repeat scan at D56 and D112 to evaluate tumour response. If there is response then a 3rd cycle may be given.

Side effects observed include pyrexia, rigors, nausea and vomiting, and hypotension. If a patient experience a drug-related AE/SAE then the dose for the next infusion is decreased to 75% of that previously given, if there is a further reaction then the dose is reduced to 50% of the original. Treatment is well tolerated with only one patient withdrawn due to toxicity (grade 3 hypotension in first cycle). In cycle one 30% (12/43 pts) required a dose reduction due to grade 1 or 2 toxicity and only one patient required a dose reduction in the second cycle of treatment.

To date 39 patients out of 45 have reached D112 evaluation. The patient with maximum response has achieved a reduction in the measured size of the lesions by 90% after 3 cycles (PR by RECIST criteria on CT scan). This patient received ABR-214936 as second-line treatment. Approximately 36% of the evaluable patients have SD or better at the 4 month assessment. 4 patients have received 3 cycles of treatment

ABR-214936 is a promising and active agent in advanced RCC. It has been demonstrated to be safe and well tolerated. The study has now fully recruited and follow-up is ongoing.