4511 POSTER

Selective organ preservation in muscle-invasive transitional cell carcinoma of the bladder: Pilot study for a randomised phase III trial

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Introduction: The 'gold standard' treatment for bladder cancer is considered to be Cystectomy. Radiotherapy has been used in some centres but its use has been handicapped by uncertainties as to whether a complete response is likely to be attained. For many it would be more acceptable option if we could identify patients who would be most likely to benefit before treatment a process termed 'selective bladder preservation' (SBP). Neo-adjuvant chemotherapy (neo-ct) is increasingly being used on the basis a clear survival benefit. (Lancet 361: 1927−34, 2003) and pathological response to treatment is associated with outcome (J Urol 147: 606−8). We have undertaken a pilot study to test is if neo-CT could be used to select patients for bladder preservation, giving radiation to patients with pathological down staging after neo-CT.
Materials and Methods: Patients with T2/T3 TCC bladder with satisfactory renal function received 3 cycles of neo-CT (accelerated MVAC), followed by rigid cystoscopy 2 weeks later. Patients down-staged to /=pT2).
Results: 35 patients were treated (2000–2007) Median age 63 (34−79); male 29, female 6. Complete Response (pT0) was seen in 25/35 patients (71%), and pTa/pT1 in a further 4/35 (11%). 29 (82%) patients underwent bladder preservation. After a median of 21 months follow up (range 2−53) 10 (29%) patients have died (metastatic bladder cancer 7, other causes 3). 4 patients have required salvage cystectomy (invasive recurrence 2; CIS 1; pT1G3 1). 23 patients (66%) are alive in remission (1 after treatment for superficial disease), and 2 alive with active disease (superficial cancer 1; metastatic disease 1). Of surviving patients; 18/25 (72%) are alive with an intact bladder and 25 (71%) had intact bladder at last follow up or death. Toxicity has been acceptable with 1 episode each of grade 4 bowel and bladder toxicity.
Conclusion: Selective bladder preservation in patients with favourable pathological response to neo-CT represents a realistic option to cystectomy. This approach is to be tested in a randomised multicentre phase II/III trial that was launched in March 2007. Updated results with minimum 6 month follow up will be presented at the meeting

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Risk-adapted treatment in clinical stage 1 (CS1), non-seminomatous germ cell testicular cancer (NSGCT)

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Between July 1995 and July 2005, a total of 921 Norwegian and Swedish CS1 NSGCT were included into a prospective, community-based multicenter SWENOTECA study. All patients were restaged 6 weeks after orchidectomi (orch.). Based on the presence/absence of vascular invasion (VASC+/−) in the primary tumour, and the patients preference, close surveillance or treatment with brief adjuvant chemotherapy (CT) were chosen. From 1995 until late 1997 one or two courses of cisplatin, vinblastine and bleomycin (CVB) were used. Due to unacceptable toxicity of CVB the CT was changed to cisplatin, etoposide and bleomycin (BEP) in late 1997. Median follow-up is now 5.2 years. Survival status for all patients has been checked through the national registries. Nine patients have died during follow-up. None died from progressive cancer or from evident side effects of adjuvant CT. One patient died as a result of complication during salvage CT after relapse following surveillance. The toxicity of one or two courses of adjuvant BEP was acceptable. Only 5% of patients receiving adjuvant BEP required hospitalisation due to toxicity, compared to 55% of the early patients receiving adjuvant CVB. Five of the 11 patients relapsing after adjuvant CT had mature teratoma and were cured by surgery alone. One patient relapsing one year after adjuvant BEP was resistant to BEP salvage CT, but was cured by a combination of other CT, surgery and radiation therapy. Only four relapses occurred more than three years after orch., one of these had received adjuvant CT (BEP $\times$ 1). Relapse rates according to risk group and adjuvant CT are listed in the table.

Risk group	Adjuvant chemotherapy	No. of patients	No. of relapses	Relapse rate (Kaplan-Meier)	Median time to relapse (yrs)	Median observation time (yrs)
All pts		921	72 (7.8%)	8.8%	1.0 (0.2−6.4)	5.2
VASC+	None	16	7 (43.8%)	43.8%	0.7 (0.2−1.3)	5.9
	CVB $\times$ 1	4	0	0%		6.7
	CVB $\times$ 2	55	1 (1.8%)	1.8%	0.9	7.8
	BEP $\times$ 1	150	6 (4%)	4.4%	1.3 (0.3−3.3)	3.5
	BEP $\times$ 2	69	0	0%		4.6
VASC−	None	446	54 (12.1%)	13.5%	1.0 (0.2−6.4)	5.5
	CVB $\times$ 1	41	3 (7.3%)	7.5%	1.3 (0.3−2.5)	7.9
	BEP $\times$ 1	138	1 (0.7%)	0.8%	1.0	3.5
	BEP $\times$ 2	2	0	0%		1.3

Conclusions: Relapse rates following restaging six weeks after orch. are low. Surveillance is an excellent option for VASC− CS1 NSGCT. One course of adjuvant BEP $\times$ 1 will reduce the risk of relapse by about 90% in both VASC+/− CS1 NSGCT. A second course of BEP will further reduce the risk of relapse by 90%, and virtually eliminates relapses in VASC+ patients.

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Phase 1/2 study of sunitinib in combination with gefitinib in patients (pts) with metastatic renal cell carcinoma (mRCC)

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Background: Sunitinib malate is an oral, multitargeted tyrosine kinase inhibitor of VEGF- and PDGF-receptors with substantial antitumor activity against mRCC (JAMA 2006; 295: 2516). This phase 1/2 study was conducted to evaluate the safety and efficacy of sunitinib in combination with gefitinib, an EGF-receptor inhibitor.
Methods: Eligibility included mRCC with a clear cell component, measurable disease, and an ECOG performance status of 0 or 1. Pts were treated with sunitinib at assigned dose level (37.5 mg or 50 mg) orally once-daily for 4 weeks on, followed by 2 weeks off (Schedule 4/2) and gefitinib at 250 mg daily in the phase 1 part of the study, and the maximum tolerated dose (MTD) of sunitinib was determined. Additional pts were enrolled in the phase 2 part to further evaluate the safety and efficacy of the combination. The primary endpoint for the phase 2 part was objective response rate (ORR) according to RECIST.
Results: A total of 42 pts were enrolled; 11 pts in phase 1 and 31 pts in phase 2. Median age was 65 years (range: 29–78), and 36 pts (86%) had $\geqslant$2 metastatic sites. Twenty-eight pts (67%) had prior cytokine therapy, 11 pts (26%) had no prior cytokine therapy, and 3 pts (7%) received prior vaccine therapy. Based on the 2 dose-limiting toxicities observed in phase 1 at the 50-mg dose level (grade 3 fatigue and grade 2 ejection fraction decline), sunitinib 37.5 mg on Schedule 4/2, in combination with gefitinib 250 mg daily, was determined to be the MTD. The median duration on treatment was 8.3 months for phase 1 and 4.6 months for phase 2. The ORR was 38% (95% CI: 24–54), and 19 pts (45%) achieved a stable disease. The median progression-free survival was 11.3 months. In phase 1, the most common grade 3 treatment-related adverse events observed were diarrhea and nausea (n = 2); 3 pts discontinued gefitinib permanently due to recurring diarrhea and skin toxicities and continued on sunitinib monotherapy. Diarrhea (10%) and gastrointestinal hemorrhage (6%) were the most common grade 3 treatment-related adverse events in phase 2. Two pts from phase 2 were withdrawn from the study due to ejection fraction decline and cardiac arrhythmia, both of which were reversible after treatment discontinuation.
Conclusions: The study established the dose and feasibility of sunitinib in combination with gefitinib. The relative efficacy data compared to sunitinib monotherapy will be assessed with longer patient follow-up.