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PUBLICATION

Neoadjuvant chemotherapy in bladder cancer: Is cystectomy mandatory in case of complete response?

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Purpose: To evaluate retrospectively the results of neoadjuvant chemotherapy (m-VAC) in bladder cancer. To discuss the possibility of avoiding cystectomy in case of complete response (CR).

Methods: Forty patients with bladder cancer (stages: 6 T1G3, 13 T2, 15 T3, 6 T4) were treated with m-VAC regimen (three cycles) and then restaged by CAT, cystoscopy and multiple biopsies. Cystectomy wasn't performed in case of CR, and CT was continued for three more cycles.

Results: 34/40 patients were evaluable for response. 12 complete responses (5/6 T1G3; 5/13 T2; 2/12 T3) and 8 partial responses (4/13 T2; 3/12 T3; 1/6 T4) were obtained. The 12 patients in CR didn't undergo cystectomy, and CR is confirmed in 8/12, after a median f.u. of 17 months (r: 7-46).

Conclusions: - Neoadjuvant m-VAC induced 35% CR + 23% PR. - In 2/3 of patients who didn't undergo cystectomy CR is confirmed after a medium term f.u.

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PUBLICATION

The efficacy of gemcitabine in controlling pain and improving performance status in men with hormone-refractory prostate cancer (HRPC)

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Purpose: A previous phase II study of single-agent (Gemcitabine) GEMZAR[®] in men with HRPC and bidimensionally measurable disease demonstrated an objective response rate of 17%. This trial was then designed to test in symptomatic men with HRPC the effect of gemcitabine (1200 mg/m² weekly \times 3 every 4 weeks) on Kamofsky Performance Status (KPS) and pain palliation.

Methods: A response in KPS was defined as an improvement of ≥ 20 points for at least 4 weeks and a response in pain was defined as a $\geq 50\%$ decrease in analgesic consumption and an improvement of ≥ 20 points on the pain intensity scale using a visual analogue scale card (VAS).

Results: To date, 22 men have been enrolled, 2 being ineligible. The median age was 72 years and 50% of the men had a baseline KPS of 70. The median number of gemcitabine cycles was 2. Of the 20 eligible and evaluable patients, 4 (20%) met the criteria for achieving significant clinical symptomatic benefit. Overall, 2 men had stable serial serum PSA levels and 2 had a PSA decrease of at least 25%. Ten men had objectively measurable disease sites with 1 PR seen and 3 others having stable disease. Toxicity was mild with grade 3 anaemia, leukopenia, thrombocytopenia and nausea and vomiting seen in 12.5%, 25%, 6.3% and 4.8% of patients respectively.

Conclusion: Gemcitabine appears to have some modest anticancer activity in men with HRPC. This level of activity might be enhanced if the drug is combined with other active agent(s).

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PUBLICATION

Transcatheter embolization vs surgical ligation in the treatment of bleeding bladder neoplasms

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Purpose: To evaluate effectiveness of transcatheter embolization for control of bleeding complicating bladder neoplasms as an alternative to surgical ligation of internal iliac arteries.

Materials and Methods: Between 1984 and 1994, arterial embolization was performed in 21 patients while 19 patients underwent surgical ligation of the internal iliac arteries. All patients had intractable hemorrhage from unresectable bladder carcinoma. Autoclots/Valon/Gelfoam were utilized for occlusion.

Results: Post embolization, bleeding was completely controlled in 16 (76%) patients and decreased markedly in 5 patients. Hemorrhage was stopped in 11 of 19 (58%) patients after surgical ligation.

Hematuria recurred in 9 of 21 (43%) after embolization and in 13 of 19 (68%) patients after surgical ligation during 0.5-6.5 mo. For treatment of recurrences medical therapy (16) and repeated embolization (6) were

successful. The long-term survival depended on effectiveness of following treatment such as chemotherapy and/or radiation therapy.

Conclusion: Arterial embolization is more effective than surgical ligation for control of bleeding from bladder cancer.

Renal and testicular cancer

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ORAL

Subcutaneous (SC) Interleukin-2 (IL-2) plus alpha interferon (IFN- α) and 5 fluorouracil (5 FU) in out-patients (pts) with metastatic renal cell carcinoma (MRCC). Scapp II trial

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Purpose: The aim of this study was to confirm through a French multicenter trial the efficacy of this association already published by Atzpodien.

Methods: IL-2 (Proleukin[®]) and IFN α (Roferon[®]) have been administered by SC route three days a week (W) during 8 W respectively at 18 MUI and 9 MU. 5 FU (750 mg) has been given every Monday by IV route

Results: 83 pts with MRCC were included in this trial. At the moment, 56 pts are evaluable. The dosage was decreased or the treatment interrupted for 26 pts (toxicity) and for 4 pts (progressive disease). 12 pts were in objective response (1CR), 16 pts with stable disease (SD). Toxicity was more important than in SCAPP I trial (IL-2 (SC) alone). OMS grade III and IV toxicities were observed. In this program responding pts and pts with stable disease received 2 W maintenance cycles every 6 W. The 20-month survival represent 60%. According to the statistical method (triangular test) used in this trial, this program was interrupted in August 96.

Conclusion: This SC schedule unlike the results published by ATZPODIEN shows that the treble combination 5 FU, IFN α , IL-2 has the same efficacy than IL-2 alone given by IV or SC route with more toxicity. Other programs recently published confirm these data. The definitive results will be presented in September.

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ORAL

A randomized clinical trial comparing SC Interleukin-2, SC Alpha-2A-Interferon, and IV bolus 5-fluorouracil against oral tamoxifen in progressive metastatic renal cell carcinoma patients

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In various clinical phase II studies, Interleukin-2 based chemo-immunotherapy has produced objective tumor regressions in selected patients with progressive metastatic renal cell carcinoma. We conducted a prospectively randomized trial to compare outpatient SC Interleukin-2, SC Alpha-2a-Interferon, and IV bolus 5 fluorouracil against oral tamoxifen.

Patients and Methods: Of a total of 78 pts (59 male; 19 female; median age, 58 years; range, 34 to 80 years), 41 pts were randomized to receive 8 week cycles of SC Interleukin-2 (10 MIU/m² BID days 3, 4 and 5 of weeks 1 and 4; and 5 MIU/m² days 1, 3 and 5 of weeks 2 and 3), SC Alpha-2a-Interferon (6 MIU/m² day 1 of weeks 1 and 4 and days 1, 3 and 5 of weeks 2 and 3; and 9 MIU/m² days 1, 3 and 5 of weeks 5-8), and IV bolus 5-Fluorouracil (1000 mg/m² once weekly, weeks 5-8); 38 pts received oral tamoxifen (45 mg/m² BID, weeks 1-8). Pts were stratified according to known clinical predictors (J Urol 155: 19, 1996) to allow for equal risk distribution in both treatment arms.

Results: Therapeutic efficacy was evaluated on an intention to treat basis. Among 41 pts receiving out-patient SC Interleukin-2, SC Alpha-2a-Interferon, and IV bolus 5-FU, there were 7 complete responders (lung, lymph nodes, bone), and 9 partial responders (lung, liver, lymph nodes, adrenals, and others), with an overall objective response rate of 39% (95% confidence interval, 24%-55%). In contrast, tamoxifen produced no objective remissions in a total of 37 pts (95% confidence interval, 0%-9%). According to Kaplan-Meier, overall survival and progression free survival from start of therapy were significantly improved in pts receiving chemo-immunotherapy when compared to pts who were treated with tamoxifen (overall survival: median not reached after 42 months vs median

of 14 months, Breslow $p < 0.04$; progression free survival: median of 13 months vs median of 4 months, Breslow $p < 0.01$).

Conclusion: In patients with progressive metastatic renal cell carcinoma, outpatient chemo immunotherapy with SC Interleukin-2, SC Alpha-2a-interferon, and IV 5-FU is more effective (objective response rate, progression free survival, and overall survival) than single agent tamoxifen

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ORAL

Survival in renal cell carcinoma (RCC) – A randomised evaluation of tamoxifen versus interleukin-2, α -interferon (leukocyte) and tamoxifen

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Purpose: Biotherapy causes encouraging results in terms of objective responses. No conclusive studies exist with a controlled evaluation of survival in advanced RCC. The aim was to compare IL-2/IFN- α with relatively atoxic tamoxifen (T).

Methods: Randomized multicentre study (life expectancy >3 months, PS WHO 0-2). Interim analysis when 100 patients evaluable. The control patients (n = 63) received only tamoxifen 40 mg p.o. daily. The other patients (n = 65) subcutaneous IL-2/IFN- α in two treatment cycles of 42 days (see Atzpodien) and maintenance treatment (5 days, every 4 weeks) 1 year or until progression. Two patients in the T only group received biotherapy when the disease progressed without any effect. The patients received appropriate local treatment.

Results: The interim analysis showed no advantage for either group. Inclusion of patients was stopped. Mean follow-up: 11 months (range 0.4-48). The final survival analysis displayed no differences from the day of primary diagnosis, first evidence of metastasis, or from the onset of treatment. This was valid with regard to intention to treat or when directed only to patients that managed at least one treatment cycle of IL-2/IFN- α . CR was seen in both groups. Adverse effects were pronounced in the IL-2/IFN- α group.

Conclusions: The results raise doubt about IL-2/IFN- α as a routine treatment in advanced RCC. Difference in expenses of drugs and health care (drug costs/patient: IL-2/IFN- α 27,000\$ vs Tamoxifen 360\$) and quality of life are also of importance. The study emphasizes the need of further controlled studies.

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ORAL

Testis cancer: Carcinoma-in-situ in testes with germ cell tumour

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Testicular tissue of 380 consecutive patients (169 Seminoma and 211 NSGCT) from 1990 to 1995 has been examined in semithin sectioning technique adjacent and distant to solid germ cell tumours. The samples were fixed in glutaraldehyde and osmium tetroxide then embedded in Epon. Semithin sections (1 μ m) were stained with toluidine blue-pyronine. 303 (80%) patients showed CIS in biopsies near or distant of the tumour. Of 327 testes either tumour-near as -distant biopsies were examined. CIS was found in 262 testes tumour-near (80%), in 206 tumour-distant (63%) and both in 196 (60%). CIS only tumour-near showed 65 (20%), only tumour-distant 10 testes (3%).

In 78% of seminomas CIS was found tumour-near and in 54% tumour-distant, of non-seminomas in 86% -near and 67% -distant.

A weak statistically significant relationship between tumour size and occurrence of CIS in the biopsies is demonstrated.

As long as no prospective parameters of high probability are established, every testicle with a germ cell tumour should be respected as CIS-contaminated. The individual decision for radiation or surveillance after organ-preserving surgery depends on the patients intention regarding the fertility. Not to develop a solid tumour in future, testes which have CIS should be irradiated.

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ORAL

Early stage testicular seminoma – A prospective multicenter trial

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Purpose: Adjuvant radiotherapy in stage I, IIA/B testicular seminoma (Royal Marsden Classification) offers cure rates of 95% and 80–90%, respectively. However, treatment volume and total dose are still object of discussion. Thus, we conducted a multicenter prospective clinical trial for radiotherapy of early stage testicular seminoma with reduced total treatment doses and portals.

Method: Patients with stage I (CSI) seminoma received radiotherapy to the paraaortic lymph nodes only. Treatment portals reached from the upper border of thoracic vertebra 11 (T11) to the lower border of lumbar vertebra 4. Stage IIA/B (CSIIA/B) patients were treated to the paraaortic and ipsilateral iliac lymph nodes. A hockey stick field stretched from the upper border of T11 to the upper border of the ipsilateral acetabulum. Total dose in 2 Gy daily fractions was 26 Gy for CSI, 30 Gy and 36 Gy for CSIIA/B, respectively.

Results: Between 4/91 and 3/94 827 patients were entered into the trial. 492 patients with CSI disease and 59 patients with CSIIA/B disease were eligible for an interim analysis in 12/96. Mean follow up was 28 months. In CSI and CSIIA/B there were 18 (3.7%) and 2 (3.4%) relapses, respectively. No in-field recurrence was observed. 18/20 patients were salvaged. One patient died of embolism after surgery for relapse, a second patient was lost to follow up after diagnosis of recurrent disease. Overall survival (28 months follow up) accounts to 99.6% in CSI and 100% in CSII. Acute side effects of adjuvant treatment were moderate. 59% of all patients suffered from nausea, 14.9% experienced diarrhea during treatment.

Conclusions: Low dose radiotherapy with reduced portals in early stage testicular seminoma yields high cure rates with only moderate acute side effects.

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ORAL

Lessons from prospective multicenter study on seminomas

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Purpose: We conducted a prospective multicenter study to assess the prognostic value of HCG in seminomas.

Methods: From 1986–1991 we recruited 806 seminomas from 96 urological departments in FRG, Austria, Switzerland, 726 were evaluable. 288 of these cases were retrospectively reviewed from 14 of the participating hospitals (all seminomas of the same time period) because the original idea to compare the results with historical series, proved to be insufficient. The outcome after standard therapy (radiotherapy in stages IIB and chemotherapy in more advanced stages) was established. Univariate and multivariate analyses were performed in order to assess adverse prognostic factors.

Results: In the cubital vein, the incidence of HCG is 35%, of LDH and PLAP 34% and 56% resp. 84% of all seminomas are marker positive. Nearly all seminomas produce HCG, in most cases it is measurable only in the testicular vein. HCG is associated with tumor mass but it has no prognostic relevance. Multivariate analysis revealed metastatic disease, $pT > T$, LDH and its prolonged marker decay as prognostic factors, multivariate analysis $pT > T$ and metastatic disease. Stage IIB disease showed a poorer outcome after radiotherapy than more advanced stages after chemotherapy.

Conclusion: Elevated HCG has no influence on the prognosis of seminomas. This fact results in a stage related uniform therapy for HCG positive and negative seminomas. Stage IIB disease should probably be better managed by chemotherapy.

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ORAL

Long-term survival and late toxicities after high-dose chemotherapy in patients suffering from germ cell cancer

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Purpose: High-dose chemotherapy (HDCT) followed by autologous stem cell rescue can cure patients suffering from refractory or relapsed germ-cell