1145 POSTER

EVALUATION OF POST OPERATIVE IMMUNODEPRESSION (P.O.I.) AFTER MAJOR SURGERY FOR UROLOGIC CANCERS

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Cancer is generally considered as a cause of immunodepression. A transient impairment of immune response, possibly caused by surgical trauma or general anesthesia, has been observed post-operatively. P.O.I. seems to correlate with an increase in infections and metastatization. We investigated 20 patients (pts) submitted to major surgery with general anesthesia for urological cancers (mean age 65.3 years, range 41–73). Exclusion criteria were: need for steroid therapies, metabolic diseases, immunodeficiency syndrome. A complete immunological and clinical evaluation was made at days −3, +1 and +7 in respect to surgery. These data have been obtained: transient leukocytosis on day 1 associated with a rise in the absolute neutrophil count and a significant fall in the lymphocyte count between days −3 and +7 ($p < 0.0001$). Significant increase of the CD4/CD8 lymphocyte ratio ($p = 0.00124$) on day +7 with a slight decrease in T-cell (but with increase of activated T-cells). No changes for NK cells, B lymphocytes and T/B lymphocyte ratio. Transient increase of the cortisol level (p = n.s.) after surgery. Immunoglobuline (Ig) G values fell from day −3 to day +7 ($p < 0.0005$), while IgM rose almost to significant values, no changes for IgA. Our data, blood lymphocyte depletion together with some modifications of lymphocyte populations and changes in Ig levels (reported for the first time) provide evidence of P.O.I. phenomenon. Correlation of these data with infection episodes (3 cases) are under evaluation and will be presented.

1146 POSTER

A BLADDER SPARING APPROACH IN ELDERLY PATIENTS WITH INVASIVE BLADDER CANCER (BC)

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This study was carried out to evaluate the influence of age in terms of toxicity, response and survival in elderly pts with muscle invading BC treated with a bladder sparing approach including an alternated chemoradiotherapy after TUR. Twenty-eight pts with T1G3-T4 N0 M0 transitional BC entered the study. Characteristics of pts were: median age, 72 yrs. (Range 70–78); median ECOG PS, 0 (range 0-1); M/F, 23/5; T1G3, 2 pts; T2, 14 pts; T3, 9 pts; T4, 3 pts; G2, 12 pts; G3, 16 pts. The first 9 pts received 4 cycles of CDDP 20 mg/sqm and FU 200 mg/sqm dd. 1–5 during wks 1, 4, 7 and 10 alternated with radiotherapy (40 Gy in 20 fractions during wks 2, 3, 8, 9). The second group of 19 pts received 3 cycles of MTX 40 mg/sqm dd. 1, 8 and CDDP 30 mg/sqm dd. 2–4 (wks 1, 4, 7) alternated with 50 Gy of radiotherapy (20 fractions, wks 2, 3, 5, 6). All pts were evaluable. A cCR was observed in 20 pts (71%), cPR in 5 pts (10%) and a cNR in 3 pts (11%). After a median follow-up of 34 mos, 17 pts (61%) were alive and 13 pts (46%) free of tumor. In 15 pts (54%) the bladder was free of invasive disease and functioning well, although in 1 (4%) a superficial tumor recurred. The median OS and DFS was 25 mos (range 3–34) and 23.5 mos (range 3–77) respectively. Systemic G2–G3 (OMS) side effects were: leukopenia in 5 pts; thrombocytopenia in 2 pts; anemia; stomatitis and diarrhea in 1 pts. A moderate or severe cystitis or proctitis was observed in 5 pts and 4 pts respectively. This aggressive conservative approach was safe and feasible also in elderly pts, allowed bladder sparing in a high rate of pts with a survival comparable to that reported with more traditional treatment.

1147 POSTER

GEMCITABINE IN RESISTANT STAGE IV BLADDER CANCER: A PHASE II STUDY

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Gemcitabine, a novel nucleoside analogue, has significant single-agent activity in a number of chemoresistant tumours such as ovary and non-small cell lung cancer. In an early phase I study with gemcitabine (dose: $\geq$875 mg/m^2; schedule: wk ×3 q4 wks), 1 complete and 2 partial responses were observed in 14 previously treated metastatic bladder cancer patients (overall response rate 21.4%). We report a phase II study of gemcitabine in patients with stage IV bladder cancer who had been treated unsuccessfully with one previous cisplatin-containing regimen. Characteristics of all 18 patients entered into the study were: 15 males; median age 65.1 years (range 39–75), Karnofsky PS 60 (3 pts), 70 (7), 80 (4), 90 (2), 100 (2). Gemcitabine 1250 mg/m^2 was given once a week for 3 weeks followed by one week of rest (one cycle). Of 14 patients eligible for efficacy analysis (4 patients too early), having received treatment for at least 2 cycles, there were 2 complete responses and 2 partial responses for an overall response rate of 29%. All 18 patients were evaluable for toxicity. There were no WHO grade 3 or 4 non-laboratory toxicities. The only WHO grade 4 laboratory toxicity was thrombocytopenia (1 pt). WHO grade 3 laboratory toxicities were: thrombocytopenia (1 pt), ALT (1), AST (1), creatinine (1), vomiting (2), anaemia (1). This study confirms that gemcitabine has single-agent activity in stage IV bladder cancer and has a mild to modest toxicity profile.

1148 POSTER

BLADDER PRESERVATION IN T3 BLADDER CANCER: A DECADE OF FOLLOW-UP

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Neo-adjuvant cisplatin and methotrexate were given to 32 eligible patients out of 57 patients with T3 transitional cell carcinoma (TCC) of the bladder. All patients underwent standard work-up, finished with a diagnostic muscle showing biopsy leaving the rest of the tumor as an *in vivo* marker. A complete resection/staging procedure was repeated after the second and the fourth cycle, followed by definitive open surgery. The aggressive staging resulted in a near perfect balance between clinical/pathological staging. Seven patients did not complete the schedule. A total of 15 patients out of 25 had a complete response (CR). Five of the CR's elected hemi-cystectomy. All of the CR's except two survived a decade free of disease. All other patients died in five years. Downstaging to CR offers excellent prognosis and a chance for bladder preservation.

1149 POSTER

BLADDER SPARING BY CHEMOTHERAPY AND RADIATION IN PATIENTS WITH INVASIVE BLADDER CANCER

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48 consecutive patients (pts) with muscle-invasive bladder cancer were treated between November 1988 and May 1993. All pts had pure transitional carcinoma, absence of diffuse Tis, and clinic N0M0 stage. 39 pts had T2–3a stages and 9 had T3b–4a. The treatment consisted of RTU, neoadjuvant chemotherapy M-VAC (CT) (2–4 cycles), and radiotherapy (RT) (44 Gy). RT was continued to 64 Gy in pts with biopsy-proven absence of invasive cancer (CR). Cystectomy was performed in pts with residual invasive tumor. 9 pts did not receive RT: 6 with failure to CT underwent immediate cystectomy, and 3 with CR received only CT.

The CR rate to neoadjuvant treatment was 75%. After a mean follow-up of 35 months, 24 pts (50%) had preserved bladders free of invasive tumor and functioning well. The actuarial survival and disease free survival at 3 years were, respectively, 49% and 56%. Of the 24 currently surviving pts 87% have their bladder preserved. 5 pts required salvage cystectomy for recurrent invasive cancer or diffuse Tis. 9 pts had recurrent superficial bladder tumors, and 5 of them preserved their bladders after further RTU and BCG.

The response to CT had prognostic value for survival ($P = .0004$). Long-term bladder sparing was significantly associated with absence of hydronephrosis and bladder-confined disease (T2–T3a). Severe complications were: 1 death for fulminant hepatitis after CT, 2 late radiation cystitis that required cystectomy, with one death in postoperatory, and colovesical fistula that needed rectosygmoidectomy. The long-term bladder preservation is feasible in a selected group of pts by multimodality treatment. Most surviving pts had their bladders intact.

1150 POSTER

RADIOTHERAPY PLUS CARBOPLATIN VERSUS RADIOTHERAPY IN LOCALLY ADVANCED BLADDER CANCER

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To improve the treatment results and to specify the place of a conservative treatment in locally advanced bladder cancer, we designed a prospective randomized study using carboplatin with radiotherapy as concurrent combination (group A) and radiotherapy alone (group B). 59 patients in

group A were treated from October 1, 1992 to October 1, 1994 (51/T3, 4/T4, 4/N+, all Mo). Group B included 38 patients (28/T3, 2/T4, 8/N+, all Mo). In both groups radiotherapy was applied on LINAC (10 MV) with locoregional technique to a dose 65 Gy by conventional fractionation. Patients in group A received carboplatin weekly at daily dose of 150 mg, every fifth day, one hour prior to irradiation, up to total dose of 900 mg. Achieved response rates were in group A: CR = 89%, PR = 4%, PD = 7% and in group B: CR = 63%, PR = 11%, SD = 21%, PD = 5%). Hematological toxicity grade I and II (by WHO criteria), predominant leucopenia and thrombocytopenia, was registrated in majority of patients in group A. Mean follow-up time was 20 months (range 3–26). Two-year overall survival as 86% and 70%, disease free survival as 69% and 50% in group A and in group B; respectively. Invasive local relaps occurred in 5/59 patients in group A and 6/38 patients in group B. Metastatic disease with local control confirmed in 7/59 patients in group A. Local relaps with disseminated disease had 5/38 patients in group B. Results showed that addition of carboplatin to radiotherapy increased complete response rate, local control and early survival in patients with locally advanced bladder cancer, but short follow-up, not permit definitive conclusion concerning long-term survival and bladder preservation.

1151 POSTER

NEOADJUVANT MVAC CHEMOTHERAPY IN BLADDER CANCER: THE CENTRE FRANCOIS BACLESSE (CFB) EXPERIENCE

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The efficiency of MVAC (Methotrexate 30 mg/m^2 J_1–J_{15}–J_{J22}, Vinblastine 3 mg/m^2 J_1, Doxorubicine 40 mg/m^2 J_1, Cisplatin 70 mg/m$_2$ J_1) given as neoadjuvant chemotherapy (CT), was evaluated in a series of newly diagnosed patients treated at a single institution. From April 1988 to March 1993, 71 patients were referred to CFB of whom 40 were given MVAC as neoadjuvant CT. Initial patients' characteristics were: male/female ratio 4.7; mean age 57 years (range 31 to 75); there were 9 T_0T_1 with grade III, 16 T_2T_3, 7 T_4 and 8 T_x; 19 patients were N_0, 4 N_+, and 17 N_x. CT consisted of 3 to 4 courses of MVAC (35 patients); 5 patients were only administered 2 courses because of toxicity. Surgery was performed after CT in 30 patients (21 radical cystectomy); in 10 patients, secondary treatment consisted of irradiation.

After surgery, residual disease was present at histological examination in 20 patients; in the other 10 patients no tumour was microscopically found (objective and complete responses respectively 55% and 33%). Globally, at the end of therapy, 15 patients were in complete remission, 15 in partial remission, 7 had progressive disease, and 3 were not evaluable.

Toxicity (grade 2 to 4): CT induced haematological toxicity in 24 patients, renal toxicity in 5, cardiac toxicity in 3, and 3 patients died during CT.

With a median follow-up of 56 months, the 4 year overall survival rate from first CT course was 67%; the 4-year freedom from progression rate was 63%.

1152 POSTER

GEMCITABINE IN THE TREATMENT OF PATIENTS WITH ADVANCED TRANSITIONAL CELL CARCINOMA: A PHASE II STUDY

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Gemcitabine is a nucleoside analogue with broad-spectrum activity in several solid tumours. In a Phase I trial, responses were seen in patients with MVAC-refractory bladder cancer. Currently 21 patients with no prior chemotherapy for metastatic transitional cell cancer have been entered on a Phase II trial of gemcitabine at 1200 mg/m^2 weekly × 3 every 4 weeks. Patient characteristics include: 14 males, 7 females; median age 71 (range 42–88), median Karnofsky performance status 80 (range 60–100); 20 metastatic, 1 locally advanced disease; 2 prior adjuvant or neoadjuvant chemotherapy and 2 with prior radiation therapy. Currently 18 patients are evaluable for response with 3 too early. There have been 11 partial responses among the 18 evaluable patients. Sites of response have included pelvic and periaortic lymph nodes, liver and lung metastases. Toxicity has been modest in this study with no Grade 4 drug-related side effects. Grade 3 nausea and vomiting have been encountered as have Grade 1 and 2 leukopenia, myalgias, skin rash and fever. One patient with a partial response developed pneumocystis pneumonia with lowered T-4 counts and was removed from study. When he subsequently progressed (approximately 5 months later) he was retreated with gemcitabine (and trim-sulfa prophylaxis) and again has had a partial response. These data suggest that gemcitabine has promising activity in patients with transitional cell cancer and merits combination studies with other active agents in this disease such as cisplatin (with which preclinical synergy has been demonstrated) and paclitaxel.

1153 POSTER

TRANSURETHRAL RESECTION (TUR) AND CHEMOTHERAPY FOR MUSCLE-INVASIVE BLADDER CANCER: LONG-TERM RESULTS

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116 patients with muscle-invasive bladder cancer (15 T2, 94 T3, 7 T4: 23 G2, 91 G3, 2 GX, 115 Nx, 1 N1) were treated by "extensive" TUR and chemotherapy, either with high dose methotrexate (HDMTX) or cisplatin combinations. Follow-up is 3.9 to 15.2 years (median 11.6 years). The median age was 67 (range 37–88) and tumour size ranged from less than 2 to 7 cms. The median disease-specific survival is 7 years for the entire group, 4 years for HDMTX and has not been reached at 10+ years for the cisplatin combination group. T category and tumour size, but not histological grade, predict for outcome.

The results indicate that, for selected patients, this approach offers an excellent chance of bladder conservation without compromising cure rates. Results, in terms of local control and survival, are comparable with more conventional treatment approaches.

1154 POSTER

PRESERVATION OF THE ORGAN IN THE THERAPY OF INFILTRATING BLADDER TUMOURS

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From 1986 to 1994, in the II Clinic of Urology, 109 patients affected by invasive bladder carcinoma, without any random schedule, have been subjected to 3 different treatments: (1) Radical cystectomy; (2) Neoadjuvant chemotherapy (N.C.) + radical cistectomy; (3) N. C. + conservative surgical therapy. The difference of survival between group 1 and group 2 and 3 is important from the statistic point of view, and is respectively $P = 0.0209$ and $P = 0.0190$ after adjustment for age, stage, lymph node status (cox model). In the patients of group 3 (13 patients) we have considered it possible to carry out a conservative surgical treatment, in relation to the clinical-pathological response after N. C. In 9 cases, in which we have obtained 7 complete responses and 2 partial responses > than 90%, the conservative surgical therapy consisted of bladder TUR; in the remaining 4 patients for whom we have obtained a partial response > than 50% the therapy consisted of a bladder resection. These results seem to suggest that some patients affected by infiltrating bladder tumour, with a good response to N.C. and well selected, may be evaluated for a conservative treatment.

1155 POSTER

A PHASE III TRIAL OF NEOADJUVANT CHEMOTHERAPY (NCT) IN PATIENTS (PTS) WITH INVASIVE BLADDER CANCER (IBC). PRELIMINARY RESULTS: NCT IMPROVES PATHOLOGICAL COMPLETE RESPONSE RATE

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Introduction: As we reported previously (Eur J Cancer 1991;27(S12):107; Ann Oncol 1994;5(S8):66) treatment with CBDCA,