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A PHASE II STUDY OF CISPLATIN, CARBOPLATIN AND METHOTREXATE IN PATIENTS WITH METASTATIC OR LOCALLY RECURRENT TRANSITIONAL CELL CARCINOMA OF THE UROTHELIUM.

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The purpose of the study was to evaluate the efficacy of increased platinum-doses by adding carboplatin 200 mg/m² to a regimen of cisplatin 100 mg/m², and methotrexate 250 mg/m² with folinic acid rescue every 3 weeks in patients with metastatic or recurrent transitional cell carcinoma of the urothelium. All patients had histologically verified metastatic or locally recurrent disease (2 local, 43 metastatic). No patients had previously received chemotherapy. Median age was 63 years, performance status ≤ 2, M/F ratio 35/10. A response rate of 44% (95% CL: 28-60%) was achieved among 41 evaluable patients with 6 complete and 12 partial responses. The overall median survival was 7 months (range 1-20+ months), 9+ months for responding and 5 months for non-responding patients. Half of the patients had ≥ grade III hematological toxicity, two patients died of neutropenic sepsis. Renal toxicity, nausea, vomiting and peripheral sensory neuropathy were moderate. The study confirmed the efficacy of combination-chemotherapy in patients with advanced urothelial cancer. However, the addition of carboplatin to the combination of cisplatin and methotrexate did not improve response rate or survival compared with previous studies of the two-drug combination.

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THE PROGRESSION OF SUPERFICIAL BLADDER CANCER

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In the two year period authors diagnosed 123 patients with superficial bladder cancer (SBC) (T_1 G_1-G_3). Fifty-four were diagnosed as G_1, 50 as G_2 and 19 as G_3. All of them were treated with initial therapy (TUR) and were followed up in a 5 year period. Invasive cancer developed in 1 patient in G_1 group (1,8%), 3 in G_2 (6.6%) and 16 (84.2%) in G_3 group. Average time of progressive to invasive carcinoma was 21 months, range (3-48), T_1G_3 group showed average time of progression of 6 months. Authors strongly believe that T_1G_3 SBC should be treated as invasive carcinoma of bladder because of its malignant potential and because high percentage of patients develop invasive bladder carcinoma.

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NEOADJUVANT M-VAC IN HIGH GRADE-HIGH STAGE TRANSITIONAL CELL CARCINOMA (TCC) OF THE URINARY BLADDER (UB)

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Between 1986-1991, 35 patients (pts) with invasive TCC of the UB were entered into a phase II study of neoadjuvant chemotherapy.After transurethral resection of the bladder tumor (TURBT), 2 courses of methotrexate, vinblastine, adriamycin and cisplatin (M-VAC) were given. All pts had radical cystectomy and those with pathological T3b and T4 tumors received 4 more courses of chemotherapy. The mean age was 65; 2pts had T1 tumors, 25 had T2 and T3a, 4 pts had T3b and 4 pts had T4; 2 pts had grade II, 29 had grade III and 4 had grade IV. Of the 35 pts, 19 (54%) responded to chemotherapy with complete remission in 15 (43%) and a partial remission in 4 (12%); 16 pts (46%) did not show any objective response. The median survival of the responders has not been reached with a 22-month follow-up. All pts had grade III-IV GI toxicity and alopecia. Myelosuppression was the dose-limiting toxicity. In view of the encouraging results, accrual of pts continues. Updated results will be presented.

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RADIOTHERAPY PLUS FIFTH DAY LOW DOSE PLATINUM COMPOUNDS (CISPLATIN AND CARBOPLATIN) IN LOCALLY ADVANCED BLADDER CANCER

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RT plus platinum compounds are widely used in combination despite still unclear biological basis and mechanism of their potentiation. We started a prospective nonrandom study on 01.01.1991. with the aim to ameliorate local tumor control and possibility of curative treatment as well as treatment toxicity.
Patients characteristics: 69 pts. with locally advanced bladder cancer (st. T_3 and T_4), were treated with radiochemotherapy. Med. age was 62 years, and M:F ratio was 3,5:1.The whole group had TCC gr.III, with primary tumor in 41 pts. and solitary tumor in 42 pts.(tumor 4 > cm . in 5o% pts.).
Treatment: EBRT was performed on linear accelerator with locoregional technique, conventional fractionating and TD 65 Gy. Fifth day during the RT course, a 20 mg. i.v. bolus cisplatin 1 hour prior RT was administered in 49 pts. Total dose of cisplatin was 120 mg per course. Carboplatin was given (75 mg. i.v.) to 15 patients in the same way like cisplatin, with total dose of 450 mg. In 5 pts. carboplatin was administered in dose of 150 mg (fifth day) during the course of RT and the total dose was 900 mg.
Tolerance: The toxicity was mild in both groups of pts: 2/49 pts. in cisplatin group experienced natusea and 2/49 experienced hematological toxicity gr. II as well as 1/20 pts. from carboplatin group.
Response: Cisplatin group: CR 67%; PR 16%; RR 83%. Carboplatin group: CR 70%; PR 8,9%; RR 78,9%. Mean follow-up period is 11 months, and all pts. from CR group are still without disease (NED). It is not enough for conclusion concerning late complications and some clinical benefit, but the treatment was well tolerated and we are going to increase carboplatin dose in this combined modality treatment in our ongoing study.

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PHASE II STUDY WITH METHOTREXATE (M), CARBOPLATIN (C), MITOXANTRONE (N) AND VINBLASTINE (V) IN AVANCED BLADDER CARCINOMA (ABC).

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16 patients (p) with ABC, were treated with: M 30 mg m2/IV day (d) 1-15-22; C 250 mg/m2/IV d2; N 6 mg/m2/IV d2 and V 3 mg/m2/IV d2-15-22; scheduled at 28 d intervals. 15 p are evaluables for response. Mean age: 62.5 years (range 51-75). There were 12 males and 3 females. Median WHO PS 1(0-2). P were classified as: T2 3 p, T3 7 p, T4 1 p, N1-3 2 p, M1 2 p. Follow-up ranged from 5-24 mo (median 12 mo).

RESULTS: The overall response rate was 66.6% (95%CI=42.1-84.3%), with 8 CR: 1 CRc and 7 CRp, 53.3% (95%CI=30.1-75% and 2 PR, 13.3% (95%CI=3.8-37.7%). The mean response duration and the median survival was: 13.9 mo and 14.1 mo. The most important Toxicity (WHO), over 75 cycles, was: Leucopenia G1-2:66.6%; anemia G1-2:66.6%; Thrombocytopenia G1-2:22.6%; N/V G1-2:24%.

CONCLUSIONS: Our preliminary results indicate that combined M-CNV is active against ABC, showing moderate toxicity

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COMBINED CHEMORADIOTHERAPY OF BLADDER CANCER (PRELIMINARY REPORT)

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Combined chemoradiotherapy was performed in 18 patients with bladder cancer. According to TNM classification, the patients were distributed as follows: $T_2N_xM_o$ - I; $T_{3a}N_xM_o$ - 4; $T_{3b}N_xM$ - 6; T_4 - 7.
After catheterization of hypogastric arteries, i.a. chemotherapy was given. Modified M-VFC scheme was used: I-st day 30 mg/m² i.a. methotrexate, 2-nd day 3 mg/m² i.v. vinblastin, 50 mg/m² i.a. farmorubicin and 3-d day 70 mg/m² i.a. cisplatin. 10-14 days later, the 2-nd course of chemotherapy was performed. Standard fractionating of 2 Gy was done for 5 days weekly (total dose 50 Gy). Twice, at the beginning and by the end of radiation therapy, cisplatin was infused i.v. in dosage of 70 mg/m². 10 patients (55,6%) were complete responders, 3(16,6%) achieved partial response and 3 (16,6%) showed regression less than 50%.