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COMBINATION CHEMOTHERAPY CONTAINING CISPLATIN/IFOSFAMIDE AND VINBLASTINE OR ETOPOSIDE IN BULKY SEMINOMA

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Since 1982 63 pts with seminomatous germ cell tumor were treated with cisplatin-containing therapy. 39 pts had stage IIC/D, 11 stage III, 13 stage IV. HCG was elevated in 26 pts up to 599 U/l. Chemotherapy protocol consisted of VIP in 39 pts, EIP in 18 cases, 5 PVB/PEB and 1 ECBC. 18 pts were pretreated with radiotherapy, 4 with carboplatin,1 polychemotherapy. Results: Until 2/93 61 pts were evaluable, 2 are still in treatment. 55/61 reached CR,documented surgically in 14 pts.2 pts suffered early deaths,2 died of progression,1 of gastrointestinal bleeding,1 of sepsis during salvage therapy. Only 1 pt relapsed after 29 months and reached a second CR lasting 78+ months. Now 55/61 pts are NED (90%) - 16/18 pretreated (89%),39/43 nonpretreated (91%).Median observation time 54+ months.Toxicity was high: apart from 2 early deaths,most pts had severe thrombo/leukopenia, 1 tumor lysis syndrome.After reduction of etoposide (75mg/m²) and ifosfamide (1,2g/m²) no further toxic death was observed.Thus we consider this EIP protocol as standard procedure,resulting in a higher CR rate than with PEB, with no lung complications and a very low relapse rate.

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RADIOTHERAPY, SURVEILLANCE OR ADJUVANT CHEMOTHERAPY FOR STAGE I GEMR CELL TUMOURS.

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Studies of adjuvant chemotherapy, Bleomycin, Etoposide, Cisplatin for non-seminoma and Carboplatin for Seminoma have been undertaken by the Anglian Germ Cell Tumour Group since 1983. Since 1985 to 1990 patients received 2 courses and since 1990 one course has been used. The table summarises the overall results.

	All Cases		Seminoma		Non-Seminoma	
	No.	Relapse	No	Relapse	No.	Relapse
Radiotherapy median FU=51 mths	80	5%	80	5%	0	0%
Surveillance median FU=33 mths	214	29%	69	25%	145	30%
Chemotherapy median FU=24 mths	118	2%	80	1%	37	3%

So far there have been 0 relapses of 37 patients receiving one course of adjuvant (median FU 9 months: range 6 to 30 months) compared to 2 of 81 receiving two courses (median FU 33 months).

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SURVEILLANCE POLICY IN STAGE I TESTICULAR CANCER AT A SINGLE INSTITUTION.

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Between 1984-1992, 135 stage I patients (p) with germ cell tumors submitted to surveillance policy. From 1990 p with high risk of relapsed (HRR) were offered adjuvant chemotherapy.

71 p. with seminoma and 64 with non seminomatous tumor (NST) followed that policy. Overall relapses for seminoma were 10(14%): 7/45(16%) before 12/89, 1/18(6%) p without HRR and 2/7(29%) p with HRR since 1990. The time to relapse range from 5 to 61 mos (median 9,4). In NST, 14 out of 64(22%) relapsed, 11/36(31%) before 12/89 and 3/28(11%) since 1990. The median time to relapse was 6 mos (range 3-45). All patients with relapses receved chemotherapy with platinum assotiations. Overall group but 1 p with NST are disease free with median follow-up 43 mos (range 3 to 122).

CONCLUSIONS: A. Surveillance policy may avoid 80-85% adjuvant readiotherapy in seminoma and 90% lymphadenectomies in NST without change overall survival. B. Intensive surveillance up to 5 years is necessary to detect late relapses. C. Adjuvant chemotherapy in HRR p may reduce the relapse rate.

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CARBOPLATIN-BASED CHEMOTHERAPY IN GOOD PROGNOSIS METASTATIC NON SEMINOMA OF THE TESTIS (NSGCT): AN INTERIM REPORT OF AN MRC/EORTC RANDOMISED TRIAL

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Between 1989 and 1993, 589 patients with metastatic good prognosis NSGCT were randomised to 4 cycles of Bleomycin (30 U iv day 1), Etoposide (120mg/m² /day iv days 1, 2, 3), Cisplatin (100mg/m2 total dose divided iv on either days 1 + 2 or on days 1-5) or to the same schedule with cisplatin replaced by carboplatin at a dose to achieve a serum concentration x time of 5mg/ml x mins (dose = 5 (GFR+25) when GFR = glomerular filtration rate. Good prognosis was defined by the absence of all of the following adverse features; ≥20 lung metastases, liver bone or brain involved, AFP > 1000 U/L, HCG > 10000 U/L, mediastinal or cervical mass > 5cms, abdominal mass > 10cms.

The complete response rate was 93% on BEP versus 88% on CEB (p = 0.12). The failure-free rate at one year was lower on CEB (80%) than BEP (90%) with a 95% confidence limit for the difference of 4% - 16% (logrank p = 0.01, failure defined as non remission, viable undifferentiated tumour at post surgery or relapse). With median follow up of 12 months there is no statistically significant overall survival difference (logrank p = 0.1). We conclude that the carboplatin-based schedule as administered in this trial was inferior, though further follow up may allow assessment of the accuracy of carboplatin dosing, and differences in patient subgroups.

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NONINVASIVE DIAGNOSIS OF NEPHROTOXIC EFFECTS OF CHEMOTHERAPY WITH CIS- AND CARBOPLATIN

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In order to improve the noninvasive monitoring of subtle renal injury during therapy with nephrotoxic drugs we investigated theefficiency of a combined analysis of the urinary activities of fructose-1,6-biphosphatase (FBPase) and N-acetyl-β,D-glucosaminidase (NAG) as well as the excretion of α_1-microglobulin (α_1-mic), albumin and immunoglobulin G (IgG) during chemotherapy with cis- and carbolplatin.

23 previously untreated patients with testicular cancer entered the study: 8 patients were treated with single agent carboplatin, 15 patients received 2 or 3 cycles chemotherapy according to PEB- or PEI-regimen. The control group consisted of 20 healthy male persons. Using daily spontaneous second morning urine, tubular dysfunction was monitored by increased urinary activities of FBPase, a gluconeogenic key enzyme localized only in the proximale tubule and the lysosomal enzyme NAG. Disorders of proximal tubular reabsorption were assessed by the enhanced excretion of α_1-mic, whereas disturbances of glomerular filtration were identified by increased excretion of albumin and IgG. In addition, two usual parameters of kidney function, creatinin clearance and serum creatinin were monitored. During the observed interval of therapy cisplatin induced a significant increase in the excretion of NAG, FBPase, α_1-mic and albumin, which is indicative for both tubular and glomerular lesions. Therapy with carboplatin led to albuminuria indicating glomerular dysfunction. All other parameters remained unaltered. Serum creatinine and creatinine clearance were within normal range in all patients studied.

The present investigation shows that the combined analysis of the urinary activity of NAG and the excretion of α_1-mic, albumin and IgG provides a very sensitive method to detect tubular and/or glomerular dysfunction. The analysis of FBPase activity guarantees a very sensitive and sitespecific monitoring of proximal tubular injury during therapy with nephrotoxic compounds.

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CLINICAL CHARACTERISTICS AND LONG-TERM OUTCOME AFTER CISPLATIN-BASED CHEMOTHERAPY FOR PRIMARY EXTRAGONADAL GERM CELL TUMORS

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Between 1979 and 1992 we treated 44 primary extragonadal germ cell tumors (PEGCT) with cisplatin-based chemotherapy. 16 nonseminomatous PEGCT arose in the retroperitoneum (median age 35 years, range 24-51 yrs), 13 in the mediastinum (median age 26 yrs, range 17-35 yrs). Haematogenous spread was found in 3 patients (23%) with mediastinal and and in 13 pts (81%) with retroperitoneal tumors. HCG was elevated in 5 pts (38%) with mediastinal and in 12 pts (75%) with retroperitoneal nonseminomatous PEGCT. AFP was elevated in 12 pts (92%) with mediastinal and in 8 pts (50%) with retroperitoneal tumors. 7 pts (54%) with mediastinal tumors achieved no evidence of disease (NED) status, 1 of whom experienced a late relapse and died; 7 pts (44%) with retroperitoneal tumors are alive with NED status (median follow-up 68 months). 3 seminomas arose in the mediastinum, 12 in the retroperitoneum (median age 40 yrs, range 26-53 yrs). HCG was elevated in 7 pts (47%) up to 100 U/l; haematogenous spread was not found in any pt. 13 pts (87%) are currently alive with NED status (median follow-up 77 months). 3 pts with retroperitoneal tumors (1 seminoma, 2 nonseminomatous tumors) developed a testicular tumor, all of whom are alive with NED status after orchidectomy. In conclusion, mediastinal and retroperitoneal nonseminomatous PEGCT have distinct clinical features but carry a similar prognosis. Pts with pure seminomas have a high chance of cure.