901 ORAL

CONVENTIONAL AND MOLECULAR CYTOGENETIC ANALYSIS OF TESTICULAR GERM CELL TUMORS

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Conventional cytogenetic analysis of testicular germ cell tumors (GCT) revealed an isochromosome (12 p) as a specific aberration in more than 80% of cases. However, chromosome analysis is hampered by the need for short-term cell cultures and the complexity of anomalies in the mostly polyploid karyotypes. Furthermore, homogeneously stained regions and double minute chromosomes, as signs of amplification of unknown chromosomal material, are frequently found. Comparative genomic hybridization (CGH) allows the detection of chromosomal gains and losses in tumor DNA throughout the whole genome without the need for dividing cells. This method might therefore overcome at least parts of the limitations of conventional analysis. We studied DNA from fresh tissue of 10 testicular GCT's by CGH. In cases, where banding analyses where also available, both methods yielded comparable results. CGH analysis of all examined tumors showed a gain of 12p, mostly of the whole p-arm. In two tumors, an intense amplification of 12p material restricted to the chromosomal region 12p12 was found. In two other cases, gains of small chromosomal regions at 4q12 and 6p21 were also detected. Thus, these regions are highly suspicious of containing genes which may play an important role in the pathogenesis of testicular GCT's. Moreover, among other anomalies, gains of chromosomes 8, 14, 19, 21 and X as well as loss of chromosome 13 were frequent findings. In conclusion, CGH provides new insights into genetic alterations of testicular GCT's. By means of CGH, we detected chromosomal regions where amplified genes may be localized. Further investigations are necessary to confirm and to expand these findings and to identify the genes involved.

902 ORAL

OPTIMAL FIELD SIZE IN ADJUVANT TREATMENT OF STAGE I SEMINOMA

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From 7/1989 to 5/1993 478 men with seminoma stage I (T1–T3; no ipsilateral inguinal operation prior to orchiectomy) have been included in a phase III study assessing the field size of abdominal radiotherapy (30 Gy/3 wks). Group 1: paraaortic (p.a.) field from Th11 to L5, the lateral borders including the processus transversi. Group 2: "dog-leg field" (p.a. + ipsilateral iliac field to the mid obturator level).

Results: With a median follow-up time of 29 months, 114 relapses have occurred, two of them within the pelvic area (2 years relapse-free survival 97%; 95% C.I./96%, 99%). Relapses were diagnosed between 4 months and 3 years from start of radiotherapy. Acute grade ≥ 3 gastrointestinal toxicity was observed in 11% and 17% of the patients with p.a. and dog-leg field, respectively. In Group 1 grade ≥ 2 myelotoxicity occurred in 5% of the patients and in 13% of the patients from Group 2. 8 patients developed peptic ulcer after radiotherapy. After 1 year 11% patients in Group 1 and 30% of those in Group 2 were azoospermic.

Conclusions: In patients with seminoma stage I (T1–T3) and with undisturbed lymph node drainage of the primary tumour adjuvant radiotherapy to the p.a. lymph nodes is associated with reduced gastrointestinal, haematological and gonadal toxicity compared to standard pelvic + p.a. irradiation. The recurrence rate is low with either field.

903 ORAL

RISK-ADAPTED TREATMENT OF CLINICAL STAGE 1 (CS1) NONSEMINOMA TESTIS CANCER (NSTC)

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246 patients (pts) with CS1 NSTC were included into a prospective multicenter protocol during 1990–94 and treated according to 3 risk strata: Pts without tumor cell invasion of vascular structures in the testis (VASC−) and elevated serum AFP levels (AFP+) at orchiectomy were considered low risk (LR) and surveilled only. VASC− & AFP− or VASC+ & AFP+ pts were presumed intermediate risk (IR) and path. staged (PS) by retroperitoneal lymph node dissection (RPLND). VASC+ & AFP− pts were regarded as high risk (HR) and received adjuvant chemotherapy (BEP × 3) *Preliminary results at a median obs, time of 32 months:* Crude survival of all 246 pts are 100% and all relapsing pts are in remission. Of 225 fully evaluable pts: Relapse rate in the 99 LR pts are 23% and 76% had elevated serum tumor markers at relapse. One of 32 (3%) HR pts relapsed (resectable retroperitoneal mature teratoma). Of 94 IR pts 38% had either PS2 at RPLND or relapsed despite PS1. AFP status at orchiectomy had no real predictive value for subclinical metastases in this study, but may indicate increased safety during surveillance by early warning of relapse.

904 ORAL

OUTCOME ANALYSIS AFTER SALVAGE TREATMENT OF TESTICULAR GERM CELL TUMOURS

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Long-term outcome of salvage treatment was reviewed in 67 unselected patients relapsing during or after their primary cisplatin-based chemotherapy for metastatic testicular cancer. Salvage treatment predominantly consisted of cisplatin-ifosfamide-based chemotherapy ± surgery. With a median follow-up of 90 months 20 patients (30%) are alive with no evidence of disease. Prognostic factor analysis included year of diagnosis, age, primary site (testicular versus extragonadal), initial tumour burden, relative dose intensity of cisplatin, response to primary therapy, relapse-free interval, and tumour burden and marker status at relapse. Univariate analysis identified age ≤ 35 years, testicular origin, low tumour burden at diagnosis and at relapse, complete response (CR) to primary therapy and a relapse-free interval >3 months as predictors of favourable outcome. Multivariate analysis confirmed age ≤ 35, CR to primary therapy, and a relapse-free interval >3 months. Patients with these good-risk features had a 5-year survival of 72%. Prognosis for the remaining patients is poor with only 11% 5-year survival emphasising the need for innovative and more aggressive approaches.

905 ORAL

SEXUAL DYSFUNCTIONS AFTER TESTICULAR CANCER (TC)

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Introduction: 90% of pts with TC are cured. Little research is available on posttreatment sexual function (SF). Prevalences and type of sexual morbidity in TC was studied.

Methods: A questionnaire study was designed to assess SF and sent to 314 TC pts treated between 1977–94.

Results: Questionnaires returned in 84% (N = 265). Median pts age 37 (SD ± 10) yrs. Median follow-up 7 (SD ± 4) yrs. Treatment: orchiectomy + surveillance (N = 58), radiotherapy (RT, N = 45), chemotherapy (CHT, N = 28), CHT + retroperitoneal lymph node dissection (RPLND, N = 134). Impairment of SF in 116 pts (43%): reduced libido, potency disturbances, decreased orgasm and reduced/absent ejaculation were most prominent. Significant decrease in SF was present in pts with adjuvant treatment vs surveillance (24% vs 44%, $P < 0.01$). No difference in SF was present between RT-group vs CHT (+RPLND)-group. Decrease of SF in the CHT + RPLND group vs CHT alone was seen ($P = 0.08$), although pts treated with RPLND suffered more from ejaculation and potency disturbances. Deterioration in SF was observed with increasing age ($P < 0.01$).

Conclusion: High prevalence of sexual dysfunction following orchiectomy and adjuvant therapy for TC is documented in the study.

906 POSTER

MVIP CHEMOTHERAPY (CT) IN VERY ADVANCED, REFRACTORY (REF) OR RELAPSED (REL) GERM CELL TUMOURS (GCT)

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38 pts with primary GCT of the testis (35) or the CNS (3) received methotrexate (M) 250 mg/m^2 as a 24 h infusion with fol. acid d.1, cisplatin (P) 100 mg/m^2 d.4, etoposide (V) 100 mg/m^2 d. 4–6 and ifosfamide (I) 5 g/m^2 d.5 with mesna (MVIP). Of those, 18 with large/very large volume disease only (MRC staging) received MVIP as primary CT. Toxicity was considerable with no toxic deaths. There were 6 CCR + 5 CPR/PCR (61%) who are off CT/NED for $26^+(9^+–41^+)$ mos. 4 (22%) CPR pts died after 6 (3–10) mos, including 2 of the 3 CNS pts. 3 recent pts have achieved CPR so far and are still responding further. The same CT was given as 2nd line in 9 ref and 11 rel (P or carboplatin) pts. Of

8 CCR pts, 5 are off CT/NED for $47^{+}(20^{+}-58^{+})$ mos and 3 relapsed and died after 13 (11–18) mos. Of 12 CPR pts, 3 were PCR and are off CT/NED for $35^{+}(29^{+}-40^{+})$ mos, while 9 died after 6 (3–13) mos. Total off CT/NED pts 8 (40%). Ref NED pts 2/9 (22%) and rel NED pts 6/11 (55%). Overall long term NED status with MVIP 19/38 (50%). We conclude that MVIP is very active in those very poor risk cases.

907 POSTER

ENDOCRINOLOGIC LATE SEQUELAE AFTER CHEMOTHERAPY FOR TESTICULAR CANCER

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Endocrine abnormalities regarding the androgens or estrogens and their regulatory hormones have been reported in patients (pts) after chemotherapy (CTX) for metastatic testicular cancer and may influence important cardiovascular risk factors.

Objective and pts: To study the influence of different CTX regimens, dosage, pts age and time since CTX on serum levels of FSH, LH, testosterone, total estrogens, estradiol, estrone, DHEA, DHEAS and 17-OH-progesterone and their correlation to serum cholesterol, liver enzymes, body mass index and blood pressure in pts treated with unilateral orchidectomy and CTX for testicular cancer. 63 pts with a median (med) age of 30 [19–53] years, and a med follow-up of 40 [16–128] months were included. Treatment: PVB: 21 pts; PEB: 22 pts; PEB + vincas: 13 pts; other: 7 pts; (P = cisplatin, V = vinblastine, E = etoposide, B = bleomycin).

Results: Elevated levels for LH, FSH, DHEA and 17-OH-progesterone were found in 48%, 63%, 68% and 51% of pts, respectively. 9 of 30 (30%) pts with elevated LH had low testosterone levels indicating decompensated Leydig cell insufficiency. FSH and LH levels were correlated to cumulative doses of P ($P = 0.006$ and 0.016) and age at time of CTX. Elevated gonadotropins were found in 50% of pts after standard PEB-therapy in contrast to 82% of pts with vincaalcaloide-containing regimens ($P < 0.04$). Andrenal androgenes (DHEA/S) correlated to cumulative dose of P ($P = 0.006$) and were significantly associated with serum cholesterol levels and body mass index in pts <40 years.

Conclusions: Major endocrinological abnormalities after CTX persist in >50% of the pts cured of testicular cancer. CTX-induced shifts in hormonal ratios—especially of the adrenal androgenes (DHEA/S)—may be associated with elevated cholesterol levels, leading to an increased cardiovascular risk for these young pts.

908 POSTER

EXTRAGONADAL GERM CELL TUMOURS (EGGCT): EXPERIENCE AT HANNOVER UNIVERSITY MEDICAL SCHOOL

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EGGCT can arise as retroperitoneal (ret) or mediastinal (med) primary tumours. Although treated like primary gonadal germ cell tumours, their prognosis has been regarded worse.

65 patients (pts) with a median age of 28 years (18–78) treated between 1970 and 1993 at Hannover University Medical School were included into this retrospective analysis. Histology was seminoma (S) in 13 (20%) pts (4 ret; 9 med) and non-seminomatous germ cell tumour (NS) in 52 (80%) pts (26 ret, 24 med). Among pts with NS histology 58% and 60% had elevations of AFP and β-HCG, respectively; 76% of pts had an elevation of serum LDH. 47 pts (71%) had metastases in addition to the extragonadal primary tumour, (7 bone, 12 liver, 24 lung). Most pts were treated with either chemotherapy (CTX) alone (10 pts) or CTX + surgery (43 pts). 16 pts received additional or definitive radiotherapy. 12 of 13 pts with S (92%) achieved CR or PR; 32 pts with NS (63%) achieved CR or PR M- to initial treatment and 19 pts (37%) were failures. After a median follow up of 33 months (12–259) 10 pts with med and 13 with ret EGGCT have relapsed. 3-year overall survival for EGGCT pts with S was 78% versus 58% with NS histology. For NS pts no significant difference in overall survival between med and ret localizations of EGGCT was found. The use of platinum/etoposide/ifosfamide-based initial CTX (22 pts) for NS pts proved to be superior to other combination regimens (35 pts) (2-year survival 76% vs 57%).

909 POSTER

CHEMOTHERAPY IN FAR ADVANCED SEMINOMA

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Since 1982 80 pts. with histologically proven seminoma have been treated with cisplatin-containing chemotherapy. All had far advanced stage of disease: 46 stage II C/D, 16 stage III, 15 stage IV. Pretreatment was administered to 30 pts, 19 with radiotherapy, 7 with carboplatin and 4 with other chemotherapy. Treatment protocol was vinblastine, ifosfamide, cisplatin (VIP) in 38 pts., etoposide, ifosfamide, cisplatin (EIP) in 33 pts., and PVB/PEB or ECBC in 6 pts. Until 3/95 66/77 pts. reached CR (86%), 15 surgically documented. 5/77 (6%) reached PR, 6/77 pts (8%) died. 2 pts. relapsed (3%) and have reached a 2nd CR. 71/77 (92%) are currently alive and show no evidence of tumor progression (median observation time 60+ months). Toxicity was high with 2 early deaths, severe thrombo- and leukopenia WHO grades 3/4, 4 severe infections and 1 tumor lysis syndrome. The EIP protocol with daily 75 mg/m^2 etoposide and 1.2 g/m^2 ifosfamide and 20 mg/m^2 cisplatin is our standard treatment for seminoma and is being compared to carboplatin monotherapy in the still ongoing randomized trial.

910 POSTER

IFOSFAMIDE-BASED SALVAGE CHEMOTHERAPY FOR PATIENTS WITH RESISTANT GERM CELL TUMORS—OUR EXPERIENCES

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Between 1985 and 1993, 78 male patients were treated in our Institute with germ cell tumors. All patients in Stage A, B1 and B2 were cured with PVB respectively PEB protocol-59 patients (76%). From 19 patients in Stage B3 and C, complete remission was achieved in 10 (52.6%) patients. All patients who had failed to be cured—9 (47.4%), received salvage chemotherapy (PEI protocol) consisting of cisplatin, etoposide and ifosfamide (with mesna protection). Cisplatin was given at the dosage of 20 mg/m^2 on days 1–5, etoposide at the dosage of 75 mg/m^2 on days 1–5 and ifosfamide was given at the dosage of 1.2 gr/m^2 on days 1–5 with mesna protection. Complete remission was achieved in 4 patients (44.4%) with chemotherapy alone in 2 patients and additional in 2 patients following by surgical resection of vieble tumor. Pathohistological finding was in 1 patient necrosis and in 1 malignant tissue was present (embryonal carnimona). This patient received one cycle PEI-protocol after surgical resection as consolidation chemotherapy. The toxicity was acceptable during the chemotherapy (all patients received adequate premedication). On the basis of our results, although only a small number of patients was included, we suggest that this protocol may be regarded as a very acceptable therapeutic procedure in the treatment of patients with resistant germ cell tumors.

911 POSTER

TREATMENT AND OUTCOME OF PATIENTS WITH EXTRAGONADAL GERM CELL TUMORS

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48 patients, 32 with abdominal and 16 with mediastinal extragonadal germ cell tumors were included in this study. 2 were women with mediastinal primaries. At presentation most patients had advanced disease. The median size of the tumors were 128 mm (abdominal) and 116 mm (mediastinal), respectively. Of the 48 patients, 14 had metastasis to liver, brain, and/or bone at time of diagnosis. Patients with metastasis to these organs had particularly poor survival. 7 patients died due to treatment-related toxicity. The median age of these seven patients were significantly higher than among the other patients. The 5-year survival of all 48 patients was 55%. 29 patients received CR after chemotherapy, determined by CT-scan and/or biopsy. 28 of these are still alive.