821 POSTER

A prognostic model for response and outcome in patients with extragonadal germ cell tumors - an international multivariate analysis

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Purpose: This investigation evaluates prognostic variables in patients with seminomatous and nonseminomatous extragonadal germ cell tumors (EGCT) in order to identify relevant factors for long-term outcome following cisplatin based chemotherapy.

Methods: Patients from six countries treated in at eleven centers in Europe and United States between 1975 and 1996 were retrospectively evaluated. Multivariate analyses of prognostic variables for survival and for response to chemotherapy were performed.

Results: Data were available from 635 EGCT patients, 104 seminomas and 524 nonseminomatous EGCT (n=7 not specified). For nonseminomatous EGCT the following independent adverse factors were identified: presence of either liver [hazard ratio (HR): 1.7], lung (HR: 1.4) or central nervous system (CNS) metastases (HR: 2.5), primary mediastinal tumor site (HR: 2.3), elevation of pretreatment beta-human chorionic gonadotropin (HR: 1.5). For extragonadal seminoma no adverse feature was identified. Integration of this variables produced the following prognostic grouping: 'excellent prognosis', all seminomatous EGCT, comprising 17% with a 89% 5-year survival rate; 'intermediate high', 'intermediate low' and 'poor', all nonseminomatous EGCT with score values of 0/1, 2/3 or >3, respectively, comprising 20%, 52% and 11% of EGCT with a 69%, 55% and 17% 5-year survival rate. The decreased survival among the different groups was due to a lower rate of favourable objective remissions and a higher rate of relapses. In addition, CART modelling confirmed histology and location of primary as the major prognostic division points. Multivariate testing for the probability to respond to chemotherapy has revealed nonseminomatous histology, primary mediastinal tumor site, presence of liver, lung and CNS metastases as independent adverse factors.

Conclusion: In EGCT prognostic variables for the outcome and for response to chemotherapy could be identified which in part differ from gonadal GCT. The proposed models might help to better understand the specific prognosis of EGCT and to tailor risk-adapted treatment strategies.

822 POSTER

Improved survival in patients with testicular germ cell tumours

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Introduction: The treatment results in an unselected series of testicular germ cell tumours (TGCT)from a geographic area is presented.

Patients: 690 new TGCT cases were seen from 1.1 1980 to 31.12.2000 from Western Norway. After orchiectomy all patients were staged by CT scans of the abdomen and thorax (only chest X-ray for seminomas the first decade), full blood tests including the tumour markers alpha-feto protein (AFP), human choriogonadotropin (HCGbetha) and lactate dehydrogenase (LDH). We used the Royal Marsden Staging system, based on the first examination: Stage 1: tumour localised to the testicle; stage 2 abdominal lymph nodes (A: <2cm, B 2-5 cm, C>5 cm); stage 3 mediastinal or supraclavicular lymph nodes; stage Mk+ only positive markers; stage 4 distant spread). All patients with non-seminomas were treated according to the SWENOTECA II-IV protocols. Stage 1 and 2 A had a staging retroperitoneal lymphadenectomy in the first decade. Later stage 1 patiens without vascular invasion had surveillance only, while stage 1 patients with vascular invasion had 1-2 courses of the BEP20 regimen. Patients failing (defined as slow decrease of tumour markers) initial therapy in higher stages had ifosphamide added to the regimen or underwent two courses of high dose chemotherapy with stem cell support up front. Seminoma patients had gradually reduced radiation doses from 40 to 36 to 30.6 to 25.2 Gy (2 or 1.8 Gy daily) by L-fields during the periode. The last years they could chose between radiation or surveillance only. Stage 2 B and higher received chemotherapy with EP/BEP20 or PEI regimen. All cases were followed for at least 10 years except one patient who emigrated after two years.

Results: There were 382 seminomas and 308 non-seminomas. Ony 6 non-seminoma patiens died of the disease, and one from sepsis due to chemotherapy. Progressing disease or recurrence was observed in 14%. The 10-year survial rate for all patients was 98.1%. Cancer specific survival for non-seminomas was 97.1% (Stage 1:99% (n=186); Stage 2:96.6% (n=66), Stage 3 and Mk+: 100% (n=3 and 11); Stage 4:89.2% (n=42). For all seminomas the 10-year cancer specific survival rate was 99.0% (Stage 1: 100% (n=305); Stage 2: 96.3% (n=68); stage 3: 100% (n=6); Stage 4: 67% (n=3). Only 2.7% seminomas failed initial therapy.

Conclusion: Most new TGCT are currently cured by tailored therapy as a cancer specific survival in the order of 98% can be obtained in unselected patients.

823 POSTER

Phase II study of salvage dose-dense chemotherapy in patients with disseminated non-seminomatous germ cell tumors (NSGCT): Final results

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Purpose: To assess the efficacy and toxicity of a dose-dense alternating chemotherapy regimen in patients with refractory or relapsing NSGCT.

Methods: Chemotherapy consisted in the so-called BOP-CISCA-POMB-ACE regimen (bleomycin, vincristine, cisplatin/cisplatin, cyclophosphamide, doxorubicin/cisplatin, vincristine, methotrexate, bleomycin/etoposide, dactinomycin, cyclophosphamide) + G-CSF. Chemotherapy was recycled every 7 to 14 days and was followed by surgery.

Results: From 10/93 to 10/96, a total of 33 patients were enrolled (cisplatin-sensitive: 14, refractory: 15, absolute refractory: 4). Thirteen patients (39%) had received >1 previous chemotherapy regimen and 25 (76%) had a predicted unfavorable prognosis according to the MSKCC classification. Thirteen patients (39%) had a complete response to therapy. With a median follow-up time of 65 months (range 35–83 months), the 3-year overall survival (OS) rate was 46% (95% CI: 31%–54%) and the 3-year progression-free survival was 33% (95% CI: 21%–54%). Toxicity: G4 neutropenia (58%), G4 thrombocytopenia (61%), G4 anemia (15%), G3-4 stomatitis (30%), toxicity-related deaths (n = 2). The MSKCC classification for relapsed NSGCT seemed to allocate patients more adequately into prognostic groups (3-year OS: 75% vs 37%, $p < 0.04$) than did the MRC classification.

Conclusion: The combination of the dose-dense BOP-CISCA-POMB-ACE regimen and aggressive surgery is active as salvage therapy for NSGCT. These results compare like results of intensive regimens with hematopoietic support.

824 POSTER

Long term effect of oral testosterone substitution therapy on bone mineral density and hormone profil in patients with bilateral testicular cancer

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Purpose: The aim of this clinical study was to evaluate the use of long term oral testosterone undecanoate substitution therapy in patients who underwent bilateral castration due to bilateral testicular cancer.

Methods: 46 patients with primer hypogonadism were enrolled into this clinical research study. All patients received daily 2 x 80 mg testosterone undeconate as long term androgen replacement therapy. Blood samples were drawn between 8-9 am. for haematology, biochemistry and hormone measurement. Bone mineral density was obtained from all patients by single energy quantitative CT of the lumbar spines. BMD was also assessed in 25 patients on the lumbar spine and femoral neck by DEXA to compare the different methods.

Results: The mean age of patients was 40,8 years (range: 24-53) at the time of beginning of study. The mean age of patients at the time of evaluation was 40,8 years (range: 26-53) The mean age was 28,9 years (range:16-51) at the time of first castration, and 35,8 years (range: 31-51) at the time of second castration. Mean interval between appearance of the two tumors is 5,2 years. The histological diagnosis were seminoma in 21 cases, and 25 patients have non-seminoma at the time of first castration. If the first histological diagnosis was seminoma, the second testicular tumor was significantly also seminoma (P-value: 0.0000).Of the 46 subjects in the study group, two patients had testosterone levels that were within the reference

range of morning testosterone in healthy men. Mean level of testosterone was 3,46 nmol/L(SD:1,98 nmol/L), high level of FSH (mean 58,2 IU/L) and LH (18,75 IU/L) were measured. The difference to the lower limit of testosterone reference range is statistically significant (P-value: 0.0000). In the total group of patients with oral testosteron substitution 20 displayed with serum oestradiol below the normal range. Only 6 patients of the group showed normal BMD. The average of BMD values were significantly low, with a mean of 61%, compared to age matched control). DHEA levels were statistically significant low in patients with low BMD values.

Conclusion: Oral testosterone undecanoate substitution therapy is not optimal for long term substitution treatment to maintain normal hormone level and BMD value in these patients.

825 POSTER

Long-term fatigue and quality of life (QL) after cure for testicular cancer (TC): a comparison with survivors of Hodgkins disease (hd) and the general population (GenPop)

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Aim: To assess the prevalence of long-term fatigue in TC survivors.

Methods: A mailed questionnaire with SF-36, HADS and a validated Fatigue questionnaire was answered by 791 TC survivors (mean age: 45 years), 12 years (mean) after primary diagnosis. Among these, 660 pts. had an out-patient examination and blood sampling.

Results: 16% of the TC pts. had chronic fatigue as compared to 24% after HD and 11% in the GenPop. Type of previous treatment (surgery only, radiotherapy only, chemotherapy +/-), duration of follow-up and age at survey were not associated with fatigue, whereas this was the case for current co-morbidity, educational level, and current and previous psychological distress. Depression was more correlated with fatigue than anxiety. Chemotherapy given to those aged ≥40 years and ≤20 years at diagnosis was a risk factor for post-treatment fatigue. In general, the mental health of TC survivors was superior to that of HD survivors and of the GenPop. TC survivors displayed higher levels of anxiety but lower depression scores than the GenPop. Most QL parameters (SF-36) of TC survivors were more favourable than those of HD survivors. Except for pain, the scores of the QL dimensions were similar to those of the GenPop. In patients <50 years at survey, subclinical gonadal insufficiency was associated with chronic fatigue. For all patients, the HADS-Depression score remained an independent predictor of chronic fatigue together with the Mental and Physical Component Summaries of the SF-36.

Conclusion: Chronic fatigue and decreased QL represent a lesser problem in middle-aged TC survivors than in HD survivors, but remain a larger problem than in the GenPop. Mental health, in particular depression, seems to be an important predictor of fatigue together with somatic health. Patients aged ≤20 or ≥40 years at chemotherapy appear to represent risk groups for chronic fatigue.

826 POSTER

Clinical characteristics, treatment and outcome of patients (pts) with bilateral testicular germ cell tumors (BTGCT)

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Purpose: The clinical characteristics, treatment and outcome of BTGCT in connection with the widespread use of cisplatin based chemotherapy was analyzed in a retrospective study.

Methods: The study involved 2386 pts treated between 1988 and 1998 with testicular cancer in our Department at the National Institute of Oncology.

Results: 72 pts had BTGCT; 19 cases (0.8%) were synchronous and 53 cases (2.2%) metachronous. Of the 19 synchronous BTGCT pts (median age 37.7 years, range 19-71) 13 had concordant seminoma (70%) and 7 discordant histology. The clinical stages were: 8 I/A, 5 I/B, 1 II/A, 2 II/B, 1 III/A, 2 III/B. The 5-year overall survival was 85%, three pts died, 2 due to tumor progression. The median follow-up is 93 months, range 31-150). In 53 pts with metachronous BTGCT median age at the diagnosis of the 1st tumor was 28 years (range 16-41), median time to second tumor was 76 months (range 18-203). Nine had concordant seminoma, and 9 concordant nonseminoma. Among the 53 pts 2 had a family history of TGCT, 5 (13%) had testicular maldescent (in 2 cases bilateral), 7 testicular atrophy, 1 azoospermia. 68% of the pts were younger than 30 years at the 1st tumor diagnosis. At the 1st TGCT diagnosis the following clinical stages were detected: 14 I/A, 21 I/B, 15 II/A, 2 II/B, 1 III/B. 22 pts were treated with chemotherapy. At the 2nd TGCT diagnosis 26 I/A, 16 I/B, 3 II/A, 1 II/B and 7 III/B stages were registered. In 38 cases chemotherapy was used. No relapse occurred between the two tumors. The 5-year overall survival was 95% (median follow up 42 months, range 27-121). Two relapses occurred after primary therapy, 1 patient died due to tumor progression.

Conclusion: The overall incidence of BTGCT is low, the majority of patients have a good prognosis. These results argue against the introduction of systemic contralateral biopsy at the 1st TGCT diagnosis in all pts in Hungary. Better identification of pts at risk for a 2nd TGCT is not possible by the proposed clinical risk factors, that is why education and long term follow up are important in the early detection of a second TGCT.

Immunobiology and biological therapies

827 POSTER

Immunotherapy for stomach cancer with the apoptosis-inducing human monoclonal antibody SC-1

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Purpose: Stomach carcinoma belongs to most dangerous malignant diseases worldwide. Treatment is mostly limited to radical gastrectomy, lymphadenomectomy and in cases of irresectable tumors to chemotherapeutical approaches. But even then, according to the number of people killed worldwide by this cancer, the prognosis is very poor and there is a big need for additional adjuvant therapies.

Methods: We have recently described the human monoclonal antibody SC-1, which was isolated from a patient with gastric cancer by hybridization of lymphnode cells with a heteromyeloma cell.

The moderately affinity-maturated IgM antibody (DP49) SC-1 binds to a novel modified form of membrane-bound CD55 (DAF-B, decay-accelerating factor), that is specifically overexpressed on stomach carcinoma cells and absent on other tumor cells or healthy tissue. DAF-B therefore exists in two different glycosylated forms on stomach carcinoma cells, in addition to the ubiquitously distributed 70 kD isoform, which protects cells from lysis through autologous complement, a specific modified 82 kD DAF-B is coexpressed. A tyrosine phosphorylation of 60, 75 and 100 kD proteins and a serine dephosphorylation of a 35 kD protein is observed shortly after SC-1 induced apoptosis. SC-1 apoptosis involves activity of caspases 6, other investigated caspases like caspases 3, 8 and 9 seem not to be involved in this process. In addition SC-1 apoptosis is independent of p53 and bcl-2.

Results: The antibody binds to 25% of tested intestinal-type and 70% of diffuse-type stomach adenocarcinoma. The antibody induces specific apoptosis in vitro and in vivo in animal studies. Used in a clinical trial with 44 stomach carcinoma patients, significant apoptotic and regressive effects on tumor cell proliferation in primary tumors and metastases could be observed without any toxic side effects.

Conclusion: Human cancer patients are the best source for tumor-specific and tumor-reactive reagents (cells, factors, antibodies) and the human hybridoma technology offers the only and unique technique for identification of new targets on tumor cells, new tumor-cell related mechanisms and complete human antibodies for diagnostic and therapeutical purposes. Human antibodies like SC-1 give hope for more effective and less harmful treatment of carcinoma and for the understanding of tumor-related mechanisms.

828 POSTER

Combined maintenance treatment of cancer patients responders to previous chemotherapy with immunotherapy (recombinant interleukin 2), hormone therapy (medroxyprogesterone acetate) and antioxidant agents: clinical outcome, effects on cachexia symptoms, on proinflammatory cytokines and evaluation of quality of life

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An open, non-randomized phase II study was carried out including all patients treated with whatever chemotherapy or combined modality regimen