SIOP Educational Session

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Patho-biology of human germ cell tumors

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Human germ cell tumors (GCT) are a heterogeneous group of neoplasms. They can occur in different anatomical locations, predominantly in the gonads (both ovary and testis) and in the midline of the body, including the retroperitoneal-, mediastinal-, and hypothalamus/pineal gland regions. This distribution has been related to the migration route followed by primordial germ cells from the yolk sac to the genital ridge. The clinical behavior of these tumors depends on the sex of the patient, the age at clinical presentation, and the histology of the tumor. Within the testis, for example, three groups of GCT can be distinguished; I). yolk sac tumors and teratomas of neonates and infants, II). seminomas and nonseminomas of adolescents and adults, the so-called TGCT, and III). the spermatocytic seminomas. These different entities of GCT have specific characteristics, including genomic aberrations. This supports existence of different pathogenetic pathways, and genes involved. Recent knowledge on the pathogenesis of GCT, with special attention to genomic changes, will be highlighted in this presentation. The final aim is to develop a clinical-relevant classification system for GCT.

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Malignant gonadal germ cell tumours (MGCTs) in children

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Background: Published results from national studies of MGCTs in children show that 90-100% of testicular and 80-100% of ovarian tumurs are cured. Treatment refinements to raise overall cure rates to 100% and to reduce morbidity must take into account the clinical, histological and biological features which differ from those in adults.

Methods: Paediatric MGCTs were illustrated using UKCCSG data. Publications from national groups and preliminary updated results from UKCCSG's GCII study were reviewed to identify strategies for improving treatment.

Results: Preliminary results from UKCCSG's GCII study (Jan 1987-Feb 2003) showed 85 of 99 testicular MGCTs were yolk sac tumours (YST), 12 malignant mixed teratomas (MMT), 2 embryonal carcinomas (EC), 1 seminoma. All YSTs occurred before age 5 years, as did 5 MMTs. In boys aged 5-9 years there were 2 MMTs and 1 seminoma, while 2 ECs and 5 MMTs occurred in boys aged >10 years. Disease was stage I in 84 cases. The 99 ovarian tumours were YST 29, MMT 33, germinoma 34, EC 2 and choriocarcinoma 1. Only 5 girls were aged 10 years. Their stages were I 37, II 13, III 36, IV 11, uncertain 2. In Germany and the UK "watch and wait" (W&W) after complete excision of respectively 81 and 93 testicular tumours, with chemotherapy only for recurrence (16 and 15%), achieved 100% OS. Among 41 ovarian stage I W&W cases 10 progressed but were cured with chemotherapy. 3 of 21 UK cases recurred, 2 cured with chemotherapy but 1 died from surgical complications. For stages II-IV testicular MGCTs after surgery and chemotherapy OS in 30 German cases was 84% and in 16 UK cases is 100%. The American Inter-Group Study achieved 100% OS for 34 stage II and III cases and 91% for 43 stage IV. For stages II-IV ovarian MGCTs OS in 61 UK cases is 92% while for American girls it is 94% for 16 stage II, 98% for 58 stage III and 93% for 16 stage IV. Carboplatin-based chemotherapy is given in the UK and Cisplatin-based by the other national groups. Multivariate analyses in France and the UK showed AFP level, histology, site and stage are predictors of risk which should be used to plan future protocols.

Conclusions: MGCTs in children differ from those in adults. Cure rates are nearly 100% for boys with testicular and over 90% for girls with ovarian MGCTs. After complete resection of stage I MGCTs, W&W with chemotherapy for recurrence is safe for testicular and probably for ovarian tumours. High survival rates and small numbers impair the detection of significant differences between series. Multivariate analyses on pooled data might identify a high-risk group for whom more toxic treatments are justified.

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Pediatric Extracranial Non-gonadal Malignant Germ Cell Tumors (EMGCT): Implication of site, age and dissemination

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Objectives: In Children and adolescents germ cell tumors account for 3-4% of all malignancies. Extragonadal sites such as head and neck, urogenital and coccyx mainly appear in young children, mediastinal and retroperitoneal tumors are diagnosed in adolescents as well as in young adults. Age therefore seem to play an important role in tumor biology of GCTs. Platinbased multimodal treatment has increased EFS of pediatric EMGCTs to over 80%. In adult EMGCTs site, stage and marker elevation are of prognostic relevance and survival in pts with advanced stage and high markers is decreased. Considering these observations prognostic factors in pediatric EMGCTs prospectively enrolled onto the german multicentre cooperative MAKEI trials are evaluated. Patients and Treatment: Until 1/2002, 198 protocol pts with EMGCTs have been accrued in MAKEI 83-96. Age: > 10yrs: 30 pts; < 10yrs: 168 pts. Sites: coccyx: 112 pts, mediastinum: 37 pts, retroperitoneal/abdominal: 26 pts, urogenital: 17 pts, other localisation: 6 pts. According to stage 200 to 800 mg/m2.Cisplatin are administered with Etoposid/Ifosfamid. Preoperative chemotherapy followed by delayed tumor resection is favourized in pts with extended disease. Non-metastatic pts: n=103 (> 10 yrs: 13 pts, < 10 yrs: 90 pts) are compared to metastatic pts: n= 95 (> 10yrs: 17 pts < 10 yrs: 78 pts).

Results: (10 yrs event-free survival): Age 10 yrs non metastatic: 0,92+0,07 (CR 12/13); age>10 yrs metastatic: 0.27+0,1 (CR 5/17) p< 10 yrs, (p 10 yrs confers a poor outcome.

Conclusions: This analysis determines a poor-prognostic group among pediatric EMGCTs defined by the parameters non-gonadal localisation, age > 10 years, and metastatic disease, whereas non-metastatic pts >10 yrs have an excellent prognosis. Metastases seem to be of major importance especially in older patients. Further molecular biological evaluation may explain the differences and new therapeutic concepts are needed to improve the prognosis of patients with these risk factors. (Supported by Deutsche Krebshilfe)

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Gonadal adult tumours

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Background: The purpose of the presentation is to give an overview of the current treatment guidelines for adult testicular germ cell tumors and compare them to the treatment of pediatric testicular germ cell tumors.

Methods: The European Germ Cell Cancer Collaborative Group has generated a European Consensus Paper in 2003 which has been developed at a European Consensus Conference on Germ Cell Tumors in Essen, Germany in November 2002. The previous German Consensus Paper (Eur Urol 2001) and the Guidelines of the European Association of Urology (Eur Urol 2001) have been discussed, updated and merged in this new consensus statement.

Results: The recommendations for diagnosis and treatment of germ cell tumors include updated information for the stage-by-stage management of germ cell tumors. In comparison to the pediatric germ cell tumors it becomes clear, that with the end of puberty adolescent germ cell tumors