SIOP Educational Session

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Patho-biology of human germ cell tumors

L. Looijenga. *Erasmus MC - Josephine Nefkens Institute, Department of Pathology/Lab. Exp. Patho-Oncology, Rotterdam, The Netherlands*

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

J.R. Mann[1], K. Robinson[2], F. Raafat[1], J. Imeson[2], P. Gornall[1], M. Sokal[3], E. Gray[4], P. McKeever[5], J. Hale[6], A. Oakhill[7]. *[1] The Birmingham Children's Hospital, ONCOLOGY, Birmingham, United Kingdom; [2] UKCCSG Data Centre, Leicester, United Kingdom; [3] City Hospital, Nottingham, United Kingdom; [4] Medical School, Aberdeen, United Kingdom; [5] University of Leicester, Leicester, United Kingdom; [6] Institute of Child Health, Newcastle upon Tyne, United Kingdom; [7] Royal Bristol Children's Hospital, Bristol, United Kingdom*

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

U. Göbel. *Universität Düsseldorf, Department of Pediatrics Oncology, Düsseldorf, Germany*

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

P. Albers. *University Hospital of Bonn, Department of Urology, Bonn, Germany*

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

do not differ from adult tumors. However, prepubertal germ cell tumors usually have a different pathogenesis and treatment options are separately defined. Adolescent tumors differ regarding treatment dependent on the primary treating physicion (pediatric oncologist, medical oncologist, urologic oncologist) but the outcome is not different. However, the compliance is much better if the patient is accompanied by parents who take responsibility for the care.

Conclusions: The treatment of germ cell tumors is very much standardized in the pediatric as well as the adult population. For adolescent patients it does not matter who is the primary physician they consult. As long as the treatment follows the published guidelines, an excellent outcome can be achieved in nearly all stages.

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Malignant CNS Germ Cell Tumors (CNS GCTs): A review of the State of Art

G. Calaminus. *Universität Düsseldorf, Department of Pediatric Oncology, Düsseldorf, Germany*

Objectives: Primary CNS GCT account for about 2% of all intracranial neoplasms before 20 years of age. Histologically, CNS GCT are analogous to extracranial GCT. They can be divided into germinoma and non-germinomatous GCT (NGGCT). NGGCT include teratoma, embryonal carcinoma, Yolk sac tumor and choriocarcinoma, occurring as mixed tumors in about 30%. In case of expression of tumour markers (AFP- representing Yolk sac elements, β-HCG- representing choriocarcinoma) in serum/CSF, they are called secreting. Tumor markers therefore can be used for clinically guided diagnosis and treatment response. Germinoma are exquisitely radio- and chemosensitive, NGGCTs are less sensitive to RT. In the past 10 years increased clinical research reflected in institutional as well as multicenter trials in Europa, the United states and Japan was initiated.

Research targets: In germinoma the attempt is to decrease late effects of extensive radiotherapy and in malignant NGGCTs to define risk adapted treatment strategies and increase survival rates. In key publication of the last 5 years and in ongoing multicenter/multinational trials three main issues are targeted: Germinoma: Is chemo +RT equal to craniospinal RT?(Alapetite MPO, Abstr., 2002, Fouladi Childs Nerv Syst,1998): Is chemo equal to RT at all? (Balmaceda JCO, 1999). In case of RT alone, what are the lowest dosages necessary for disease control? (Shibamoto Radiology, 2001; Bamberg JCO, 1999; Hardenbergh Int.J.Rad.Oncol.Biol.Phys.,1997) Malignant NGGCT: what are the most effective drug regimen? (Buckner JCO, 1999, Itoyama Neurosurgery, 1995; Calaminus MPO, Abstr.2002) what is the necessary dosage and extent of RT? (Aoyama JCO, 2002) Are they curable by chemo alone? (Balmaceda JCO, 1999; Baranzelli J Neurooncol.,1998).

Results: For germinoma data of the French SFOP protocol and the ongoing SIOP CNS GCT96 reveal that in localized disease focal RT with chemo is not able to control subclinical ventricular disease and that incomplete staging is a major risk factor. In malignant NGGCTs according to the SIOP data the extend of AFP elevation and residual disease after RT is of prognostic value.

Conclusions: Prognosis of malignant CNS GCTs has dramatically improved. The majority of patients can be cured by combined treatment with lowered RT dosages. Treatment planning has to take into consideration extent of disease, markers, histology and response to treatment.

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Radiotherapy guidelines in the treatment of malignant paediatric CNS Germ Cell Tumors (GCTs)

U. Ricardi[1], C. Alapetite[2], D. Frappaz[3], M.L. Garre'[4], J. Nicholson[5], F. Saran[6], R.D. Kortmann[7], G. Calaminus[8]. *[1] University of Turin, Radiation Oncology, Turin, Italy; [2] Institute Curie, Radiation Oncology, Paris, France; [3] Centre Leon Berard, Pediatric Oncology, Lyon, France; [4] Istituto Gaslini, Pediatric Oncology, Genoa, Italy; [5] University of Cambridge, Pediatric Oncology, Cambridge, UK; [6] Royal Marsden Hospital, Radition Oncology, London, UK; [7] University of Tuebingen, Radiation Oncology, Tuebingen, Germany; [8] University of Duesseldorf, Pediatric Oncology, Duesseldorf, Germany*

The aims of SIOP protocol CNS GCT 96 were to standardise diagnostics and treatment of GCTs in respect to histology: in germinoma to compare in a non-randomized fashion craniospinal radiotherapy (CSI) with chemotherapy followed by focal radiotherapy; in secreting tumors, if AFP > 25 ng/ml and/or β -HCG > 50 IU/l, to evaluate the response to 4xPEI as preoperative chemotherapy, consolidated by radiotherapy tailored to extent of disease (CSI in metastatic patients and focal irradiation in localized disease).

From a radiotherapic point of view, special considerations should be made regarding treatment of localized pure germinoma. In patients with localized disease, the otpimal treatment approach for subclinical disease is still controversial. In order to reduce the potential toxicity associated with craniospinal irradiation, considered as the reference treatment, recent clinical studies tended to limit the radiation volumes, using some courses of chemotherpy followed by focal irradiation only (option B of the SIOP CNS GCT 96 protocol, SFOP protocol TC-90). The combined chemo-radiotherapy approaches yelded excellent cure rates, but the pattern of relapses (9% in option B SIOP series and 14% in SFOP series, occurred mainly in the ventricular system outside the radiation treatment volumes) and the predominance for ventricular subependymal dissemination clearly showed that the chemotherapy was not sufficient to sterilize subclinical ventricular disease. This increased risk of ventricular relapse, marginal to radiation fields, prompted the SIOP CNS GCT group to consider widening the radiation volumes in combined modality treatment from focal to whole ventricular irradiation (WVI) for the forthcoming protocol.

Recommendations for volume definition (third ventricle, lateral ventricles and fourth ventricle) and technical considerations for WVI will be carefully presented: technical guidelines of the SIOP CNS GCT group for optimal WVI will be reported, since the very irregular shape of the planning target volume and the new radiation modalities (such as 3D-conformal and intensity-modulated radiation therapy) make the fields arrangement extremely crucial in order to have the best conformality index.

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Regional deep hyperthermia and pei-chemotherapy in children and adoles-cents with unresectable malignant germ cell tumors: an approach for cure

R. Wessalowski. *Universität Düsseldorf, Pediatric Hyperthermia, Düsseldorf, Germany*

Objective: The purpose of the present study in children and adolescents with recur-rent, unresectable GCTs was to improve the efficacy of anticancer drugs by regional deep hyperthermia (RHT) using a non-invasive radio frequency technique.

Patients: From VII/1993 to IV/2002 a total of 25 children and adolescents (21 girls, 4 boys) aged between 13 months and 23 years (median: 3;10 years) with recurrent, unresectable germ cell tumors were treated with chemotherapy and RHT. All patients suffered from either a local relapse (n = 23) or a primary unresectable tumor (n = 2). Tumor site: 21 pelvis, 3 abdomen, 1 head and neck. Histology: 4 teratomas, 1 dys-germinoma, 16 yolk sac tumors, 4 embryonal carcinomas. Therapy: 2000 mg/m2 ifosfamide (with mesna uroprotection), 100 mg/m2 etoposide on days 1 - 4, and 40 mg/m2 cisplatinum (with mannitol diuresis) on days 1 + 4 com-bined with RHT (42 - 44 °C) on days 1 + 4. Side effects and complications: Myelo-suppression WHO grade III/IV in all pts, nephrotoxicity in abdominal tumors WHO grade II-IV. Osteonecrosis in 3 pts, MDS in 1 pt. Tumor response (MRI/CT): 13 CR, 6 PR (response to thermo-chemotherapy 82%). Subsequent surgery led to 13 complete and 3 further incomplete resections. Addi-tional radiotherapy in 7 pts (22 - 44 Gy) ± RHT. Status: In the light of an exceptional late relapse after 56 months Kaplan-Meier-Analysis showed an EFS of 0.42 (14/25 pts) and a survival rate of 0.57 (17/25 pts) with a follow-up from 5 to 102 months (median 29 months).

Conclusion: RHT can increase the efficacy of the multimodal relapse therapy in germ cell tumors. This up-date with a doubled number of patients and a longer fol-low-up period validates previous treatment results (Wessalowski et al. Klin. Pädiatr. 1997, 209:250-6). Supported by Deutsche Krebshilfe, Elterninitiative Kinderkrebsklinik Düsseldorf e.V., and Kinderkrebsfürsorge Wickede e.V.