3rd (GCT-2008 protocol) was admitted 18 months ago. No patients with CNS as primary site of GCT disease were included.
Results: From 120 patients with pure germinoma component, 109 were female, 9 testicular, 107 ovarian, 1 sacrococcygeal, 2 mediastinal and 1 retroperitoneal. Increased AFP was seen in 10 of 83 patients with this information, BHCG 33/88, LDH 46/76. For the entire group 10 y OS was 94.8%. According with staging 47 Stage (S)-I, 18 S-II, 46 S-III, 9 S-IV (10 y OS with no statistical significance). Ovarian cases were 107, 42 S-I, 17 S-II, 41 S-III and 7 S-IV. Non-metastatic 81 (10 y OS 96.2%), 20 lymph node metastases (94.7%) and 6 other (liver, lung or both; 10 y OS 100%). S-I+II were 59 patients (10 y OS 96.5%) and 48 S-III+IV (95.7%). No statistical significance was found for age (< or > 11 years), increased LDH, alpha-fetoprotein or BHCG. Our data suggests that no patient should be treated as high-risk. Complementary analysis should be done among S-II and S-III to define which patients should receive chemotherapy and which should be classified as low-risk and receive no chemotherapy.

Clinical Trials and Updates II

GCT-39 Outcome of children with malignant germ cell tumours by response status at the end of induction chemotherapy

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Background: The management of paediatric malignant germ-cell-tumours (MGCTs) includes induction therapy with 3–4 cycles cisplatin/etoposide/bleomycin (PEb). The current practice recommends 2–3 cycles of PEb (total 6 cycles) as consolidation therapy if response is not complete at end-of-induction (EOI), different to that used in adult patients who receive a standard number of cycles. No evidence exists supporting a PEb consolidation phase in paediatric MGCT patients.
Methods: We retrospectively reviewed all patients enrolled in a phase III, single-arm trial for low-risk and intermediate-risk MGCTs (AGCT0132). All patients received 3 PEb cycles and underwent response assessment at EOI. Complete response (CR) was defined as negative tumour-markers and no viable residual lesion. Patients in CR received no further chemotherapy. Patients not in CR received 3 additional PEb cycles as consolidation. Event-free survival (EFS) and overall survival (OS) was calculated using Kaplan-Meier method.
Results: Among 210 patients enrolled, 193 patients had CR at EOI, and their post-induction 4 yr-EFS and OS was 93% and 99%. Fifteen patients were not in CR at EOI and received additional chemotherapy; their 4 yr-EFS and OS was 51% and 60%, respectively. Children with MGCTs with partial response after EOI had inferior outcomes despite additional cycles of PEb chemotherapy. Consolidation is therefore of unclear benefit. Although our results are limited by small sample size and lack of comparator, we propose that paediatric MGCT patients who fail to achieve a CR after standard induction chemotherapy should receive a salvage regimen with different agents rather than consolidation with more cycles of the same chemotherapy.

GCT-40 Alpha-fetoprotein (AFP) as a predictor of outcome for children with germ cell tumours: A report from the Malignant Germ Cell International Consortium (MaGIC)

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Background: Several studies describe the correlation between unsatisfactory tumour marker decline and poor prognosis in adult patients treated for germ-cell-tumours (GCTs). In paediatric patients data is limited. We retrospectively analyzed data collected from paediatric patients treated on Children's Oncology Group (COG) Protocol AGCT0132 to determine whether a relationship exists between AFP decline and outcome.
Methods: One hundred and thirty-one patients with GCTs enrolled on Children's Oncology Group Protocol AGCT0132 were eligible for analysis of AFP decline. Serum AFP half-life was calculated from levels collected post-operatively, as a baseline, and after the start of chemotherapy, excluding values in the first 7 days of chemotherapy to accommodate unpredictable increases in the initial days of treatment. AFP decline was defined as automatically satisfactory (AFP normalized within the first two AFP measures following the start of chemotherapy), calculated satisfactory (AFP half-life $\leq$7 days following the start of chemotherapy), and unsatisfactory.
Results: The 3-year cumulative incidence of relapse (CI-R) was 11% (95% confidence interval - CI: 6.0–18%) for patients with satisfactory decline and 38% (95% CI: 13–64%) for unsatisfactory decline ($p = 0.006$). In stratified analyses, this effect was limited to patients $\geq$11 y and standard-risk (SR2) disease ($p = 0.004$ and $p = 0.007$, respectively). Three-year overall-survival for patients with satisfactory versus unsatisfactory decline was not statistically significant. This study is the first to show association between AFP decline and CI-R in paediatric patients. Although no association between marker decline and outcome was shown, recognition of patients at high-risk of relapse may allow early therapy intensification and impact future clinical trial design.

GCT-41 Outcomes of the use of carboplatin in the treatment of paediatric malignant germ cell tumours (GCTs) in the UK – Experience from GCII and GCIII trials

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Background: To reduce cisplatin-related toxicity in the treatment of paediatric malignant germ-cell tumour (MGCT), the UK Children's Cancer and Leukaemia Group evaluated survival and toxicity of carboplatin-based JEb chemotherapy (carboplatin 600 mg/m^2 or AUC 7.9; etoposide 360 mg/m^2; bleomycin 15 mg/m^2) in the GCII and III trials.
Methods: GCII used an n+2 strategy of JEb courses. GCIII risk-stratified patients to low-risk (stage 1); high-risk (AFP >10,000 U/L; stage IV except germinomas and testis <5; Stage II-IV thoracic) and intermediate risk. Low-risk patients received chemotherapy only if disease progressed, intermediate-risk patients received 4 and high-risk patients 6 cycles of JEb. In GCIII, two-thirds of carboplatin doses were calculated by GFR, the rest by surface-area.
Results: From 1989–1997, 137 patients were treated with JEb on GCII (median 5 cycles; range 3–8). Five-year event-free survival (EFS) was 88% and overall survival (OS) 91%. From 2005–9, 65 patients were treated with JEb on GCIII: 4 relapsed low-risk, 23 intermediate-risk and 38 high-risk. Five-year EFS and OS was 92% and 95% and in non-germinomas 91% and 94%. 37% were adolescents (21% non-germinoma) with only one relapse. Myelosuppression was a common but manageable toxicity; significant nephro- or ototoxicity was rare in both studies. For cisplatin-treated patients in the UK, deafness was seen in 10% and renal impairment in 45%. There was no discernible difference in carboplatin dose whether calculated by body surface-area or creatinine clearance. JEb chemotherapy leads to excellent survival in paediatric MGCT with minimal documented long-term toxicity. Carboplatin will be evaluated against cisplatin in AGCT1531.

GCT-42 Validation of the MaGIC paediatric germ cell tumour risk stratification

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Background: A new risk stratification for metastatic nonseminomatous paediatric germ cell tumours (NS-GCT) was published in 2015 by the Malignant Germ Cell International Consortium (MaGIC) based on analysis from 25 years of clinical trial data from Children's Oncology Group and Children's Cancer and Leukaemia Group (United Kingdom, UK). The MaGIC risk stratification identified age ≥11 y, advanced stage and extragonadal or ovarian primary as adverse prognostic indicators; this served as the basis for three new international clinical trials. To validate the risk stratification, three independent datasets have provided by the UK, French and Brazilian Pediatric Clinical Trial groups.
Methods: The MaGIC risk stratification was tested in datasets from 326 Brazilian patients with NS-GCT, treated on one of three protocols, TCG91, TCG99, TCG2008 and 45 UK patients treated on GC3 (not part of original MaGIC analysis). A non-mixture cure model was used to characterize the relationship between variables and event-free survival. The likelihood ratio test of a p-value >0.05 was used to eliminate terms using stepwise selection. The predicted probability of remaining event-free survival was estimated from the 2015 model. The C-index at 5 years (Uno et al. Statist Med 2011) was used to assess the robustness of this prediction. An additional 239 French cases have subsequently been made available.
Results: The original MaGIC risk stratification was verified in two independent datasets from the UK and Brazil, supporting its use in prospective clinical trial design. Further results based on the additional French cases will be presented.

GCT-43 Clinical characteristics, treatment, and outcomes of children with primary vaginal endodermal sinus tumours

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Background: To analyze the clinical characteristics, treatment and outcomes of children with primary vaginal endodermal sinus tumours.
Methods: We conducted a retrospective analysis on clinical and pathological data of 21 children with pathologically confirmed primary vaginal endodermal sinus tumour treated at Peking Union Medical College Hospital between January 1997 and January 2018. Median age was 11 months (range: 4 months to 4 years). All patients were treated with chemotherapy, mainly PEB (cisplatin/etoposide/bleomycin) after an intravenous port was implanted into the subclavian vein. Detection of serum alpha-fetoprotein level, examination under anesthesia and biopsy were performed before and after treatment to evaluate tumour status.
Results: Vaginal bleeding or blood-tinged discharge was the most common clinical presentation. The patients received an average of 5.7 courses of chemotherapy (range 3–13 courses). 20 patients obtained complete remission (95.2%). The patients were followed up for a median of 44 months (range: 6 months to 20 years). Nineteen patients (90.5%) remained alive. One child died of disease progression. One infant received 4 courses of PEB chemotherapy and died of infection and heart failure. Two patients developed vaginal recurrence and obtained complete remission after chemotherapy again. Vaginal endodermal sinus tumours are rare in children and extremely sensitive to chemotherapy. To allow preservation of sexual and reproductive function, PEB chemotherapy without surgery should be considered for children with vaginal endodermal sinus tumours.