age was 9.3 years (1.8–19.9 years). Most patients had an extragonadal tumour (63.6%) and yolk-sac was the main histological subtype (48.5%). About 60% were metastatic at diagnosis. Regarding the pre-HSCT disease status: 4 patients were in first remission, 12 in second remission, 8 in third remission or beyond and 9 had refractory disease. The main conditioning regimen was with Carboplatin, Etoposide and Melphalan (72.7%). Three patients died from transplant-related complications (9%). Fifteen patients (45.5%) had disease progression or relapse after HSCT and 14 of them died. Fifteen patients (45.5%) are alive in complete remission, with a median follow up of 4.9 years (1.1–17.4 years). None of the 9 patients who had refractory disease at the beginning of the conditioning regimen survived. The role of HSCT in the treatment of children with GCTs should be investigated in prospective trials.

Poor-Risk Tumour Patients

GCT-67 Long term follow-up of the MRC TE23 randomized phase II trial of intensive induction chemotherapy (CBOP/BEP) in poor prognosis germ cell tumours (GCT) (CRUK/05/014; ISRCTN53643604)

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Background: Up to 50% of men with poor-prognosis nonseminomatous GCT die with standard BEP chemotherapy. An intensive regimen, CBOP/BEP (carboplatin, bleomycin, vincristine, cisplatin/BEP), met response targets in a phase II, multicentre, open-label, randomized trial. Here, we report long term outcomes and prognostic factors.
Methods: Patients with extracranial GCT and IGCCCG poor-prognosis features were randomised to 4xBEP or CBOP/BEP (2xCBOP, 2xBO, 3xBEP with bleomycin dose 15,000 iu). Low-dose, stabilising chemotherapy prior to entry was permitted. This analysis focuses on progression-free survival (PFS), overall survival (OS) and toxicity (all secondary outcomes), and exploratory analysis of prognostic factors and the impact of marker decline (as defined in GETUG13).
Results: 89 patients (43 CBOP/BEP) were randomised. After median 63 months follow-up, 3-year PFS is 55.7% (95% CI 39.7%, 69.0%) for CBOP/BEP arm, 38.7% (24.7%, 52.4%) for BEP (HR 0.59 (0.33, 1.06), $p = 0.079$). 3-year OS is 65.0% (48.8%, 77.2%) and 58.5% (43.0%, 71.2%), respectively (HR 0.79 (0.41, 1.52), $p = 0.49$). 12-month toxicity was affected by subsequent treatments, with no clear differences between arms. There was no grade ≥3 late toxicity in the CBOP/BEP arm. In multivariate models, use of pre-protocol chemotherapy was the only factor associated with poorer PFS (HR 2.09 (1.14, 3.81), $p = 0.017$). Mediastinal primary (HR 2.13 (1.02, 4.46), $p = 0.045$) and use of pre-protocol chemotherapy (HR 3.40 (1.74, 6.63), $p < 0.001$) were associated with poorer OS. In this study, use of low dose induction chemotherapy was associated with poorer outcomes. Further study in an international phase III trial is warranted.

GCT-68 Haematological neoplasms arising in patients with primary mediastinal nonseminomatous germ cell tumour are clonally related and represent secondary somatic malignant differentiation

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Background: One in 17 patients with primary mediastinal germ cell tumour develops a haematological malignancy and the survival in such patients is poor. Intriguingly, the presence of isochromosome 12p, a clonal marker common to GCTs but absent in *de novo* myeloid neoplasms, has been demonstrated as shared across GCTs and myeloid neoplasms in such individuals. While these data suggest a clonal relationship between the two, the exact nature of the shared origin is unknown.
Methods: To trace the clonal evolution of these seemingly unrelated cancer types and identify recurrent genomic lesions in leukaemias present in GCT patients, we applied whole exome sequencing (WES), targeted genomic analyses, and/or RNA-seq to leukaemias, GCTs, and germline DNA in a series of patients with myeloid neoplasms and concurrent GCTs.
Results: We studied 12 patients with GCT and synchronously or metachronously occurring myeloid neoplasms (8 AML, 5 MDS/CMML, 2 histiocytic sarcoma (some had >1 haematologic malignancy)) with an average of 4 months between the two diagnoses. All were young men (median age 26 years) with PMGCT and nonseminomatous histology and a 3-month median survival from leukaemia diagnosis. In each case, at least one copy number alteration or coding mutation was shared across the GCT and hematopoietic neoplasm, demonstrating the shared origin of both lesions. The most common genomic alterations in leukaemias beyond i(12p) included mutations activating RAS-PI3K-AKT signalling or inactivating TP53. These data conclusively demonstrate that myeloid neoplasms developing in patients with PMGCT represent secondary somatic differentiation of cells that are present in the GCT.

Debate

GCT-69 Debate: This house believes that BEP should no longer be standard therapy for poor risk disease: Opposing view

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Background: Since the addition of etoposide and cisplatin to bleomycin in the 1980s, the BEP regimen has been the international standard for poor risk germ cell tumour (GCT). In this debate, we review the relevant data and detail the phase 3 trials that have failed against BEP. We also outline the strategies that have been more successful than changing current cytotoxic options in poor risk GCT,

but ultimately conclude that, BEP when delivered optimally, should remain the standard of care for poor risk GCT.
Material and methods: Review of phase 3 trials comparing alternative regimens against BEP. Comprehensive literature review on outcomes and adherence to guidelines.
Results and conclusions: No regimen to date has proven to be superior to BEP. The alternatives studied have demonstrated significant additional toxicity without clear improvement in patient survival. Developments in supportive medications have enabled maintenance of dose density with BEP. Moreover, it has been shown that outcomes are better with management in specialist centres and adherence to guidelines for optimal patient care. For patients needing further chemotherapy after BEP, taxane-containing salvage regimes and/or high dose chemotherapy can be utilised. There is some limited evidence that treatment switch is beneficial if optimal tumour marker decline is not achieved. A greater biological understanding of platinum resistance and transformation of teratoma will help guide targeted drug development. We advocate the use of alternative treatment regimens only in the context of clinical trials (such as P3BEP which is investigating the acceleration of the BEP regime).
Disclaimer: Please note that the views expressed in this abstract, and during the debate *per se*, may not necessarily reflect the views and beliefs of those individuals proposing and/or opposing the motion.

Relapsed and Resistant GCT Disease

GCT-70 Current clinical management of relapsed testicular cancer, including the SWENOTECA experience

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Background: Testicular cancer is one of the most curable neoplasms, with a 5-year survival rate of 95% even in the metastatic setting. However, based on large retrospective cohort studies, patients experiencing relapse after initial cisplatin-based chemotherapy have a 5-year survival rate of only 50%. The chance of survival may be dependent upon prognostic variables, possibly enabling a model to guide salvage treatment and intensification of treatment.
Methods: Based on international guidelines and recent publications, the current body of knowledge of the treatment of relapsed testicular cancer will be presented. These data are discussed in view of the SWENOTECA experience from treatment of metastatic testicular cancer.
Results: Although many patients with relapse following initial treatment with cisplatin-based chemotherapy will die of disease, there are new data on improved survival from patients treated in the latest decade. Intensification of treatment based upon prognostic variables at relapse may be a valid approach to improve survival. In addition, centralisation of treatment to high volume centres, gives these rare patients the highest chance of survival. All patients with relapse after initial cisplatin based chemotherapy should be included in clinical trials or registered prospectively in a clinical quality registry.

GCT-71 Cisplatin resistance in germ cell tumours: Biological mechanisms and therapeutic avenues

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Background: Cisplatin resistance in germ cell tumours is an unresolved problem. Despite adequate first-line treatment, approximately 15% of patients with advanced disease cannot be cured. Salvage chemotherapy, mainly high-dose salvage therapy, followed by single or combined treatment with platinum compounds, taxanes, or gemcitabine, are still the most active approaches in resistant disease. While targeted therapy with sunitinib, pazopanib, sorafenib, or everolimus has yielded disappointing results in trials, the role of immunotherapy with brentuximab vedotin or immune checkpoint inhibitors is still unclear. Recently, retrospective analyses described significant prognostic relevance of the systemic immune-inflammation index (SII) and PD-L1 expression on tumour-infiltrating lymphocytes irrespective of IGCCCG-criteria, suggesting a biological role of tumour microenvironmental inflammation in disease outcome. Furthermore, epigenetic treatment combinations are considered another avenue worth exploring.
Methods: A literature search of PubMed and MEDLINE was conducted. Review articles were hand-searched for additional information.
Preliminary results: While still incompletely understood, recent years have shown progress in unravelling biological mechanisms of resistance. Alterations of the p53/MDM2 interaction, the DNA damage response, the PI3K/p-AKT pathway, as well as unique epigenetic features have emerged as independent factors of resistance. Preclinical examinations have shown activity of PARP inhibitors in and hypersensitivity of germ cell tumour cells to epigenetic treatments like inhibitors of DNA methyltransferases, histone deacetylases, and bromodomain proteins. Finally, the exciting era of antibody-drug conjugates and immune checkpoint inhibitors might open new possibilities. Several trials exploring these approaches, combined with translational research, are underway in patients with resistant disease.

GCT-72 Causes and patterns of mortality in patients diagnosed with germ cell tumour (GCT)

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Background: Most metastatic germ cell tumours (GCTs) are cured with cisplatin-based chemotherapy. Despite the global incidence of testicular GCT rising, disease-related mortality remains low. While prognostic factors of adverse GCT-specific survival have been identified, causes and patterns of death from germ cell tumours are not well-defined and would inform both clinical care and biological investigation. Potential GCT deaths are due to chemo-refractory disease, unresectable teratoma and transformed teratoma.