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.

Methods: This multi-institutional study pooled data of patients who died due to GCT from three academic, high-volume adult GCT referral centres (Dana-Farber Cancer Institute, Memorial Sloan Kettering Cancer Center, Indiana University) between 1997 and 2017. Additionally, we collected data of paediatric and adolescent GCT patients treated on clinical trials in the US, UK, Europe and South America from the MaGIC group. Site, stage, risk, histology, primary therapies and relapse data (including relapse histology, metastatic burden, salvage and palliative therapies) were collected, in addition to detailed cause of death.
Results: Data from approximately 900 patients (adult and paediatric) who died of GCT have been collated and currently undergoing analysis. First results will be presented at the International Extracranial Germ Cell Tumour Conference, Cambridge, 2019.

GCT-73 The features and management of late relapse of nonseminomatous germ cell tumours: The Royal Marsden Experience

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Background: Late-relapses (LR) of non-seminomatous germ-cell-tumours (NSGCT), (i.e. after disease-free-interval of ≥2 years), are increasingly recognised. We reviewed the features of LR in NSGCT within a tertiary referral testicular cancer service.
Methods: 3,064 patients were referred to the testis multi-disciplinary-team (January 2005 to Dec 2017). Patients who experienced LR where initial pathology demonstrated NSGCT were identified. Data from original and late presentation and management was reviewed.

Initial stage	n	Time to recurrence (Months) Median (95%CI)	Management at relapse		
			Surgery alone	Primary Chemo ±(surgery)	other
Stage 1	31	55 (48–108)	14	17 (9)	0
Stage 2	29	120 (84–192)	25	4(0)	0
Stage 3	41		30	8 (4)	3

Results: Of the 3,064 patients, 101 (3.3%) had LR, with 43 (43%) relapsing >10 years. 36 were symptomatic and 39 had raised markers (AFP 29, HCG 9, both 1). Table shows stage at initial presentation and time-to-relapse. 13 CS1 patients had received prior chemotherapy (8 adjuvant and 5 for early relapse). 59/60 CS2/3 patients received chemotherapy as primary treatment and 41 had post-chemotherapy retroperitoneal-lymph-node-dissection (PC-RPLND (bilateral template in 12). 20 of these 41 men who had a PC-RPLND experienced retroperitoneal LR (6 after bilateral template). Patient management at relapse – see Table. Time-to-recurrence was longer in CS2/3 patients ($p < 0.001$). 84 surgical procedures – histology was teratoma-differentiated in 44, yolk-sac 14, de-differentiated in 7 and viable GCT in 11, benign 8. To date, 22/101 (20 from NSGCT) patients have died, 13 of these patients relapsed at multiple sites. Men with symptomatic disease (13/36, 33%) and receiving chemotherapy and no surgery (10/17, 59%) tended to have worse survival. LR of NSGCT frequently occurs after an extended interval and typically occurs earlier in CS1 disease compared with higher stages. Aggressive surgery±chemotherapy can cure most patients.

GCT-74 Gene expression studies in platinum-resistant testicular germ cell tumours

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Background: Although testicular germ cell tumours (TGCT) are mostly curable using cisplatin-based chemotherapy, a small subset are platinum-resistant and have poor prognosis. To better understand platinum-resistance, we conducted gene expression studies using a case-control cohort of platinum-resistant and platinum-sensitive TGCT, comparing differences between (i) platinum-resistant and sensitive primary tumours; (ii) platinum-resistant primary and paired resistant post-chemotherapy metastases; and (iii) platinum-sensitive primary and paired post-chemotherapy teratoma.
Methods: An institutional database identified platinum-resistant (defined as recurrence/persistence following platinum-based chemotherapy) and platinum-sensitive patients (matched by IGCCCG risk). Where available, archival specimens were retrieved and macro-dissected to ensured >80% cellularity. Gene-expression analyses used Nanostring nCounter and a customized list of 30 genes selected for potential role in platinum-resistance. Differences were compared using t-tests, with $p < 0.0017$ considered significant.
Results: We identified 19 platinum-resistant and 22 platinum-sensitive patients with available primary tumour specimens. Age (median: 34 y versus 28 y), IGCCCG risk (poor: 32% versus 27%) and histology (non-seminoma: 84% versus 86%) were similar. Median time to relapse in resistant patients was 3.4 mo; median follow-up for sensitive patients was 53.8 mo. Six resistant patients had paired post-chemotherapy metastases; 5 sensitive patients had paired post-chemotherapy teratoma. Gene expression in platinum-resistant *versus* platinum-sensitive primary tumours were not significantly different. When comparing platinum-resistant primary and paired post-chemotherapy metastases, OCT4 expression was significantly reduced in metastases ($p = 0.0003$). When comparing platinum-sensitive primary and paired post-chemotherapy teratoma, expression of both XPA ($p = 0.0010$) and AKT1 ($p = 0.0005$) were significantly increased in teratoma. This hypothesis-generating study suggests OCT4 loss as a potential biomarker of platinum-resistance.

GCT-75 Evaluation of inductor factors in the epithelial-mesenchymal transition (EMT) in testicular germ cell tumours (TGCT) and their roles in cisplatin resistance

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Background: A mechanism related to the development of cancer, metastasis and drug resistance is the epithelial-mesenchymal transition (EMT), a process in which epithelial cells lose their characteristics and acquire mesenchymal cell phenotype. EMT can be induced by several transcriptional factors, including Snail, Slug, Zeb1, and Twist. However, the molecular mechanisms involved in EMT induction in the TGCTs has not been elucidated. The aim of this study is to evaluate the inducing factors of EMT in TGCTs, as well as in the cisplatin resistant treatment.