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GENITOURINÁRNE MALIGNITY

Chovanec M, Lauritsen J, Bandak M, Oing C, Kier GG, Kreiberg M, Rosenvilde J, Wagner T, Bokemeyer C, Daugaard G.
Late adverse effects and quality of life in survivors of testicular germ cell tumour
Nat Rev Urol. 2021 Apr;18(4):227-245.

Currently, ~95% of patients with testicular germ cell tumour (TGCT) are cured, resulting in an increasing number of TGCT survivors. Although cured, these men face potential late adverse effects and reduced quality of life. Survivors face a twofold increased risk of second malignant neoplasms after chemotherapy and radiotherapy, with evidence of dose-dependent associations. For survivors managed with surveillance or treated with radiotherapy, the risk of cardiovascular disease (CVD) is comparable to the risk in the general population, whereas treatment with chemotherapy increases the risk of life-threatening CVD, especially during treatment and after 10 years of follow-up. Other adverse effects are organ-related toxicities such as neuropathy and ototoxicity. Pulmonary and renal impairment in patients with TGCT treated with chemotherapy is limited. Survivors of TGCT might experience psychosocial distress including anxiety disorders, fear of cancer recurrence and TGCT-specific issues, such as sexual dysfunction. Late adverse effects can be avoided in most patients with stage I disease if followed on a surveillance programme. However, patients with disseminated disease can experience toxicities associated with radiotherapy and chemotherapy, and/or adverse effects related to surgery for residual disease. The severity of adverse effects increases with dose of both chemotherapy and radiotherapy. This Review discusses the most recent data concerning the late adverse effects of today›s standard treatments for TGCT.

Letkovska K, Babal P, Cierna Z, Schmidtova S, Liskova V, Kalavska K, Miskovska V, Horak S, Rejlekova K, Chovanec M, Mardiak J, Janega P, Mego M.
Prognostic value of apoptosis-inducing factor (AIF) in germ cell tumors
Cancers (Basel). 2021 Feb 13;13(4):776.

Apoptosis is a strictly regulated process essential for preservation of tissue homeostasis. This study aimed to evaluate expression of apoptosis inducing factor (AIF) in testicular germ cell tumors (GCTs) and to correlate expression patterns with clinicopathological variables. Formalin-fixed and paraffin-embedded specimens of non-neoplastic testicular tissue and GCTs obtained from 216 patients were included in the study. AIF expression was detected by immunohistochemistry, scored by the multiplicative quickscore method (QS). Normal testicular tissue exhibits higher cytoplasmic granular expression of AIF compared to GCTs (mean QS = 12.77 vs. 4.80, $p < 0.0001$). Among invasive GCTs, mean QS was the highest in embryonal carcinoma, yolk sac tumor and seminoma, lower in teratoma and the lowest in choriocarcinoma. No nuclear translocation of AIF was observed. Nonpulmonary visceral metastases were associated with lower AIF expression. Metastatic GCTs patients with high AIF expression had better overall survival compared to patients with low AIF expression (HR = 0.26, 95% CI 0.11-0.62, $p = 0.048$). We observed significantly lower AIF expression in GCTs compared to normal testicular tissue, which is an uncommon finding in malignant tumors. AIF downregulation might represent one of the mechanisms of inhibition of apoptosis and promotion of cell survival in GCTs.

Ciernikova S, Mego M, Chovanec M.
Exploring the potential role of the gut microbiome in chemotherapy-induced neurocognitive disorders and cardiovascular toxicity
Cancers (Basel). 2021 Feb 13;13(4):782.

Chemotherapy, targeting not only malignant but also healthy cells, causes many undesirable side effects in cancer patients. Due to this fact, long-term cancer survivors often suffer from late effects, including cognitive impairment and cardiovascular toxicity. Chemotherapy damages the intestinal mucosa and heavily disrupts the gut ecosystem, leading to gastrointestinal toxicity. Animal models and clinical studies have revealed the associations between intestinal dysbiosis and depression, anxiety, pain, impaired cognitive functions, and cardiovascular diseases. Recently, a possible link between chemotherapy-induced gut microbiota disruption and late effects in cancer survivors has been proposed. In this review, we summarize the current understanding of preclinical and clinical findings regarding the emerging role of the microbiome and the microbiota-gut-brain axis in chemotherapy-related late effects affecting the central nervous system (CNS) and heart functions. Importantly, we provide an overview of clinical trials evaluating the relationship between the gut microbiome and cancer survivorship. Moreover, the beneficial effects of probiotics in experimental models and non-cancer patients with neurocognitive disorders and cardiovascular diseases as well as several studies on microbiota modulations via probiotics or fecal microbiota transplantation in cancer patients are discussed.

Beyer J, Collette L, Sauvé N, Daugaard G, Feldman DR, Tandstad T, Tryakin A, Stahl O, Gonzalez-Billalabeitia E, De Giorgi U, Culine S, de Wit R, Hansen AR, Bebek M, Terbuch A, Albany C, Hentrich M, Gietema JA, Negaard H, Huddart RA, Lorch A, Cafferty FH, Heng DYC, Sweeney CJ, Winquist E, **Chovanec M**, Fankhauser C, Stark D, Grimison P, Necchi A, Tran B, Heidenreich A, Shamash J, Sternberg CN, Vaughn DJ, Duran I, Bokemeyer C, Patrikidou A, Cathomas R, Assele S, Gillessen S;
International Germ Cell Cancer Classification Update Consortium. Survival and new prognosticators in

metastatic seminoma: results from the IGCCCG-update consortium.

J Clin Oncol. 2021 Mar 17:JCO2003292.

Purpose: The classification of the International Germ-Cell Cancer Collaborative Group (IGCCCG) has been a major advance in the management of germ-cell tumors, but relies on data of only 660 patients with seminoma treated between 1975 and 1990. We re-evaluated this classification in a database from a large international consortium.

Materials and methods: Data on 2,451 men with metastatic seminoma treated with cisplatin- and etoposide-based first-line chemotherapy between 1990 and 2013 were collected from 30 institutions or collaborative groups in Australia, Europe, and North America. Clinical trial and registry data were included. Primary end points were progression-free survival (PFS) and overall survival (OS) calculated from day 1 of treatment. Variables at initial presentation were evaluated for their prognostic impact. Results were validated in an independent validation set of 764 additional patients.

Results: Compared with the initial IGCCCG classification, in our modern series, 5-year PFS improved from 82% to 89% (95% CI, 87 to 90) and 5-year OS from 86% to 95% (95% CI, 94 to 96) in good prognosis, and from 67% to 79% (95% CI, 70 to 85) and 72% to 88% (95% CI, 80 to 93) in intermediate prognosis patients. Lactate dehydrogenase (LDH) proved to be an additional adverse prognostic factor. Good prognosis patients with LDH above 2.5× upper limit of normal had a 3-year PFS of 80% (95% CI, 75 to 84) and a 3-year OS of 92% (95% CI, 88 to 95) versus 92% (95% CI, 90 to 94) and 97% (95% CI, 96 to 98) in the group with lower LDH.

Conclusion: PFS and OS in metastatic seminoma significantly improved in our modern series compared with the original data. The original IGCCCG classification retains its relevance, but can be further refined by adding LDH at a cutoff of 2.5× upper limit of normal as an additional adverse prognostic factor.

Gillessen S, Sauvé N, Collette L, Daugaard G, de Wit R, Albany C, Tryakin A, Fizazi K, Stahl O, Gietema JA, De Giorgi U, Cafferty FH, Hansen AR, Tandstad T, Huddart RA, Necchi A, Sweeney CJ, Garcia-Del-Muro X, Heng DYC, Lorch A, **Chovanec M**, Winquist E, Grimison P, Feldman DR, Terbuch A, Hentrich M, Bokemeyer C, Negaard H, Fankhauser C, Shamash J, Vaughn DJ, Sternberg CN, Heidenreich A, Beyer J;

International Germ Cell Cancer Classification Update Consortium. Predicting outcomes in men with metastatic nonseminomatous germ cell tumors (NSGCT): results from the IGCCCG update consortium

J Clin Oncol. 2021 Apr 6:JCO2003296.

Purpose: The classification of the International Germ Cell Cancer Collaborative Group (IGCCCG) plays a pivotal role in the management of metastatic germ cell tumors but relies on data of patients treated between 1975 and 1990.

Materials and methods: Data on 9,728 men with metastatic nonseminomatous germ cell tumors treated with cisplatin- and etoposide-based first-line chemotherapy between 1990 and 2013 were collected from 30 institutions or collaborative groups in Europe, North America, and Australia. Clinical trial and registry data were included. Primary end points were progression-free survival (PFS) and overall survival (OS). The survival estimates were updated for the current era. Additionally, a novel prognostic model for PFS was developed in 3,543 patients with complete information on potentially relevant variables. The results were validated in an independent data set.

Results: Compared with the original IGCCCG publication, 5-year PFS remained similar in patients with good prognosis with 89% (87%-91%) versus 90% (95% CI, 89 to 91), but the 5-year OS increased from 92% (90%-94%) to 96% (95%-96%). In patients with intermediate prognosis, PFS remained similar with 75% (71%-79%) versus 78% (76%-80%) and the OS increased from 80% (76%-84%) to 89% (88%-91%). In patients with poor prognosis, the PFS increased from 41% (95% CI, 35 to 47) to 54% (95% CI, 52 to 56) and the OS from 48% (95% CI, 42 to 54) to 67% (95% CI, 65 to 69). A more granular prognostic model was developed and independently validated. This model identified a new cutoff of lactate dehydrogenase at a 2.5 upper limit of normal and increasing age and presence of lung metastases as additional adverse prognostic factors. An online calculator is provided (https://www.eortc.org/IGCCCG-Update). Conclusion: The IGCCCG Update model improves individual prognostication in metastatic nonseminomatous germ cell tumors. Increasing age and lung metastases add granularity to the original IGCCCG classification as adverse prognostic factors.