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GENITOURINÁRNE MALIGNITY

Chovanec M, Adra N, Abu Zaid M, Abonour R, Einhorn L.

High-dose chemotherapy for relapsed testicular germ cell tumours

Nat Rev Urol. 2022 Dec 7.

Relapsed testicular germ cell tumours (GCTs) might be cured with salvage chemotherapy. Accepted salvage treatment is conventional-dose chemotherapy (CDCT) or high-dose chemotherapy (HDCT). HDCT with peripheral blood stem cell transplant might produce a higher number of durable responses than CDCT. We discuss studies reporting on outcomes of salvage HDCT in relapsed GCTs. The most reproducible results were achieved with HDCT with two cycles of etoposide and carboplatin or three cycles of the paclitaxel, ifosfamide, carboplatin and etoposide regime. Using these two regimens, sustained cure rates of 50-66% were reported in phase I, phase II and retrospective studies published in the past two decades. Cure rates in patients with cisplatin-resistant disease are between 30% and 45%. Two phase III randomized studies were conducted with certain limitations and were unsuccessful in showing a survival benefit of HDCT. Thus, salvage treatment remains a controversial topic. Salvage HDCT with peripheral blood stem cell transplant and CDCT are two recommended treatment options for relapsed GCTs. Consistently reported cure rates from phase I, phase II and large retrospective studies support the use of HDCT in the hands of an experienced team of oncologists.

Chovanec M, Cheng L.

Advances in diagnosis and treatment of testicular cancer

BMJ. 2022 Nov 28;379:e070499.

Testicular cancer is a curable cancer. The success of physicians in curing the disease is underpinned by multidisciplinary advances. Cisplatin-based combination chemotherapy and the refinement of post-chemotherapy surgical procedures and diagnostic strategies have greatly improved long term survival in most patients. Despite such excellent outcomes, several controversial dilemmas exist in the approaches to clinical stage I disease, salvage chemotherapy, post-chemotherapy surgical procedures, and implementing innovative imaging studies. Relapse after salvage chemotherapy has a poor prognosis and the optimal treatment is not apparent. Recent research has provided insight into the molecular mechanisms underlying cisplatin resistance. Phase 2 studies with targeted agents have failed to show adequate efficacy; however, our understanding of cisplatin resistant disease is rapidly expanding. This review summarizes recent advances and discusses relevant issues in the biology and management of testicular cancer.

MIKROBIÓM A NÁDORY

Nikolaieva N, Sevcikova A, Omelka R, Martiniakova M, **Mego M,** Ciernikova S.

Gut microbiota-microRNA interactions in intestinal homeostasis and cancer development

Microorganisms. 2022 Dec 31;11(1):107.

Pre-clinical models and clinical studies highlight the significant impact of the host-microbiota relationship on cancer development and treatment, supporting the emerging trend for a microbiota-based approach in clinical oncology. Importantly, the presence of polymorphic microbes is considered one of the hallmarks of cancer. The epigenetic regulation of gene expression by microRNAs affects crucial biological processes, including proliferation, differentiation, metabolism, and cell death. Recent evidence has documented the existence of bidirectional gut microbiota-microRNA interactions that play a critical role in intestinal homeostasis. Importantly, alterations in microRNA-modulated gene expression are known to be associated with inflammatory responses and dysbiosis in gastrointestinal disorders. In this review, we summarize the current findings about miRNA expression in the intestine and focus on specific gut microbiota-miRNA interactions linked to intestinal homeostasis, the immune system, and cancer development. We discuss the potential clinical utility of fecal miRNA profiling as a diagnostic and prognostic tool in colorectal cancer, and demonstrate how the emerging trend of gut microbiota modulation, together with the use of personalized microRNA therapeutics, might bring improvements in outcomes for patients with gastrointestinal cancer in the era of precision medicine.

Danis R, **Mego M**, Antonova M, Stepanova R, Svobodnik A, Hejnova R, Wawruch M.

Orally administered probiotics in the prevention of chemotherapy (± radiotherapy)-induced gastrointestinal toxicity: a systematic review with meta-analysis of randomized trials

Integr Cancer Ther. 2022 Jan-Dec;21:15347354221144309.

Background: Chemoradiotherapy-induced gastrointestinal toxicity may lead to a significant impairment of the oncological patient's quality of life, as well as to reduced adherence to the treatment, which may have a negative impact on survival and mortality rates.

Objective: The aim of this review was to investigate whether oral probiotic administration prevents chemotherapy (± radiotherapy)-induced gastrointestinal toxicity, particularly diarrhea.

Methods: We searched the MEDLINE, Web of Science, and SCOPUS databases for randomized controlled trials in English published between 1990 and 2020. We conducted statistical data analyses expressing the treatment effect size as a risk ratio (RR) together with a 95% confidence interval (CI). Implications are based on trials rated as having a low risk of bias (RoB).

Results: We included 8 trials (n = 697 participants), from which 3 studies

rated as low RoB contained primary endpoint data; the risk of developing grade 3/4 diarrhea in patients receiving probiotics was reduced by 78% compared to the control group (RR = 0.22 [95% CI 0.05-1.08]; P = .06; n = 114 participants). Probiotics showed preventive effects in patients treated with chemotherapy alone (RR = 0.34 [0.12-0.94]; P = .04, n = 121 participants) and in patients with colorectal cancer (RR = 0.56 [0.34-0.92]; P = .02; n = 208 participants). The reduction in the incidence of overall diarrhea was not significant.

Conclusions: Probiotics failed to prove a preventive effect of statistical significance against the development of severe and overall diarrhea in cancer patients treated with chemotherapy (± radiotherapy). However, we cannot rule out that the effects of probiotics are clinically relevant, especially in certain subgroups of patients. This needs to be clarified in further well-performed studies.

Ciernikova S, Sevcikova A, Stevurkova V, **Mego M.**

Tumor microbiome – an integral part of the tumor microenvironment

Front Oncol. 2022 Nov 24;12:1063100.

The tumor microenvironment (TME) plays a significant role in tumor progression and cancer cell survival. Besides malignant cells and non-malignant components, including immune cells, elements of the extracellular matrix, stromal cells, and endothelial cells, the tumor microbiome is considered to be an integral part of the TME. Mounting evidence from preclinical and clinical studies evaluated the presence of tumor type-specific intratumoral bacteria. Differences in microbiome composition between cancerous tissues and benign controls suggest the importance of the microbiome-based approach. Complex host-microbiota crosstalk within the TME affects tumor cell biology *via* the regulation of oncogenic pathways, immune response modulation, and interaction with microbiota-derived metabolites. Significantly, the involvement of tumor-associated microbiota in cancer drug metabolism highlights the therapeutic implications. This review aims to summarize current knowledge about the emerging role of tumor microbiome in various types of solid malignancies. The clinical utility of tumor microbiome in cancer progression and treatment is also discussed. Moreover, we provide an overview of clinical trials evaluating the role of tumor microbiome in cancer patients. The research focusing on the communication between the gut and tumor microbiomes may bring new opportunities for targeting the microbiome to increase the efficacy of cancer treatment and improve patient outcomes.

HEMATOLOGICKÉ MALIGNITY

Cholujova D, Beke G, Hunter ZR, Hideshima T, Flores L, Zeleznikova T, Harrachova D, Klucar L, Leiba M, **Drgona L**, Treon SP, Kastritis E, Dorfman DM, Anderson KC, Jakubikova J.

Dysfunctions of innate and adaptive immune tumor microenvironment in Waldenström macroglobulinemia

Int J Cancer. 2022 Dec 19.

Waldenström macroglobulinemia (WM) is a rare subtype of non-Hodgkin lymphoma characterized by malignant lymphoplasmacytic cells in the bone marrow (BM). To dissect the pathophysiology of WM, we evaluated clonal cells by mapping of B cell lymphomagenesis with adaptive and innate immune tumor microenvironment (TME) in the BM of WM patients using mass cytometry (CyTOF). In-depth immunophenotypic profiling of WM cells exhibited profound expansion of clonal cells in both unswitched and switched memory B cells and also plasma cells with aberrant expression variations. WM B lymphomagenesis was associated with reduction of most B cell precursors assessed with the same clonally restricted light chain and phenotypic changes. The immune TME was infiltrated by mature monocytes, neutrophils and adaptive T cells, preferentially subsets of effector T helper, effector CTL and effector memory CTL cells that were associated with superior overall survival (OS), in contrast to progenitors of T cells and myeloid/monocytic lineage subsets that were suppressed in WM cohort. Moreover, decrease in immature B and NKT cells was related to worse OS in WM patients. Innate and adaptive immune subsets of WM TME were modulated by immune checkpoints, including PD-1/PD-L1&PD-L2, TIGIT/PVR, CD137/CD137-L, CTLA-4, BTLA and KIR expression. The response of ibrutinib treatment to the reduction of clonal memory B cell was associated with high levels of immature B cells and effector memory CTL cells. Our study demonstrates that CyTOF technology is a powerful approach for characterizing the pathophysiology of WM at various stages, predicting patient risk and monitoring the effectiveness of treatment strategies.

Cattaneo C, Salmanton-García J, Marchesi F, El-Ashwah S, Itri F, Weinbergerová B, Gomes Da Silva M, Dargenio M, Dávila-Valls J, Martín-Pérez S, Farina F, Van Doesum J, Valković T, Besson C, Poulsen CB, López-García A, Žák P, Schönlein M, Piukovics K, Jaksic O, Cabirta A, Ali N, Sili U, Fracchiolla N, Dragonetti G, Adžić-Vukičević T, Marchetti M, Machado M, Glenthøj A, Finizio O, Demirkan F, Blennow O, Tisi MC, Omrani AS, Navrátil M, Ráčil Z, Novák J, Magliano G, Jiménez M, Garcia-Vidal C, Erben N, Del Principe MI, Buquicchio C, Bergantim R, Batinić J, Al-Khabori M, Verga L, Szotkowski T, Samarkos M, Ormazabal-Vélez I, Meers S, Maertens J, Pinczés LI, Hoenigl M, **Drgoňa Ľ**, Cuccaro A, Bilgin YM, Aujayeb A, Rahimli L, Gräfe S, Sciumè M, Mladenović M, Çolak GM, Sacchi MV, Nordlander A, Berg Venemyr C, Hanáková M, García-Poutón N, Emarah Z, Zambrotta GPM, Nunes Rodrigues R, Cordoba R, Méndez GA, Biernat MM, Cornely OA, Pagano L.

Simultaneous onset of haematological malignancy and covid: an epicovideha survey

Cancers (Basel). 2022 Nov 10;14(22):5530.

Background: The outcome of patients with simultaneous diagnosis of haematological malignancies (HM) and COVID-19 is unknown and there are no specific treatment guidelines.

Methods: We describe the clinical features and outcome of a cohort of 450 patients with simultaneous diagnosis of HM and COVID-19 registered in the EPICOVIDEHA registry between March 2020 to February 2022.

Results: Acute leukaemia and lymphoma were the most frequent HM (35.8% and 35.1%, respectively). Overall, 343 (76.2%) patients received treatment for HM, which was delayed for longer than one month since diagnosis in 57 (16.6%). An overall response rate was observed in 140 (40.8%) patients after the first line of treatment. After a median follow-up of 35 days, overall mortality was 177/450 (39.3%); 30-day mortality was significantly higher in patients not receiving HM treatment (42.1%) than in those receiving treatment (27.4%, $p = 0.004$), either before and/or after COVID-19, or compared to patients receiving HM treatment at least after COVID-19 (15.2%, p < 0.001). Age, severe/critical COVID-19, ≥2 comorbidities, and lack of HM treatment were independent risk factors for mortality, whereas a lymphocyte count >500/mcl at COVID-19 onset was protective.

Conclusions: HM treatment should be delivered as soon as possible for patients with simultaneous diagnosis of COVID-19 and HM requiring immediate therapy.

NÁDORY HLAVY A KRKU

Svajdova M, Dubinsky P, Kazda T, Jeremic B.

Human papillomavirus-related non-metastatic oropharyngeal carcinoma: current local treatment options and future perspectives

Cancers (Basel). 2022 Nov 1;14(21):5385.

Over the last two decades, human papillomavirus (HPV) has caused a new pandemic of cancer in many urban areas across the world. The new entity, HPV-associated oropharyngeal squamous cell carcinoma (OPSCC), has been at the center of scientific attention ever since, not only due to its distinct biological behavior, but also because of its significantly better prognosis than observed in its HPV-negative counterpart. The very good treatment outcomes of the disease after primary therapy (minimally-invasive surgery, radiation therapy with or without chemotherapy) resulted in the creation of a separate staging system, reflecting this excellent prognosis. A substantial proportion of newly diagnosed HPV-driven OPSCC is diagnosed in stage I or II, where long-term survival is observed worldwide. Deintensification of the primary therapeutic methods, aiming at a reduction of long-term toxicity in survivors, has emerged, and the quality of life of the patient after treatment has become a key-point in many clinical trials. Current treatment recommendations for the treatment of HPV-driven OPSCC do not differ significantly from HPV-negative OPSCC; however, the results of randomized trials are eagerly awaited and deemed necessary, in order to include deintensification into standard clinical practice.