HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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REVISÕES E METANALISES - 17° SIMPÓSIO EDWALDO CAMARGO E 1°CONGRESSO CANCERTHERA

THERANOSTICS: NUCLEAR MEDICINE IN PROSTATE CANCER

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Summary: Theranostic Nuclear Medicine is based on the idea of combining the same molecule (or drug) with different radioisotopes, both for diagnosis and treatment, a concept that emerged in the early 1940s with thyroid diseases. It has since expanded to diseases of higher incidence, such as prostate cancer with several imaging methods used to assess the extent of the disease and the corresponding radiopharmaceuticals used for treatment. For example, by detecting osteoblastic metastases by bone scintigraphy, there are corresponding radiopharmaceuticals with therapeutic properties that eliminate pain from bone metastases, reduce pain of these detected metastases and/or determine overall survival gain. The purpose of this review is to discuss the role and great importance of Theranostic Nuclear Medicine in prostate cancer, addressing the main diagnostic imaging studies with their corresponding treatments, in the Theranostic model. **Conclusão:** Nuclear Medicine plays an increasingly significant role in the diagnostic and therapeutic approach to urological malignancies. The enormous advances in SPECT/CT and especially PET/CT images now allow an assessment of these tumors in the staging, recurrence, and response to treatment settings. Molecular imaging identifies alterations not identified by anatomical imaging and for this reason, PET/CT images are becoming increasingly indispensable in specific clinical situations and with precise indications according to the type of urological neoplasia. Theranostic Nuclear Medicine is rapidly evolving in prostate cancer and is a well-established and routine treatment option. Additionally, it is a personalized therapy. The concept of using the same molecule for diagnosis and therapy opened the door to guided and effective treatment, increasing patient survival while maintaining an excellent quality of life and without serious side effects, which is a challenge in metastatic cancer treatments.

Keywords: 18F-fluoride, FDG, Nuclear medicine, PET/CT, PSMA.

https://doi.org/10.1016/j.htct.2024.04.111

EFFICACY AND SAFETY OF RADIUM-223 AND STANDARD OF CARE IN PATIENTS WITH BREAST CANCER AND BONE METASTASIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Summary: Radium-223 (Ra-223) has been used to treat metastatic bone disease in prostate cancer, improving overall survival and quality of life. Breast cancer often presents bone metastasis too, but it is often associated with other sites of disease. In such cases, the addition of Ra-223 to the standard of care (SC) may be beneficial. Therefore, our objective is to determine if the use of Radium-223 plus SC is beneficial for metastatic bone breast cancer patients through a systematic

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review and meta-analysis. A comprehensive search was conducted across MEDLINE, EMBASE, and CENTRAL databases. The search strategy included the following terms: "Breast cancer" AND "Radium-223". The selection criteria encompassed both single-arm and randomized controlled trials (RCT). MedCalc® Statistical Software was used. Hazard ratios (HR) were preferred. Odds ratios (OR) or Relative risk (RR) were used when HR was not disponible. For single-arm studies, a proportion meta-analysis was performed. Random-effects methods were used. The initial search yielded 349 articles, 28 articles were reviewed with full-text, and 5 were considered eligible (3 RCT and 2 single-arm studies). SC therapy included: capecitabine, paclitaxel, exemestane plus everolimus and hormonal therapy. Overall, the group submitted to Ra-223 showed a trend to have better symptomatic skeletal event-free survival – SSEFS - (HR: 0.855, CI: 0.643-1.138) and pain improvement (OR: 1.308. CI: 0.780-2.196), but without statistical significance. The pooled analysis showed no difference between arms for serious adverse effects (RR: 0.836. CI: 0.331-2.112). The proportion of SAE in patients submitted to Ra-223 plus SC was 20.1% (CI: 3.6-45.3%). **Conclusão:** Ra-223 plus SC in bone metastatic breast cancer patients showed a trend to better SSEFS and pain improvement. However, the low number of RCT studies and the high heterogeneity of SC are great limitations. Results from ongoing RCT (everolimus and avelumab) can change this scenario.

Keywords: Breast cancer, Meta-analysis., Radium-223, Systematic review.

https://doi.org/10.1016/j.htct.2024.04.112

EPSTEIN-BARR VIRUS AND LYMPHOMA IN RHEUMATOID ARTHRITIS: PREVALENCE AND ASSOCIATION WITH METHOTREXATE. RESULT OF SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES

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Summary: Introduction: rheumatoid arthritis (RA) is an autoimmune, inflammatory, and systemic disease, whose pathogenesis involves both the innate and adaptive immune systems. Its global prevalence varies from 0,4% to 1,3%, and the incidence increases with age. Given the increase in the general life expectancy of the population, the number of elderly patients with RA is growing, as are the complications of the disease. Several studies have demonstrated that patients with RA are at increased risk of developing lymphoproliferative diseases when compared to the general population. Some theories have emerged to explain this association, with emphasis on the role of the Epstein-Barr virus (EBV) and immunosuppressive drugs, especially methotrexate (MTX), the medication most frequently used to treat the disease. Methodology: Pubmed, Cochrane, Lilacs, Scopus, Embase and Web of Science databases were systematically reviewed in September 2023, without language or publication date restrictions. We searched for observational studies that associated EBV, RA, methotrexate and lymphoma. The recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Cochrane Collaboration were used. **Results:** the analysis of 10 studies published between 2001 and 2022, involving 674 patients with RA and lymphoma, demonstrated that 77,3% used MTX and 27,4% were positive for EBV. The most common lymphoma was diffuse large B-cell lymphoma (DLBCL). The prevalence of EBV in DLBCL patients ranges from 5-15%, compared to 27,4% in the present study. This histological subtype was also associated with lower rates of spontaneous remission and worse outcomes. The prevalence of EBV in RA patients not treated with MTX was 7,7%, compared to 46% in patients who used the drug. Spontaneous remission rates (sRR) after MTX suspension (without associated immunochemotherapy) were variable (22,9% to 69,2%), but higher in the EBV-positive group. **Discussion:** in RA patients treated with MTX, EBV is expected to be activated through 3 mechanisms. The first of these involves AR itself. Patients with the disease have a deficiency of CD8+ T cells and, consequently, a high EBV burden due to immunodeficiency. The second mechanism is the suppression of T cell activation and adhesion by MTX. The third mechanism is direct reactivation of latent EBV by MTX. Thus, MTX withdrawal appears to result in recovery of immune surveillance and interruption of the EBV-induced tumor pathway. sRR with MTX withdraw were higher in EBV-positive group and could indicate that the virus is associated with a better outcome. The different prognosis of EBV-negative cases suggests that these tumors have a distinct biology. **Conclusão:** Conclusion: our systematic review found a high prevalence of EBV positivity in patients with RA and lymphoma, suggesting an important role for the virus in lymphomagenesis in this specific population. Due to the frequent use of MTX in the RA population, data from the systematic review alone are not capable of attributing the drug's causality to other confounding factors.

Keywords: Epstein-Barr, Lymphoma, Methotrexate, Rheumatoid arthritis.

https://doi.org/10.1016/j.htct.2024.04.113

TRENDS IN RADIOISOTOPES AND RADIOLABELING METHODS

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Summary: Radiopharmaceutical research and bioscience or medical applications have changed during the decades in the function of available technologies for radioisotope production and imaging detection technologies. In the 1940s to 1960s year, radioisotopes were supplied by reactor production, such as 131I for thyroid uptake study, 197Hg, 203Hg-chlormerodrin for brain scans, 198Au-colloid for liver scans, and 85Sr-chloride for the bone scans. In the late 1960s, with the

development of the gamma camera by Hal Anger, and the 99Mo/99mTc generators by researchers of the Brookhaven National Laboratory, the focus was moved to research and diagnostic application of 99mTc radiopharmaceuticals, and these compounds have been in use until now. In that age, the chemistry of technetium, including the production of different chelators and radiolabeling processes, were developed. Cyclotron-producing radioisotopes for medical application emerged in 1955, and for a long time, it was used to produce gamma-emitting radionuclides such as 67Ga, 111In, and 201Tl. After the development of PET câmera around 1975, positron-emitting radioisotopes started to be produced routinely in cyclotrons, such as 11C, 13N, and 18F, gaining market status for diagnostic applications after Alfred Wolf and colleagues developed the 18F-FDG, around 1978. In the following year, positron-emitting radiometals 68Ga, 64Cu, and 89Zr, began to be produced on a large scale to label molecules with short or long circulation times in the body. The results in the specificity of the diagnostic opened the possibility of using 90Y and 177Lu, both beta-emitting radioisotopes, to label the same molecules for therapeutic purposes; thus, theranostics pair 68Ga or 64Cu/90Y or 177Lu started to be used in nuclear medicine. From the 2010s, true theranostic pairs gain interest, such as 44gSc/47Sc, 64Cu/67Cu, 83Sr/89Sr, 86Y/90Y, 124I/131I, 152Tb/161Tb, and 152Tb/149Tb, stated to be produced and evaluated for clinical applications. All these developments in radioisotope production and imaging systems also boosted the development of molecule radiolabeling processes, mainly through automated systems, to ensure speed, reproducibility, and less exposure to professionals involved in preparing these molecules. Furthermore, several chelating agents have been developed to complex different metals in a simple, effective, and stable way, such as the DOTA, NOTA, HBED molecules, among others. **Conclusão:** Trends in radioisotopes and radiolabeling methods result from scientific and technological developments in different areas but with congruent purposes. The result is a large number of products that can be chosen by their physical, chemical, biological, or economic characteristics.

Keywords: Cyclotron, Nuclear reactor, Radioisotopes production, Radiolabeling methods.

https://doi.org/10.1016/j.htct.2024.04.114

RADIOLIGAND THERAPY IN LYMPHOMA: PAST, PRESENT AND FUTURE

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Summary: In the 80s, radiolabeled cells helped understand the pathology of hemato-oncology. In the 90s, pre-clinical trials evaluated radiolabeled immunotherapy with monoclonal antibodies (MoAbs) such as anti-CD20 agents labeled with Iodine-131 (Bexxar®) or Yttrium-90 (Zevalin®). Due to the safe and durable responses of radiolabeled-MoAbs, the FDA approved these agents in the 2000s. Despite radioimmunotherapy's long journey, its application has recently decreased. This review will discuss the historical timeline of radioimmunotherapy, debate on advantages and difficulties, and explore trials. Furthermore, we will examine future directions of radioimmunotherapy in hemato-oncology, considering emerging molecules that may become the next theragnostic trend. **Conclusão:** Since the 1980s, radiolabeled cells have been instrumental in understanding the pathological dynamics of hemato-oncological diseases. The evolution of this approach traversed the hybridoma technique in the 1990s, leading to numerous pre-clinical trials involving Monoclonal Antibodies (MoAbs). Subsequent clinical trials, predominantly in the 2000s, extensively explored MoAbs, focusing on anti-CD20 agents labeled with either 131I (Bexxar) or 90Y (Zevalin). The FDA approved these therapies in 2002 and 2003, marking significant milestones recognizing their safety and enduring therapeutic responses. Despite this journey, there has been a consistent decline in prescriptions. Various factors contribute to this trend, encompassing availability issues, reimbursement challenges, regulatory complexities, the need for trained personnel, and intricate logistics. Recent pre-clinical and clinical trials have shifted the spotlight onto novel antibodies, peptides, and further applications of known tracers. This renewed exploration may incentivize new suppliers to redirect their attention, potentially heralding the next wave of theragnostic trends in the near future.

Keywords: Immunotherapy, Lymphoma, Radioligand, Theranostics, Therapy.

https://doi.org/10.1016/j.htct.2024.04.115

PROFILE OF MENINGIOMAS IN DOTATOC-68GA, FDG-18F AND PSMA-68GA PET/CT STUDIES: REALITY OF A PRIVATE SERVICE OF NUCLEAR MEDICINE AND LITERATURE REVIEW

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Summary: Meningiomas represent the most common group of central nervous system primary tumors, and are often incidental findings on neuroimaging exams. The World Health Organization classifies meningiomas into three grades (grades I-III), varying in risk of recurrence and mortality. Approximately 100% of meningiomas present expression of the somatostatin receptor type 2 (SSTR2), which, in recent years, has been highlighted by the literature as a possible theranostic tool, confirming the relevance of PET/CT with SSTR ligands in this context. Based on a narrative literature review, the objective was to analyze the main characteristics of meningiomas found in DOTATOC-68Ga PET/CT, FDG-18F PET/CT and PSMA-68Ga PET/CT exams performed in a private

nuclear medicine service. Subsequently, the data obtained was compared with evidence from the studies consulted. A search tool connected to the RIS database was used, utilizing the search word meningioma in PET/CT exam reports, from February 2019 to January 2024. As a result, exams from 68 patients were found, including 19 PET/CT DOTATOC-68Ga, 45 PET/CT FDG-18F and 4 PET/CT PSMA-68Ga. The absolute number per age group was 8 (40-49 years), 12 (50-59 years), 15 (60-69 years), 19 (70-79 years) and 14 (80 years or more), among which 47 were women and 21 men. Among all studies, 12 (17.6%) were indicated for meningioma specific evaluation, varying between initial diagnosis, radiosurgery programming, post-resection evaluation and uncleared focal neurological signs, which represented 57.9% (11) of the DOTATOC-68Ga PET/CT sample and 2.2% (1) of FDG-18F PET/CT. All PSMA-68Ga PET/CT studies had another indication. Within all lesions evaluated, 61 were unifocal and 7 were multifocal. The largest diameter of the lesions analyzed ranged from 5 to 66 mm (average 23 mm). Based on the 68 patients analyzed in the sample, highlighting the existence of multifocal lesions, the topographies observed were: parasagittal 23, hemispherical convexity 30, sphenoid and middle cranial fossa 12, cerebellar convexity 1, frontobasal 4, posterior fossa 2 and foramen magnum 1. All lesions evaluated by DOTATOC-68Ga PET/CT showed tracer uptake (SUV between 2.5 and 17.8, mean SUV 8.9), compared to 3 lesions evaluated by FDG PET/CT-18F (SUV between 4.9 and 7.2, mean SUV 6.1). No lesion showed significant uptake of PSMA-68Ga. **Conclusão:** In the context of increasing advances in molecular imaging with SSTR ligands for meningiomas, PET/CT studies have showed relevance, above all, in the initial evaluation (pre-surgical/pre-radiotherapeutic), in the scenario of suspected tumor recurrence, as well as for candidates to radionuclide therapy. The present work sought to analyze information that could corroborate the characteristics of such tumors in hybrid images, comparing the data found with current literature. In addition, highlight the potential use of FDG-18F uptake in the non-invasive assessment of the aggressiveness of meningiomas.

Keywords: DOTATOC-68Ga, FDG-18F, Meningiomas, PET/CT, PSMA-68Ga.

https://doi.org/10.1016/j.htct.2024.04.116