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REVIEW ARTICLE

Oral Secondary Malignant Lesions Post-Hematopoietic Stem Cell Transplantation: A Review

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ABSTRACT

Increased survival rates after hematopoietic stem cell transplantation (HSCT) have led to a higher occurrence of oral secondary malignant lesions, which are often aggressive and appear 5 to 10 years post-procedure. Many doctors and dentists feel unprepared to manage these patients. **Objectives:** This review aims to identify the most prevalent oral secondary malignant lesions in post-HSCT patients, their onset period, developmental mechanisms, and treatment options. **Methods:** A narrative literature review was conducted using the PubMed and LILACS databases (articles from January 2012 to June 2024), with the descriptors "HSCT," "mouth neoplasms," "oral cancer," and "oral squamous cell carcinoma." Studies such as reviews, meta-analyses, and case reports/series addressing the objectives were included. Bibliographic management was performed using Anara, a research support software that employs artificial intelligence for referencing, article storage, and citation. **Aspects discussed:** The main types of secondary malignancies (post-transplant lymphoproliferative disease, solid tumors like oral squamous cell carcinoma) and risk factors are addressed, with emphasis on graft-versus-host disease. **Conclusions and applications:** Oral secondary malignant lesions are a significant complication after HSCT, with graft-versus-host disease being an important risk factor. Knowledge about these lesions, their mechanisms, and treatments is crucial to guide dentists and doctors in clinical analysis and management, highlighting the need for active surveillance for early diagnosis and better prognosis.

Descriptors: Hematopoietic Stem Cell Transplantation; Mouth Neoplasms; Carcinoma; Squamous Cell; Graft vs. Host Disease.

Lesões Malignas Secundárias Orais Pós-Transplante de Células-Tronco Hematopoiéticas: Uma Revisão

RESUMO

O aumento da sobrevida após o transplante de células-tronco hematopoiéticas (TCTH) elevou a ocorrência de lesões malignas secundárias orais, frequentemente agressivas, surgindo entre 5 a 10 anos pós-procedimento. Muitos médicos e cirurgiões-dentistas sentem-se despreparados para manejar esses pacientes. **Objetivos:** Esta revisão visa identificar as lesões malignas secundárias orais mais prevalentes em pacientes pós-TCTH, seu período de aparecimento, mecanismos de desenvolvimento e opções de tratamento. **Métodos:** Realizou-se uma revisão narrativa da literatura com busca nas bases PubMed e LILACS (artigos de janeiro de 2012 a junho de 2024), utilizando os descritores "TCTH", "neoplasias bucais", "câncer oral" e "carcinoma de células escamosas oral". Foram incluídos estudos como revisões, metanálises e relatos/séries de casos que abordassem os objetivos. O gerenciamento bibliográfico foi realizado com o *software* Anara, que utiliza inteligência artificial para referenciamento, armazenamento e citações. **Aspectos discutidos:** Abordam-se os principais tipos de malignidades secundárias (doença linfoproliferativa pós-transplante, tumores sólidos como o carcinoma espinocelular oral) e fatores de risco, com destaque para a doença do enxerto contra o hospedeiro (DECH). **Conclusões e aplicações:** As lesões malignas secundárias orais são uma complicação significativa após o TCTH, sendo a DECH um fator de risco importante. O conhecimento sobre essas lesões, seus mecanismos e tratamentos é crucial para guiar cirurgiões-dentistas e médicos na análise clínica e manejo, destacando a necessidade de vigilância ativa para diagnóstico precoce e melhor prognóstico.

Descritores: Transplante de Células-Tronco Hematopoiéticas; Neoplasias Bucais; Carcinoma de Células Escamosas; Doença Enxerto-Contra-Hospedeiro.

INTRODUCTION

In recent decades, hematopoietic stem cell transplantation (HSCT) has become a primary treatment for several hematologic diseases[1]. With scientific and biotechnological advances, the success rate has progressively increased, necessitating greater attention from specialists to address late complications in these immunosuppressed patients. Its role is crucial in medicine, replacing the patient's hematopoiesis and immune system with that of the donor. Over time, its evolution from a last resort has consolidated itself as an effective treatment for complex hematologic diseases and a promoter of tolerance in solid organ transplants[2-4].

HSCT can be classified according to the source of hematopoietic stem cells used in the procedure: autologous HSCT, which uses the patient's cells, and allogeneic HSCT, which uses cells from a donor. This distinction is crucial for both clinical indication and understanding the complications associated with the procedure. Stem cell sources include bone marrow, mobilized peripheral blood stem cells, and umbilical cord blood, each with its own characteristics and advantage[s4-8].

Achieving complete donor-recipient matching in allogeneic HSCT represents a significant clinical challenge. Despite advances in high-resolution HLA typing, the likelihood of finding a compatible donor is higher in individuals with commonly occurring HLA alleles. Conversely, patients from ethnically diverse or mixed populations face greater challenges due to high genetic heterogeneity and underrepresentation in voluntary donor registries. This disparity negatively impacts access to allogeneic HSCT, even with the use of alternative graft sources, such as haploidentical cells and umbilical cord blood[9,10].

HSCT stands out for completely replacing the patient's hematopoietic and immune systems with those of the donor. For many patients, especially those with non-malignant diseases such as multiple sclerosis and systemic sclerosis, careful and early donor selection is crucial to prevent and reverse complications[7].

In autoimmune diseases, autologous HSCT has demonstrated the ability to restore immune tolerance, activating mechanisms such as thymopoiesis and increasing the presence of FoxP3-positive regulatory T cells, which are essential for self-tolerance. Furthermore, autologous HSCT offers a promising approach for the treatment of autoimmune diseases refractory to conventional therapy, allowing the administration of higher and more effective doses of previously harvested autologous hematopoietic stem cells. This therapeutic strategy is particularly attractive for aggressive malignancies such as non-Hodgkin's lymphoma and Hodgkin's disease. In the setting of relapsed diffuse large B-cell lymphoma, autologous HSCT plays a key role and has the potential to prolong progression-free survival[7] significantly.

Successful allogeneic HSCT requires immunosuppressive therapy or a prior conditioning regimen, which may involve chemotherapy and radiotherapy, to prepare the patient for allogeneic hematopoietic stem cell grafting. The selection of the conditioning regimen depends on the diagnosis, the patient's age, and comorbidities, and reduced-intensity regimens have allowed this procedure to be extended to older and more fragile patients. However, finding a compatible donor for allogeneic HSCT remains a significant challenge for many patients, highlighting the need to improve the search for suitable donors[5-7,11].

Regarding the potential secondary complications that affect these patients, we can mention the increased risk of developing secondary malignancies, among which a new neoplasm and the incidence of secondary solid tumors are the most concerning. Studies show that the development of post-transplant lymphoproliferative disease (PTLD) can occur within 2 to 4 months post-transplant; hematologic malignancies within a longer window, 3 to 5 years; and the incidence of solid tumors after five or more years[1,2,12].

The most common sites for secondary solid tumors after HSCT include the lungs, liver, brain, cervix, skin, and oral cavity, with a higher incidence of skin and mucosal tumors in these patients. The most common tumor is squamous cell carcinoma (SCC) in oral mucosal tissues, particularly in patients with graft-versus-host disease (GVHD)[1,2,12].

GVHD is a major complication of HSCT and the leading cause of morbidity and mortality after transplantation. Its chronic form (cGVHD) is an autoimmune condition resulting from an immune attack mediated by donor T lymphocytes, which recognize antigens expressed on normal tissues. It affects nearly 50% of adult post-HSCT patients. The hypothesis is that damage from the pre-transplant conditioning regimen activates antigen-presenting cells (APCs) at the time of grafting and damages the integrity of mucosal surfaces[13].

Diagnosis is based on history, context, and clinical evaluation. Clinical signs include changes similar to lichen planus. Erythematous and ulcerative changes are distinct but not diagnostic of oral cGVHD. Symptoms can lead to a significant decrease in oral intake, nutritional deficiency, and oral infections. Specific symptoms related to the oral mucosa include sensitivity to spicy, acidic, and salty foods, alcoholic beverages, and mouthwashes containing alcohol and flavoring agents. These signs can be considered a predictive index of the presence of the disease in its systemic form. Salivary gland-related symptoms include xerostomia, difficulty speaking, swallowing, and chewing, and changes in taste[13].

Clinically, oral cGVHD often mimics oral lichen planus (OLP), presenting with white reticular lesions, erythema, keratotic plaques, or ulcerations. However, these findings are not pathognomonic and require careful clinical evaluation. Symptoms

such as pain, burning sensation, sensitivity to spicy, acidic, or salty foods, as well as dry mouth, dysgeusia, and functional difficulties chewing or speaking, may manifest early and serve as indicators of the systemic presence of the disease. From a histopathological perspective, although both conditions share inflammatory aspects, studies show that cGVHD biopsies present lower CD3+ T lymphocyte infiltration compared to OLP. Furthermore, epithelial expression of HLA class II antigens is frequently found in biopsies from OLP patients, which is not observed in cGVHD samples, pre-transplant tissues, or healthy controls, which may represent a critical differentiating criterion between the two conditions. The possible malignancy of OLP is controversial, but there are increasing reports in the literature of SCC arising from OLP lesions[1,12,14].

Patients with cGVHD report multiple and simultaneous symptoms, and research has documented significant relationships between these symptoms, cytokine levels, and quality of life. There is no ideal treatment option for oral cGVHD, and the current focus is on disease control by reducing immune-based damage to target tissues and controlling symptoms[13].

SCC is a type of neoplasia and a rare but well-studied late complication of HSCT. It develops from epithelial cells of the oral mucosa of the pharynx and larynx. It is the most common malignant neoplasm arising in the head and neck, and its incidence is progressively increasing. The cause is usually related to exposure to carcinogens present in tobacco, excessive alcohol consumption, or both. Furthermore, studies increasingly indicate that tumors developing in the oropharynx are linked to prior infection with oncogenic strains of human papillomavirus (HPV).

Furthermore, genetic factors also contribute to the risk of SCC. Fanconi anemia (FA) is defined as a rare inherited genetic disease characterized by defective DNA repair. Patients with the disease have a 500- to 700-fold increased risk of developing neoplasia, particularly in the oral cavity[15].

Squamous cell carcinoma originates from epithelial cells of the mucosa lining the oral cavity, pharynx, larynx, and sinonasal tract. Although a large proportion of oral squamous cell carcinomas arise from leukoplakia, patients may present with advanced-stage disease without a clinical history of potentially malignant lesions. In most cases, oral cavity tumors are diagnosed at an early stage through the patient's identification of a lesion in the tongue, floor of the mouth, mucosa, alveolar ridges, retromolar trigone, or hard palate, presenting as a non-healing wound. The lesion often leads to symptoms that interfere with eating and speech, such as pain when chewing or dysarthria[15].

Although the mechanism of development of SCC in patients with GVHD still requires further consolidation in the literature, current studies indicate that the main risk factors that can lead to oral cancer in these patients are late primary diagnosis, type of transplant, systemic immunosuppressive therapy, occurrence of GVHD, and its treatment[1-3,12].

Although there are several studies on the development of secondary lesions in post-HSCT patients, the findings in the literature are outdated and do not reflect changes in the treatment landscape for these patients, such as mortality rates. They also lack information regarding the best treatment for these lesions.

This study is justified by its potential to provide physicians and dentists with access to information that helps them identify these lesions, enabling early diagnosis in this group of immunosuppressed patients. Furthermore, it will provide insight into their prior disease, the mechanism of neoplasm development, and how treatment should evolve. Finally, it will allow for a better understanding of the incidence and mechanism of malignant lesions in post-HSCT patients.

The objective of this review is to understand the incidence of oral malignancies in post-HSCT patients. It also seeks to discuss general aspects of HSCT and its indications, identify the most prevalent oral malignancies and their timing, describe their developmental mechanisms and correlation with systemic conditions, and highlight available treatments and their efficacy.

METHODS

This narrative literature review was conducted based on a bibliographic search of journal publications indexed in the PubMed and LILACS electronic databases. The search strategy combined controlled descriptors (MeSH/DeCS) and free keywords in the PubMed and LILACS databases, using Boolean operators. The main combination was ("hematopoietic stem cell transplantation" OR "stem cell transplant") AND ("oral cancer" OR "mouth neoplasms" OR "oral squamous cell carcinoma") AND ("graft versus host disease" OR "GVHD"). The terms were applied in English, Portuguese, and Spanish, respecting the indexing of each database. Studies published between January 2012 and June 2024 were included.

Studies such as literature reviews (narrative or systematic), meta-analyses, clinical case series, clinical trials, and case reports were included in the review, provided they were within the stipulated publication period and directly addressed the objectives of this research. There were no language restrictions for article selection. Bibliographic management was performed using Anara (Anara Labs, Inc.), a research support software that applies artificial intelligence for referencing, article storage, and citation of the studies The selected studies underwent critical reading, and relevant information was extracted through file

entries, focusing on the type of secondary oral malignancy, time of onset post-transplant, diagnosis, treatment, and underlying primary disease of the patients.

Literature review

HSCT

Hematopoietic stem cells play a fundamental role in the continuous production of blood cells throughout an individual's life. HSCT is a procedure in which both hematopoiesis and the immune system are entirely replaced by donor cells. Developed in the 1960s and 1970s, HSCT has evolved from a last resort into a well-established medical discipline, effectively treating complex hematologic diseases, restoring hematopoietic stem cell function, and promoting tolerance in solid organ transplants[4,5,8].

HSCT is classified by donor type, purpose, and cell origin. The source can be the patient (autologous) or a donor (allogeneic). Autologous HSCT generally treats cancers (e.g., multiple myeloma, a common indication), while allogeneic HSCT is predominantly for hematologic diseases (e.g., acute leukemia, mainly chronic myeloid leukemia). Stem cell sources include bone marrow, mobilized peripheral blood (the primary source in autologous HSCT and increasingly used in allogeneic HSCT, allowing for faster reconstitution), and umbilical cord blood (a safe and available alternative)[5].

In autoimmune diseases, HSCT aims to reboot the immune system by purging the pre-existing immune system and regenerating a new one. Growing evidence suggests that autologous HSCT restores immune tolerance by stimulating thymopoiesis, diversifying T-cell receptors, and increasing FoxP3+ regulatory T cells, crucial for self-tolerance[7].

Autologous transplantation presents a promising therapeutic approach for inducing long-term remission and achieving a cure in autoimmune diseases that do not respond adequately to conventional drug therapy. The infusion of autologous hematopoietic stem cells, previously collected and stored, allows the administration of higher doses than would be tolerated with standard doses, thus avoiding limiting toxicities. This procedure is particularly attractive in the treatment of patients with aggressive but chemotherapy-sensitive malignancies, such as certain types of non-Hodgkin's lymphoma and Hodgkin's disease[7].

In the setting of relapsed diffuse large B-cell lymphoma, autologous HSCT plays a crucial role. It can significantly extend progression-free survival, even as part of initial treatment in high-risk patients. Those experiencing disease relapse after a prior autologous transplant may still achieve successful outcomes with reduced-intensity allogeneic HSCT[7].

Allogeneic engraftment success requires immunosuppressive therapy or pre-HSCT conditioning (often chemo/radiotherapy in malignancies). Regimens are myeloablative (high-dose) or reduced-intensity (moderate-dose), chosen based on diagnosis, age, and comorbidities. Reduced-intensity regimens have expanded access to HSCT, but finding a compatible donor in time remains a challenge[5].

Both acute and chronic forms of leukemia represent the most common indications for allogeneic stem cell transplantation. The mechanisms underlying the efficacy of HSCT in leukemia treatment are multifaceted, involving not only the high doses of chemotherapy and radiation administered to patients before stem cell infusion, but also the immune-mediated graft-versus-leukemia (GVHL) response, which mirrors the phenomenon of GVHD.[5]

GVHD is one of the main complications of HSCT, resulting from the activation of donor T lymphocytes against recipient tissues. This exact mechanism of T lymphocyte-mediated cytotoxicity is also responsible for the ECL effect, considered one of the main therapeutic benefits of transplantation. Thus, GVHD and GVHL share similar immunological pathways, involving the recognition of host antigens by donor T cells, especially in contexts of partial minor histocompatibility antigen (MiHA) mismatch[16,17].

This overlap makes the balance between GVHL and GVHD a central therapeutic tension in allogeneic HSCT practice, since, while GVHL contributes to the elimination of residual neoplastic cells and reduces the risk of relapse, GVHD can generate severe toxicities, directly impacting patient morbidity and mortality. Studies show that strategies such as T-cell depletion or the use of immunosuppressants can reduce GVHD, but often compromise the efficacy of GVHL. Although preclinical models indicate promising pathways for separating these responses, definitive clinical evidence remains limited. Current research focuses on developing approaches that selectively enhance the antitumor response of donor T cells, such as the infusion of specific dendritic cell subsets, the use of natural killer (NK) cells, or gene editing of lymphocytes, without inducing the immunopathological response associated with GVHD[5,16,17].

Despite its curative potential, allogeneic HSCT is associated with significant morbidity and mortality risks. Among the most common complications are opportunistic infections, relapse of the underlying disease, and GVHD itself, which can take acute or chronic forms with systemic impacts. These risks are even more pronounced in elderly patients or those with pre-existing comorbidities, in whom the effect of conditioning regimen toxicity and prolonged immunosuppression tends to be more severe. Studies indicate that transplant-related mortality (non-relapse mortality) can range from 15 to 30% in high-risk populations, even with advances in clinical support protocols and reduced-intensity conditioning (RIC) therapies.

Therefore, careful selection of transplant candidates and intensive post-HSCT monitoring are essential to minimize risks and optimize outcomes[5].

Historically, long-term outcomes in malignant disease have been influenced by patient age, donor origin, and disease stage. Patients who achieve early clinical remission generally have significantly better prognoses compared to those who experience multiple relapses or who no longer respond to chemotherapy[5].

In addition to acute transplant complications, the importance of long-term follow-up of patients undergoing HSCT, especially allogeneic HSCT, is crucial. Long-term survivors are at increased risk for several late adverse events, such as the development of secondary neoplasms, organ dysfunction (pulmonary, liver, kidney), osteopenia, endocrine alterations, and metabolic disorders. Continuous clinical surveillance and periodic laboratory and imaging tests are essential for the early detection of these conditions and the implementation of appropriate prevention and intervention strategies[5].

Allogeneic hematopoietic stem cell transplantation not only plays a key role in the treatment of malignant diseases but also offers effective therapy for a wide variety of non-malignant diseases, which include conditions such as hemoglobinopathies (such as thalassemia and sickle cell disease), congenital or acquired bone marrow failure syndromes, primary immunodeficiencies, and inherited metabolic disorders. In each of these diseases, donor cells can correct the underlying anomaly, either through direct reconstruction of the hematopoietic and immune systems or through indirect delivery of enzymes or other essential components through cell membranes. Hemoglobinopathies, such as thalassemia, sickle cell disease, and other complex disorders, often result in considerable morbidity, reduced quality of life, and premature death due to the combination of anemia, hemolysis, iron overload, and ineffective erythropoiesis[5].

In mantle cell lymphoma (MCL), an aggressive, historically incurable lymphoproliferative neoplasm, the choice of first-line autologous HSCT was initially indicated based on data from the pre-rituximab era, as a consolidation strategy to prolong survival. With the introduction of intensive induction regimens containing rituximab and high-dose cytarabine (HiDAC), the benefit of autologous HSCT on overall survival (OS) has been questioned, especially in patients who achieve a complete response after chemoimmunotherapy. Recent studies and meta-analyses suggest that the benefit of consolidative transplantation depends on the intensity of the induction regimen and minimal residual disease (MRD) status, being more evident in patients who have not received intensive therapies or who remain MRD-positive after induction. Allogeneic HSCT is generally reserved for refractory or relapsed cases, especially in young patients with chemoresistant disease, given the curative potential associated with the GVHL effect. However, it carries greater toxicity and risk of GVHD. There is still no definitive consensus, and current management of MCL is moving toward individualized approaches guided by initial response, MRD status, and patient risk profile[5,18].

Despite recent advances, HSCT is still associated with a series of early and late complications, such as opportunistic infections, cumulative organ toxicity, relapse of the underlying disease, secondary neoplasms, and persistent immune dysfunction. These events negatively impact the quality of life and OS of transplant patients, especially in more vulnerable populations, such as the elderly and patients with comorbidities. In this scenario, emerging therapeutic strategies are being explored to optimize the efficacy and reduce the toxicity of HSCT. The incorporation of CAR-T cell therapy, especially in lymphoproliferative neoplasms, has shown promising results, as discussed above, and may become a first-line alternative in specific subgroups. Furthermore, allogeneic cell therapies with NK cells, gene-editing techniques such as CRISPR-Cas9 for the correction of inherited hematologic defects, and selective immunomodulation approaches have the potential to redefine the management of transplant patients in the coming years. The future of HSCT is moving towards more refined personalization, with risk-based protocols, MRD monitoring, and genomic surveillance, to increase therapeutic efficacy and reduce associated complications[19-21].

Post-transplant secondary malignancies

With increased survival, continuous care (pre, during, and post-transplant) is essential to detect late complications that impact quality of life, increase morbidity, and can reduce the life expectancy of survivors[22]. It is important to note that most fatalities after HSCT occur during the first 24 months after the procedure. However, long-term survivors remain susceptible to late complications that can result in higher morbidity and mortality than the general population of the same age and gender[23].

Recurrence of the underlying primary disease is widely recognized as the leading cause of late mortality and treatment failure in the first 2 to 4 years after HSCT. Furthermore, chronic graft-versus-host disease, infections, toxicity, and secondary solid cancers also emerge as significant factors contributing to late mortality. It is important to note that patients who do not experience disease recurrence during this initial period have relatively high subsequent survival rates. The literature indicates that disease recurrence, cGVHD, organ failure, and secondary cancers are common causes of death in later stages[22,23].

Large-scale multicenter studies have contributed to a better understanding of the incidence and risk factors involved. A retrospective analysis by the Center for International Blood and Marrow Transplant Research (CIBMTR) involving 28,874

patients undergoing allogeneic HSCT demonstrated that the cumulative rate of development of secondary solid neoplasms was approximately 3.5% at 15 years. Kaplan-Meier survival curves showed a significant decrease in OS after diagnosis of these neoplasms, particularly for cases involving the oral cavity and gastrointestinal tract[24].

Similarly, a cohort study conducted by the European Society for Blood and Marrow Transplantation (EBMT) with more than 16,000 patients followed longitudinally demonstrated a cumulative incidence of secondary malignancies of 2.7% at 10 years. The risk was significantly higher in individuals with cGVHD and prolonged use of immunosuppressants, especially calcineurin inhibitors[25,26].

According to the CIBMTR, patients who required immunosuppression for more than 24 months due to GVHD had a four- to six-fold increased risk of developing secondary solid tumors. These findings highlight the importance of prolonged and structured oncological monitoring of these patients. Current EBMT guidelines recommend active clinical surveillance for at least 10 years after HSCT, with special attention to sites such as the oral mucosa, skin, and gastrointestinal tract, reinforcing the role of dentistry in the early detection of suspicious oral changes[24-26].

Secondary neoplasms represent a cause of mortality that affects up to 10% of patients undergoing HSCT who survive at least 2 years after the procedure. These neoplasms can be broadly classified into three main categories: PTLD, hematologic malignancies, and solid cancers. It is noteworthy that, within an average observation period of 2 to 5 years after transplantation, the emergence of malignancies can already be identified. Lymphoproliferative disorders and hematologic malignancies post-transplant tend to manifest earlier after the procedure, and their incidence tends to stabilize after approximately 10 years. Studies from the CIBMTR show a standardized incidence ratio (SIR) of 2.2 (95% confidence interval (95% CI) 2.0-2.4) for solid tumors, with a cumulative risk of 3.3% at 15 years post-HSCT. In particular, oral cavity tumors have a risk seven to 16 times higher than that of the general population. Kaplan-Meier curves show a sharp decline in OS after the diagnosis of oral SCC. The interval between HSCT and oral cancer ranges from 2 to >17 years (mean ~8 years)[22,27-31].

PTLD is predominantly found in patients undergoing allogeneic HSCT and encompasses a variety of lymphoid proliferations, with B lymphocytes being the most frequently involved due to Epstein-Barr virus (EBV) infection. This clinical picture usually manifests in the early stages after transplantation, with more than 80% of cases diagnosed within the first year post-transplant[22].

Monitoring EBV DNAemia has become a fundamental tool in the prevention and early diagnosis of PTLD, particularly in centers using rituximab as prophylaxis. An extensive European multicenter study involving 4,466 allogeneic HSCTs demonstrated that the overall frequency of EBV-PTLD was 3.22%, reaching 11.2% in cases with unrelated and mismatched donors, and with an attributable mortality rate of up to 84.6%[32,33].

EBV-DNA positivity $\geq 10^4$ copies/mL in the first week after diagnosis was strongly associated with increased PTLD-specific mortality. Despite the prophylactic use of rituximab and reduced immunosuppression, relapse or refractoriness to treatment still represents a therapeutic challenge. Recently, the use of tabelecleucel, an allogeneic EBV-specific T cell product approved in the European Union, demonstrated significant clinical benefit, with objective response rates of 50% in the post-HSCT group, with no fatal adverse events related to therapy. These data reinforce the importance of regular viral surveillance, especially in recipients from alternative donors, and highlight the advancement of T cell-based therapies as promising prospects[32,33].

Recent studies have reinforced the role of clonal hematopoiesis of indeterminate potential (CHIP) as a predictive marker for the development of secondary hematologic malignancies after HSCT. The presence of somatic mutations in genes such as TP53, DNMT3A, TET2, ASXL1, and RUNX1 in pre-transplant samples has been associated with a significantly increased risk of secondary leukemias and myelodysplastic syndrome, particularly in autologous HSCT recipients[34-41].

Mutations in TP53, for example, not only correlate with a higher risk of malignant transformation but also with a worse prognosis and reduced response to treatment after the neoplasm develops. The study by Gibson et al.[40] demonstrated that patients with detectable CHIP before HSCT had a significantly higher cumulative rate of acute myeloid leukemia after transplantation, regardless of the conditioning regimen used. These findings point to the relevance of pre-transplant genetic screening strategies, aiming to identify high-risk individuals and potentially adapt clinical management and long-term follow-up[34-41].

Solid neoplasms can affect a wide variety of organs. In the context of HSCT, several exposures are associated with late complications affecting specific organs. Majhail[22] describes these exposures as including the administration of electroconvulsive therapy (ECT) as part of the pre-transplant conditioning regimen, the development of GVHD, and the prolonged use of corticosteroids or calcineurin inhibitors. Continuous administration of immunosuppressive medications after transplantation increases cancer susceptibility due to reduced immune surveillance. In particular, azathioprine is one of the immunosuppressants that most increases the risk of developing secondary neoplasms. It is important to emphasize that the risk of late complications in specific organs tends to increase over time, making active surveillance an essential recommendation for all HSCT survivors[31].

The identification of conditions such as FA, dyskeratosis congenita, or Li-Fraumeni syndrome is associated with a significantly increased risk of secondary cancers. In patients diagnosed with hematologic malignancies, a propensity for developing secondary neoplasms is observed in cases of acute myeloid leukemia and myelodysplastic syndrome. Furthermore, multiple myeloma has also been linked to an increased incidence of secondary cancers[28].

In pediatric HSCT, endocrine disorders are common, affecting more than 60% of long-term survivors, especially those who underwent transplant before age 10. Thyroid disorders, including central hypothyroidism, non-autoimmune thyroid dysfunction, autoimmune diseases, thyroid abnormalities, and nodules, are common. Pediatric survivors have a higher risk of developing thyroid nodules and cancer, with secondary thyroid carcinoma (STC) being the most common type after HSCT[42].

Individuals who undergo radiation therapy at a young age and receive higher doses are at increased risk of developing secondary malignancies. Furthermore, genetic factors may play a role in this scenario, as the use of donors incompatible with human leukocyte antigen has been associated with the development of subsequent malignancies[43]. The increased risk of radiation-related malignancies and other long-term adverse effects, especially in children, has encouraged research into therapeutic approaches that avoid radiation, including dose fragmentation and the development of protocols that do not rely on radiotherapy[28].

Although reduced-intensity, radiation-free protocols are increasingly being developed, especially to minimize late toxicities and the incidence of secondary malignancies, clinical evidence still supports the role of total body irradiation (TBI) in specific contexts. The international multicenter FORUM Trial, published in 2021, demonstrated that the combination of TBI with etoposide resulted in better OS and relapse-free survival (RFS) rates compared to radiation-free chemotherapy regimens in pediatric patients with acute lymphoblastic leukemia (ALL), with a 2-year OS of 91% vs. 75%, respectively. These results reinforce that replacing TBI with less toxic regimens should still be cautious in specific pediatric populations, despite the potential benefit in reducing long-term adverse effects[44].

In adults, the use of RIC regimens has shown promise for reducing HSCT toxicity without completely compromising clinical outcomes. In the randomized clinical trial BMT CTN 0901, involving 272 adult patients with hematologic malignancies, myeloablative regimens demonstrated better disease control (65.3% vs. 47.3% RFS at 18 months), but with greater non-relapse-related toxicity, resulting in higher mortality from non-disease-related causes. RIC regimens, on the other hand, showed a superior safety profile, especially in older patients or those with comorbidities, reinforcing their clinical applicability in specific settings. These findings support the individualization of conditioning regimen selection, considering disease risk, age, and the patient's clinical condition[45].

Post-transplant solid tumors

Although HSCT is the primary treatment for bone marrow failure, individuals who undergo this procedure face a considerable risk of developing secondary solid cancers[46]. Specifically, cancers arising in the oral cavity and pharynx are reported to be approximately seven to 16 times more frequent than secondary cancers in other parts of the body[31].

Large-scale cohort studies have demonstrated a substantially elevated risk of solid tumors among HSCT recipients, especially in the long term. A CIBMTR study, which analyzed 28,874 patients undergoing HSCT from 1987 to 2012, estimated a SIR of 2.2 (95% CI 2.0-2.4) for the development of solid tumors compared with the general population. The absolute cumulative risk at 15 years post-transplant was 3.3% (95% CI 3.0-3.7) for all types of solid cancers, with higher incidences observed for tumors of the oral cavity, liver, and upper gastrointestinal tract[47].

Another European cohort study conducted by the EBMT, including 13,367 patients with a mean follow-up of 10.3 years, found a SIR of 2.1 (95% CI 1.9-2.3), with an absolute risk of 4.2% for solid tumors at 20 years of follow-up. Non-melanoma skin cancers, oral SCC, breast cancer, and hepatocellular carcinoma were the most frequently reported. It is noteworthy that patients who received allogeneic HSCT with myeloablative conditioning had a higher risk, especially in the presence of cGVHD[48].

Di Bartolomeo et al.[49] report that this predisposition is associated with the chemotherapy and radiotherapy treatments used in the conditioning phase of the transplant, as well as with the possible occurrence of GVHD49. It is estimated that the likelihood of developing head and neck cancer, for example, is 500 to 700 times greater in patients undergoing HSCT compared to the general population. Typically, there is a latency period of 3–5 years before secondary solid cancers manifest after HSCT; however, after this initial period, the incidence of these cancers continues to increase progressively over time, with no plateau observed in their frequency[22,50].

The origin of secondary neoplasms after transplantation is complex and involves multiple factors. Several risk factors have been identified, and different pathways may contribute to the development of distinct solid tumors. The relationship between age at transplantation and the risk of secondary neoplasms is the subject of studies with varying results. There is evidence

that younger patients may be at higher risk, especially when pre-transplant conditioning involves irradiation[16]. Furthermore, the recipient's older age at the time of transplantation emerges as a relevant risk factor for the emergence of secondary solid tumors, especially in the context of autologous transplantation[51].

In general, immunosuppressive medications inhibit the abnormal immune response, primarily by reducing the T lymphocyte population. This results in a decrease in acute and chronic rejection rates. Concomitantly, these medications can also compromise immune surveillance, which in turn favors viral persistence and stimulates the proliferation and survival of abnormal cells[52].

In addition to the duration of immunosuppression, the specific nature of the agent used strongly influences post-HSCT carcinogenesis. Azathioprine, frequently used in the management of cGVHD, has been associated with a significantly increased risk of solid tumors. In a multicenter cohort of 6,845 allogeneic HSCT recipients, Curtis et al.[53] observed an eightfold increased risk of skin and oral mucosal neoplasms in patients who used azathioprine for more than 2 years (hazard ratio = 8.4; 95% CI 3.2-22.5). This increase was attributed to the incorporation of 6-thioguanine into DNA, which, under exposure to ultraviolet radiation, generates potentially oncogenic mutations[53].

Similarly, calcineurin inhibitors such as cyclosporine and tacrolimus, while essential in preventing graft rejection, also contribute to oncogenesis. These drugs inhibit the function of CD8+ T lymphocytes and NK cells, which are necessary for antiviral surveillance, and promote the production of transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF), factors that facilitate tumor angiogenesis and suppress the apoptosis of altered cells. This selective immunosuppression creates an environment conducive to the persistence and reactivation of oncogenic viruses such as HPV and EBV, increasing the risk of neoplasia in epithelial and lymphatic sites. This pharmacological interaction with viral immunity reinforces the need for specific screening strategies and individualized follow-up protocols for HSCT survivors with a prolonged history of immunosuppression[54,55].

Furthermore, there is a notable increase in the incidence of mucosal malignancies in HSCT recipients, and this correlation appears to be directly associated with increased susceptibility to HPV infection in a context of immunosuppression and dysfunction of the cellular immune response, especially in the presence of cGVHD. Persistent infection with high-risk HPV strains, such as 16 and 18, with evasion of antiviral immunity, favors tumor transformation in the oral, genital, anal, and oropharyngeal mucosae[52].

In a longitudinal study of 82 female HSCT recipients followed for up to 20 years, the cumulative prevalence of genital HPV was 4.8% at 1 year, rising to 40.9% at 20 years post-transplant (p<0.001). Women with a pre-transplant history of HPV were six times more likely to have persistent infection [odds ratio (OR) = 6.5; 95% CI 1.65-25.9], and those with genital or extensive GVHD had an increased risk of severe dysplasia (OR = 13.1; 95% CI 1.59-108.3). Although this study was exclusively female, additional data from the BMT Survivorship Study (BMTSS) registry, with almost 8,000 survivors (4,642 males and 3,991 allogeneic), demonstrated a SIR of 1.8 (95% CI 1.3-2.3) for oropharyngeal carcinoma and a SIR of 9.4 (95% CI 6.3-13.6) for cervical cancer post-HSCT, with an increased risk in patients with cGVHD (HR ~4 to 6)[54,55].

In histopathological studies of oral SCC from HSCT survivors, many cases did not present exposure to classic factors such as tobacco or alcohol. Still, they were associated with chronic mucocutaneous inflammation and persistence of high-risk HPV, especially 16 and 18. The viral oncoproteins E6 and E7 are involved in the degradation of tumor suppressor proteins (p53 and Rb), promoting evasion of apoptosis and uncontrolled epithelial proliferation in immunosuppressed tissues[56].

A study from Inamoto et al.[46] demonstrated that the frequency of secondary solid tumors did not vary significantly depending on the donor type or compatibility with allogeneic donors. In contrast, information on secondary solid cancers after autologous hematopoietic stem cell transplantation is scarce in the literature, mainly due to the frequent recurrence of malignancies after this type of transplant, making it difficult to conduct long-term follow-up studies to investigate secondary tumors. Some studies have identified differential risks of secondary cancers based on the underlying conditions that led to the transplant or the gender of the recipient. Notably, male recipients had a higher risk of developing tumors in the skin and oral cavity compared to female recipients. Furthermore, the risk of secondary cancers was found to be elevated in patients with acute leukemia or chronic myeloid leukemia, but not in individuals with lymphoma or severe aplastic anemia[46].

FA is a rare genetic condition with autosomal recessive inheritance and X-linkage, presenting remarkable phenotypic heterogeneity. It is characterized by aplastic anemia, progressive pancytopenia, a propensity for spontaneous and induced chromosome breaks, as well as congenital malformations such as short stature, hypoplastic thumbs, skin moles, and cardiac and renal anomalies. These features may suggest the diagnosis, confirmed by cytogenetic studies such as the diepoxybutane (DEB) test, which assesses the abnormal increase in chromosome breaks and repairs. Additionally, individuals with FA have a marked predisposition to hematologic disorders such as myelodysplastic syndrome and acute myeloid leukemia, as well as solid tumors, notably SCC of the head and neck and genital region. Hematologic abnormalities manifest in more than 90% of patients with FA, usually beginning around age 7[49,50,57,58].

This group of patients has an increased risk of cancer due to defects in DNA repair, a key molecular phenotype of the disease. Notably, the risk of HNSCC is up to 700 times higher in individuals with FA compared to the general population. These patients are more prone to aggressive disease, multiple primary malignancies, early cancer onset, and local recurrence. Currently, allogeneic hematopoietic cell transplantation is the only proven curative and effective therapeutic approach for these patients[57,58].

Although HSCT is the only curative treatment for bone marrow failure, it increases the predisposition to early malignancy in patients with SCC. It contributes to the development of other severe morbidities due to pre-transplant conditioning regimens, prolonged periods of immunosuppression, and the severity of GVHD. It is recommended that this group of patients undergo regular screening for potentially malignant oral diseases and cancer every 3 to 6 months. Patients with SCC are significantly sensitive to alkylating agents and ionizing radiation, a phenomenon linked to chromosomal instability. As a result, surgical treatment alone is generally the preferred approach for those who develop SCC, and it is often effective for localized tumors[57,58].

Among the most common solid tumors in patients undergoing HSCT are those affecting the oral cavity, esophagus, breast, thyroid, colon, and skin. It is important to emphasize that the prognosis of solid cancers is greatly affected by the stage at which they are initially identified[27,51].

Regarding malignant lesions in the oropharynx, oral SCC is the most common form of cancer diagnosed in these individuals. The main risk factors generally associated with the general population include tobacco and alcohol use. Furthermore, HPV and other viruses have also been identified as possible contributors to the pathogenesis of these cancers. Other reported risk factors include unfavorable socioeconomic conditions, dietary habits, tylosis, poor oral hygiene, use of chewing tobacco, chewing betel nut, occupational exposure, radiation exposure, and genetic predisposition[46].

It is important to note that chromosomal instability resulting from defective DNA damage repair may offer a plausible explanation in patients with stem cell impairment, since these patients do not exhibit traditional behavioral risk factors such as tobacco and alcohol use[50].

Among the areas of the oral cavity, it is notable that the tongue is affected in approximately 60% of cases, in contrast to a rate of 10-20% in the general population. This disparity can be attributed to the remarkable replication rate of lingual mucosa cells, constantly subjected to mechanical stimuli due to tongue movements. Studies estimate that the renewal period of the gingival epithelium lasts 41 to 57 days. At the same time, the cell cycle of the cells present on the dorsal surface of the tongue is substantially shorter, around 5 days. The high rate of cell renewal contributes to a statistically increased probability of errors during DNA replication, becoming particularly significant in patients with FA[49].

In general, complex oral problems and extensive dental caries are common in individuals with cGVHD. Consequently, the tongue frequently suffers traumatic injuries due to friction with rough and sharp tooth surfaces. Furthermore, attempts to repair DNA damage can result in a potential increase in replication errors in this context. However, it is essential to note that the incidence of oral cancer in the tongue has shown a global increase[49].

Scientific literature indicates that adenocarcinoma is the most prevalent type of solid tumor in countries with low smoking rates, while SCC leads the statistics in countries with high smoking rates. In the general population, Barrett's esophagus is the leading risk factor associated with the development of esophageal adenocarcinoma. Among the factors already identified as contributing to the development of Barrett's esophagus are European ethnicity, advanced age, overweight, and long-term gastroesophageal reflux symptoms. It is important to note that the risk of secondary cancer, specifically esophageal cancer, was significantly increased in patients with persistent chronic graft-versus-host disease and those undergoing long-term immunosuppressive therapies. Notably, cGVHD with extensive features has emerged as a significant risk factor for the development of esophageal cancer[46].

In addition to monitoring neoplasms that affect the general population, it is essential to note that patients with a history of cancer or who have undergone transplants are at a higher risk of developing cancers for which there are no routine screening recommendations. This includes tumors and sarcomas that arise in the central nervous system. Although there is no evidence to support clear screening guidelines, healthcare professionals should maintain constant vigilance and be highly alert to patients who exhibit pertinent symptoms. Central nervous system tumors can be particularly concerning in individuals who have undergone radiotherapy to the central nervous system region as part of previous therapies or who have received similar treatments[46].

All individuals undergoing HSCT should be informed of the risks associated with oropharyngeal and mucosal cancer and be instructed regarding early symptoms such as persistent ulcers, white or red lesions, dysphagia, or local pain. Annual evaluation by a dentist or oral surgeon is recommended, including clinical examination and, if appropriate, oral cytology. In high-risk patients, such as those with cGVHD, prolonged immunosuppressive toxicity, or a history of persistent HPV, it is reasonable to consider biannual evaluations[46,49,57].

Guidelines from the EBMT and organizations such as the American Society for Clinical Oncology (ASCO) recognize the importance of systematic screening for solid tumors in HSCT survivors. The EBMT Handbook (Long-Term Follow-up After HCT) recommends continuous surveillance throughout life, with consultations prompted by suggestive symptoms and targeted examinations of high-risk mucosae. These protocols emphasize the need for a multidisciplinary assessment, including dental evaluation, support for smoking cessation, sun protection, HPV vaccination, and clear patient guidance on self-examination and clinical warning signs[56].

Studies show that implementing structured screening programs with a multidisciplinary team is associated with better outcomes for head and neck tumors, including stage I diagnosis, reduced treatment complications, and improved quality of life. Intensive surveillance enhances the effectiveness of initial surgical treatments, often avoiding adjuvant radiotherapy, and allows for less aggressive interventions with a greater chance of cure[59].

Oral GVHD

The increase in clinical indications for HSCT and improvements in clinical care throughout the transplant process have not only resulted in improved long-term patient survival but also increased the incidence and prevalence of GVHD. GVHD represents a highly life-limiting complication associated with allogeneic HSCT and is an inflammatory condition originating from an immune rejection response mediated by donor T lymphocytes against host tissues. GVHD is the leading cause of late morbidity and mortality after HSCT. This condition can evolve into a chronic form, resulting in a systemic sclerosis-like condition characterized by cutaneous, intestinal, and ocular fibrosis, and contributes to the worsening of infectious complications due to the additional delay in immune system reconstitution[13,43,52,60].

Oral GVHD is the second most common site of GVHD, after skin involvement. This condition can manifest as damage to the mucosa of the lips, cheeks, and tongue, salivary gland involvement, and limited mouth opening. Various areas of the oral cavity can be affected, including the lips, labial and oral mucosa, tongue, palate, floor of the mouth, and gums. Therefore, comprehensive examinations, including assessment of salivary function and analysis of oral movements, are essential. Clinical manifestations are varied and can result in long-term complications, particularly affecting feeding ability, potentially leading to malnutrition and, consequently, contributing to the secondary development of malignant neoplasms[61].

Generally, clinical signs are sufficiently diagnostic, making biopsies unnecessary in most cases. However, in rare situations, when clinical signs alone are evident and suggest the presence of GVHD without involvement of other organs, or when malignancy is suspected, a biopsy is recommended. GVHD can manifest in two distinct forms: acute and chronic, each associated with characteristic pathological processes. Acute oral GVHD is highly uncommon and, if it does manifest, usually occurs within the first month after transplantation in about half of patients. A strong inflammatory component, without chronic features, characterizes it.

In contrast, cGVHD can begin as an inflammatory process, evolving to include more autoimmune and fibrotic elements, with possible variations in the clinical phenotype over time. It manifests predominantly in the oral mucosa and tongue, typically as hyperkeratosis, sclerotization, and lichenoid mucositis. These lesions have a high incidence of malignant transformation, often multifocal or metachronous, and high recurrence rates[13,57,61].

Fall-Dickson et al.[13] describe well the etiology and pathogenesis of acute GVHD, illustrating a pathological course characterized by three successive phases[13]. The first phase involves the activation of APCs, while the second encompasses the activation, proliferation, differentiation, and migration of effector cells. These steps culminate in the destruction of the affected tissue, triggering a positive feedback loop that perpetuates the pathological process. Several immune cell types, both innate and adaptive, play crucial roles in this context, including APCs (such as dendritic cells and macrophages), different subtypes of T helper cells (T helper (Th)1, Th2, Th17), regulatory T cells (Treg), B cells, and NK cells[13].

cGVHD affects approximately half of adult patients after HSCT, and its incidence has increased in pediatric patients, in parallel with the more frequent use of peripheral blood stem cell transplant protocols[13]. cGVHD typically presents as white reticular lesions or hyperkeratotic plaques similar to leukoplakia, along with erythema or ulceration. It can sometimes be confused with or worsened by other complications, such as infections. When an associated infection is suspected, it is recommended to collect samples for fungal culture and viral polymerase chain reaction (PCR) [to detect herpes simplex virus and cytomegalovirus (CMV)]. In cases of suspected malignancy, a biopsy is highly recommended, even if the slightest doubt remains[52,61].

The clinical diagnosis is established through clinical history, patient context, and clinical examination. Clinical signs suggestive of oral cGVHD include changes that resemble oral lichen planus. Although erythematous and ulcerative changes are observed, they alone do not indicate the presence of the disease. Specific symptoms related to cGVHD that affect the oral mucosa include sensitivity to spicy, acidic, and salty foods, alcoholic beverages, and mouthwashes containing alcohol and intense flavors. Symptoms associated with cGVHD that affect the salivary glands, such as xerostomia, difficulty speaking,

swallowing, and chewing, as well as changes in taste, have also been reported. Many patients report the simultaneous presence of multiple symptoms[13].

The oral cavity may be the only site affected by cGVHD in a subset of patients or serve as a highly predictive indicator of the presence of its systemic form. The National Institutes of Health (NIH) Staging Score for oral Chronic Graft-versus-Host Disease (cGVHD) is a subjective scale composed of four levels, based on the analysis of oral clinical signs, symptoms, and functional impact. Scores range from 0 to 3: a score of 0 indicates the absence of oral signs and symptoms of cGVHD; a score of 1 represents mild lesions, such as reticular striae or asymptomatic erythematous plaques; a score of 2 includes ulcerated and symptomatic lesions that cause discomfort and make solid food intake difficult; and a score of 3 involves severe pain, extensive ulcerations, and significant functional limitation, such as the inability to swallow soft foods. This grading allows the severity of oral cGVHD to be assessed in a standardized manner, contributing to longitudinal monitoring and clinical decision-making regarding the need for more intense therapeutic interventions[13,62].

The histopathological features of oral cGVHD include the presence of hyperkeratosis or thickened epithelium, a lymphocytic infiltrate in the submucosal interface, epithelial atrophy, and apoptosis and degeneration of basal cells. Epithelial thickening frequently manifests in the affected oral mucosa, possibly as a secondary response to inflammatory conditions resulting from the effector cell infiltrate. In more severe cases of oral cGVHD, the identification of apoptosis and degeneration of basal cells in tissue samples may indicate precursor events to the pseudomembranous ulcerations frequently observed in biopsies from sites adjacent to oral ulcers. Tissue sclerosis and fibrotic processes represent late occurrences in oral cGVHD, and although they are usually clinically associated with long-standing oral inflammation, the molecular mechanisms underlying these processes remain elusive[13].

Fibrosis in oral GVHD results from chronic inflammation and activation of scar-promoting pathways. Macrophages activated by interleukin (IL)-17 and colony-stimulating factor (CSF)-1 induce the differentiation of mesenchymal indicator cells into myofibroblasts, regulated by TGF-β and IL-1β. Myofibroblasts deposit collagen and extracellular matrix, leading to mucosal rigidity, trismus, and impaired speech and swallowing. Epithelial-mesenchymal transition (EMT) is also induced by TGF-β, contributing to loss of epithelial integrity and increased neoplastic risk[63].

There is no established treatment of choice for oral cGVHD, and the current focus is on managing the disease by reducing immunological damage to target tissues and alleviating symptoms. Patients can live with oral cGVHD and its adverse consequences for extended periods, making an effective management approach imperative. Oral cGVHD management continues until immunological harmonization occurs between the host system and the graft system. Attention is primarily focused on healing oral ulcers, mitigating oral pain and hypersensitivity, preserving or improving salivary function, and optimizing oral function[13].

Glucocorticoids, in conjunction with immunosuppressive agents, represent the initial reference therapy for cGVHD. However, it is essential to note that this approach can significantly increase the risk of opportunistic infections and the development of neoplasia. Expert recommendations and the specialized literature recognize high-potency topical steroids as the standard local treatment, although there is no established consensus on the appropriate implementation of topical approaches. Some studies also suggest viable alternatives. The specific stage of cGVHD13,52,62 determines the use of systemic immunosuppressants.

The treatment adopted follows the protocol for severe cases of classic acute GVHD, involving the administration of high doses of corticosteroids, with doses ranging from 1 to 2 mg/kg. Additionally, mouthwashes containing oral solutions of dexamethasone (0.1 mg/5 mL) and prednisolone (effervescent tablets, 20 mg/10 mL) are available. Oral dexamethasone solution is the first-line topical oral therapy; however, reported clinical response rates are relatively modest, with only 29-58% of patients achieving a partial or complete response within 1 month. The period of contact with the oral mucosa plays a crucial role; therefore, patients are instructed to hold the solution in their mouth for 5 minutes, avoiding swallowing, and to abstain from consuming food or beverages for 15 minutes after using the mouthwash, thus allowing for more effective application of the solution[13,61].

Tacrolimus ointment, available in 0.1% and 0.03% concentrations under the brand name Protopic, is the preferred therapy when the lips are affected by the condition. Extensive use of corticosteroids can result in irreversible lip atrophy. After application of tacrolimus, patients commonly experience a mild burning sensation. However, this treatment provides rapid and notable improvement in symptoms. In more severe or moderate cases of oral involvement that do not respond adequately, systemic immunosuppressive therapy may be initiated or intensified. In challenging situations, photopheresis is a beneficial option[61].

Additionally, cGVHD causes symptoms such as dysphagia, xerostomia, dysgeusia, or even loss of taste, resulting in anorexia and malnutrition. To alleviate hyposalivation, it is recommended that the patient maintain a frequent intake of small amounts of fluids such as water, tea, or herbal infusions. Other measures include the use of sugar-free candies or chewing gum, as well

as intraoral spray solutions or salivary stimulants (pilocarpine or anetholtrithione), moisturizing gels or sprays, and lubricants. Pain control is a fundamental component of management strategies, as topical anesthetics, such as viscous lidocaine, can be effective in reducing oral pain and improving sensitivity before meals, oral hygiene, or the application of local therapies. In cases of clinically significant oral pain, systemic analgesics, including opioids, are employed[13,61].

Regular dental evaluations are crucial for patients with oral cGVHD due to the risk of developing dental caries and secondary malignancies. Extensive dental caries is considered a serious complication that can occur late in life in individuals with oral cGVHD. Furthermore, dental evaluation plays a vital role in detecting SCC, as there is a well-established link between this type of cancer and oral cGVHD[13].

Genomic instability in oral mucosal cells can contribute to malignant transformation, and studies have demonstrated a significant correlation between a history of oral cGVHD and the presence of unstable microsatellites in the oral mucosa, indicating this predisposition to carcinogenesis. Several cohort studies demonstrate that oral cGVHD is an independent risk factor for oral SCC. A meta-analysis of nine cohorts showed a relative risk (RR) of 2.78 (95% CI 1.27-6.08) for developing oral cancer in patients with oral cGVHD compared with those without disease. In a Japanese cohort of 17,545 transplant recipients, the SIR for oral cancer was 15.7 (95% CI 12.1-20.1), with patients with extensive GVHD having a RR of 2.9 for oral cancer ($p<0.001$)[13,64,65].

For the comprehensive management of chronic oral GVHD, an interdisciplinary approach involving dentistry, hematology, and nutrition professionals is strongly recommended. The dental team is involved in early diagnosis, pain management, functional rehabilitation, and prevention of complications such as opportunistic infections and osteonecrosis. Hematology is responsible for immunological control of the disease and defining systemic therapeutic strategies, such as the use of corticosteroids or calcineurin inhibitors. Nutrition professionals play a crucial role in adjusting calorie and protein intake and managing dysphagia, xerostomia, and weight loss, aspects frequently observed in patients with oral cGVHD. Evidence suggests that early involvement of multidisciplinary teams is associated with reduced severity of oral manifestations and improved quality of life. Furthermore, guidelines such as those from the NIH Consensus Development Project and the EBMT formally recommend this integrated collaboration as a key component of long-term follow-up after HSCT[66].

DISCUSSION

The study of late complications of HSCT reveals the complexity and challenges faced by patients and medical teams related to this therapeutic modality. This review explores the evolution of HSCT as a well-established strategy for the treatment of various hematologic diseases, highlighting its increasing efficacy and its implications for oral health.

This review highlights the importance of a multidisciplinary approach in the care of post-HSCT patients, highlighting the need for continuous monitoring and professional education regarding the risks of late complications. Dentists must be prepared to identify and manage secondary malignant lesions early, directly contributing to improving the survival and quality of life of these immunosuppressed patients. Early detection of potentially malignant oral lesions is crucial for prognosis, reinforcing the essential role of interdisciplinary collaboration.

HSCT plays a fundamental role in replacing the patient's hematopoietic and immune systems, but it is associated with an increased risk of secondary neoplasms, especially oral cavity SCC. Recent multicenter studies have indicated standardized incidence ratios ranging from 5 to 17 for SCC in allogeneic HSCT survivors, particularly in the presence of oral cGVHD. These data support the need for more precise and targeted surveillance strategies.

Despite advances, significant gaps in current knowledge persist. There is no established consensus on the optimal frequency of screening for malignant lesions in the oral cavity in post-HSCT patients, nor on the subgroups that would most benefit from intensified monitoring strategies. Furthermore, the lack of specific molecular biomarkers limits the ability to detect early dysplastic or carcinomatous changes in the setting of chronic immunosuppression.

These gaps serve as a basis for future research. Considering the limited current understanding of the mechanisms that regulate post-HSCT carcinogenesis, further research is recommended to explore the role of conditioning-induced genomic instability, GVHD-associated immune dysregulation, and the persistence of oncogenic infections such as HPV and EBV. These factors, together, may contribute to the malignant transformation in previously damaged epithelial tissues.

At the same time, the importance of establishing evidence-based guidelines for the screening and prevention of solid tumors after HSCT, with an emphasis on head and neck cancer, is reinforced. Collaboration among hematologists, oncologists, dentists, and public health professionals is essential to ensure comprehensive and individualized care, focused on surveillance, early diagnosis, and management of oncological complications.

In summary, this study highlights the urgent need for structured screening and follow-up policies for patients undergoing HSCT. Strengthening translational research and developing ongoing educational programs for healthcare professionals represent essential strategies for mitigating the morbidity and mortality associated with secondary neoplasms, especially oral SCC. Only through collaborative and continuous efforts will it be possible to ensure a safer, more effective, and dignified path for patients facing the complex HSCT process.

CONCLUSION

This literature review investigated the incidence, risk factors, and mechanisms associated with the development of secondary malignancies in patients undergoing HSCT. With the increased survival of these individuals, a higher prevalence of late complications was also observed, especially hematologic and lymphoproliferative neoplasms and solid tumors, which significantly compromise the quality of life of long-term survivors.

Among the identified risk factors, GVHD stands out, especially its chronic form, widely recognized as one of the main determinants of solid tumor development, such as oral mucosal SCC. Data from cohort studies demonstrate that up to 10% of HSCT survivors may develop secondary malignancies over the lifetime, with SIRs for oral SCC reaching over 17 in populations with cGVHD. These findings reinforce the role of prolonged immunosuppression, viral persistence, and a chronic inflammatory microenvironment as promoters of oncogenesis.

Given this scenario, it is imperative to establish effective long-term oncological surveillance and screening strategies, especially for oral lesions in high-risk patients. Implementing structured screening programs and specialized dental follow-up can facilitate early diagnosis and timely treatment of secondary neoplasms, positively impacting the prognosis and survival of transplant patients.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

Not applicable.

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