CHEMOTHERAPY IN THE TREATMENT OF SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Abstract.

Head and neck squamous cell carcinomas (HNSCCs) rank as the sixth most prevalent cancer globally. Despite advancements in combined therapies, the overall survival rate after five years remains approximately 40% to 50%. The burden of HNSCC varied by region and related with exposure to tobacco-deriived carcinogens, excessive alcohol consumption, or both. HNSCC originates from the epithelial cells lining the mucosal surfaces of the oral cavity, pharynx, larynx, and sinonasal tract. The treatment options for patients with head and neck squamous cell carcinoma include surgery, radiation, and chemotherapy, used in different combinations depending on the TNM stage and primary site. Surgery or radiation alone is suitable for resectable tumors with clear margins and preservation of function. Radiation therapy is employed alongside surgery or in combination with chemotherapy for locally advanced disease. As multimodality treatments for HNSCC improve local control, there is a belief that systemic therapy with multiple agents can further enhance distant control and overall survival.

Keywords: HNSCCs, Chemotherapy, Cancer

Squamous cell carcinoma
SCC Head and neck

Head and neck squamous cell carcinomas (HNSCCs) are the most prevalent malignancies in the head and neck region, originating from the mucosal epithelium in the oral cavity, pharynx, and larynx. Globally, they rank as the sixth most common type of cancer, with approximately 700,000 cases diagnosed annually. The burden of HNSCC varies across regions and is closely associated with factors like exposure to tobacco-related carcinogens, excessive alcohol consumption, or a combination of both. In addition, there is a growing connection between oropharyngeal tumors and prior infection with oncogenic strains of the human papillomavirus (HPV), particularly HPV-16, as well as HPV-18 and other strains to a lesser extent.

Despite the advancements in multimodality therapy, the overall survival rate for HNSCC patients at the five-year mark remains at approximately 40% to 50%. This emphasizes the urgent need for improved treatment options. In this review, our primary focus is on systemic treatments for HNSCC, examining the available evidence for current standards of care as well as exploring promising strategies currently being developed. By delving into these treatment approaches, we aim to shed light on the advancements and potential breakthroughs that could enhance the prognosis and quality of life for individuals affected by HNSCC

Anatomical site

Head and neck squamous cell carcinoma (HNSCC) is a malignancy that originates from the mucosal epithelial cells lining various regions, including the oral cavity, pharynx, larynx, and sinonasal tract. The progression of HNSCC from a non-invasive state to an invasive one is a complex process that unfolds through several distinct stages. These stages encompass a continuum of changes, beginning with hyperplasia, followed by varying degrees of dysplasia that can range from mild to severe. Subsequently, the disease may progress to carcinoma in situ before finally manifesting as invasive carcinoma. Interestingly, it is important to note that the majority of patients diagnosed with HNSCC do not have a history of premalignant lesions, further adding to the intricate nature of this condition.

The heterogeneity of HNSCC can be attributed to the specific site of origin and the underlying causes that contribute to its development. Factors such as exposure to carcinogens or viral infections play a significant role in shaping the characteristics of

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HNSCC tumors. In each individual case, it is believed that normal adult stem cells or progenitor cells within the affected tissues serve as the potential cells of origin. These cells, upon undergoing oncogenic transformation, give rise to a subpopulation of cells known as cancer stem cells (CSCs). What sets CSCs apart is their unique ability to self-renew and differentiate into multiple cell types within the tumor microenvironment.[1]

Therapy

The management strategy for head and neck squamous cell carcinoma (HNSCC) encompasses a multifaceted approach comprising a blend of surgical intervention, radiation therapy, and chemotherapy. The specific combination of these treatment modalities is determined by the TNM stage and the precise location of the primary tumor. In certain cases, surgery or radiation therapy alone may be employed, depending on the unique circumstances of the patient. However, for the majority of individuals afflicted with locally advanced HNSCC, encompassing stage III and IVA/B, the accepted standard of care involves the utilization of platinum-based chemoradiation. It is noteworthy that this therapeutic regimen might also incorporate the implementation of induction chemotherapy (IC) as a sequential course of treatment preceding chemoradiation.

Patients diagnosed with HNSCC face a complex treatment landscape that necessitates an individualized approach tailored to their specific condition. The integration of surgery, radiation therapy, and chemotherapy allows healthcare professionals to effectively combat the disease and enhance the chances of a favorable outcome.

For patients with locally advanced HNSCC, the employment of platinum-based chemoradiation has become the gold standard due to its ability to simultaneously attack cancer cells through different mechanisms. This comprehensive treatment approach combines the cytotoxic effects of chemotherapy with the localized tumor destruction offered by radiation therapy. By integrating both modalities, platinum-based chemoradiation maximizes the chances of eradicating the tumor, preventing its recurrence, and improving overall survival rates.[1]

Surgery

Resection is the main curative approach for treating head and neck squamous cell carcinoma (HNSCC). It involves surgically removing tumors that are deemed resectable while aiming to preserve function. The choice between traditional open surgery and minimally invasive methods like transoral robotic surgery (TORS) or laser surgery depends on factors such as tumor characteristics and anatomy. TORS is an emerging option that offers the potential to preserve essential functions, either with or without neck dissection, and has shown promise as an alternative to chemoradiation.

In recent years, skilled surgeons have demonstrated the effectiveness of TORS in treating specific types of HNSCC, while also maintaining a high level of oncological efficacy and safety. The minimally invasive nature of TORS allows for precise tumor removal and reduces the risk of damage to surrounding healthy tissues. Furthermore, TORS has the potential to minimize postoperative complications and shorten recovery time compared to traditional open surgery.

To further investigate the outcomes and potential benefits of TORS and transoral laser surgery in the treatment of HNSCC, ongoing clinical trials are currently underway. These trials aim to gather comprehensive data on the effectiveness, long-term outcomes, and potential complications associated with these minimally invasive techniques. The results of these trials will provide valuable insights that can guide clinicians in making informed decisions regarding the optimal treatment approach for patients with HNSCC..[1]

Radiation

Radiation therapy (RT) is a crucial component in the treatment of locally advanced disease, often used in conjunction with surgery or chemotherapy. The radiation dosage administered typically ranges between 60 Gy to 70 Gy, with the specific amount determined by various factors including treatment timing and whether it is adjuvant or definitive therapy. The study revealed no significant differences in terms of local or regional control, overall survival, or final outcomes.

However, it is important to consider the potential risks associated with radiation therapy, particularly the risk of long-term toxicity. Administering doses exceeding 55 Gy to structures such as the salivary glands, pharyngeal constrictor muscle, and thyroid gland can result in debilitating conditions like xerostomia (dry mouth), dysphagia (difficulty swallowing), dependence on percutaneous endoscopic gastrostomy (PEG) tubes for nutrition, chronic aspiration, and hypothyroidis[1]

Chemotherapy

Advancements in multimodality treatment for head and neck squamous cell carcinoma (HNSCC) have improved locoregional control (LRC). Multiagent systemic therapy has the potential to further enhance distant control and overall survival (OS). Posner et al. conducted a phase III trial comparing induction chemotherapy with docetaxel plus cisplatin and fluorouracil (TPF) to cisplatin and fluorouracil (PF), followed by chemoradiotherapy (CRT). The study, involving 501 patients with stages III-IVb HNSCC, showed that TPF resulted in better OS, establishing it as the standard for select induction strategies.

However, the adoption of this practice has been limited due to the use of suboptimal CRT regimens with low-dose weekly

carboplatin instead of standard cisplatin. Subsequent studies have raised questions about the superiority of multiagent induction therapy followed by standard cisplatin-RT compared to CRT alone

Chemotherapy
Definition

Chemotherapy, also known as "chemo," involves the administration of medications aimed at eliminating or inhibiting the growth of cancer cells.[4] Cytotoxic drugs, known as cytotoxics, are utilized in chemotherapy as they exhibit toxicity towards cells. Currently, chemotherapy is a primary approach in tumor treatment. However, certain challenges impede the achievement of desired therapeutic outcomes. Nausea and hair loss are common side effects accompanying chemotherapy.

In addition to the challenges posed by tumor cells developing multidrug resistance (MDR), the use of a single chemotherapeutic agent often falls short of meeting clinical requirements. As a result, combination therapies that involve the simultaneous use of different drugs or treatment modalities, such as chemotherapy and radiotherapy, have gained significance in the field. These combination strategies aim to impede the replication, invasion, and metastasis of cancer cells, while also reducing side effects, overcoming MDR, and minimizing individual drug dosages to enhance overall therapeutic efficacy.

A notable example of a synergistic combination therapy involves the use of hydrophilic gemcitabine (GEM) in conjunction with hydrophobic paclitaxel (TAX). This combination has demonstrated synergistic activity against cancer cell proliferation while minimizing overlapping toxicities. By leveraging the unique properties of each drug, this approach enhances treatment effectiveness.

In clinical settings, another combination therapy strategy involves the use of vincristine (VCR) to arrest tumor cells in the M phase. Following a period of 6 to 8 hours, pancreatic cancer cells synchronously transition into the G1 phase. At this precise point, cyclophosphamide (CTX) can be effectively administered to specifically target and eliminate the tumor cells residing in the G1 phase...[5]

Goals

The objective of chemotherapy is to impede cellular proliferation and the multiplication of tumors, thereby preventing invasion and metastasis. However, this therapeutic approach also leads to toxic effects on normal cells.

Conventional chemotherapeutic agents primarily exert their effects on cancerous cells by disrupting the synthesis and proper functioning of macromolecules. This disruption can occur at various levels, including DNA, RNA, and protein synthesis, as well as impairing the function of preformed molecules. When the interference with macromolecular synthesis or function is significant, it can lead to cell death through either the direct cytotoxic effect of the chemotherapeutic agent or by triggering apoptosis, the programmed cell death pathway. However, it's important to note that with traditional agents, cell death may not occur immediately, as a portion of the cells may succumb to the treatment over time. This necessitates repeated administration of the medication to achieve a desirable therapeutic response.

The toxicity of cytotoxic drugs is most pronounced during the S phase of the cell cycle, which is the phase when DNA synthesis occurs. In contrast, drugs such as Vinca alkaloids and Taxanes exert their effects during the M phase, the phase responsible for cell division. These drugs specifically interfere with the formation of the mitotic spindle, a vital structure involved in the proper division of cells.

Understanding the mechanisms of action of chemotherapeutic agents at different stages of the cell cycle allows healthcare professionals to develop tailored treatment regimens and optimize therapeutic outcomes for cancer patients. By targeting specific phases of the cell cycle, clinicians can strategically administer chemotherapeutic agents to enhance their efficacy while minimizing unnecessary toxicity to healthy tissues. Ongoing research continues to explore new agents and combination therapies to further improve the precision and effectiveness of chemotherapy in the battle against cancer..[6]

In addition to the aforementioned approaches, combination chemotherapy offers a promising strategy to combat cancer. By utilizing multiple drugs simultaneously, this approach aims to enhance treatment responses and overcome potential drug resistance mechanisms. The effectiveness of combination chemotherapy arises from its ability to target cancer cells in both resting and dividing states, thereby hindering the development of resistant cell clones.

The regulation of cellular processes involved in cell proliferation and differentiation is an intricate web of interconnected genes, receptors, and signal transduction pathways. The field of cancer cell biology has made remarkable strides in unraveling the complexities of these mechanisms. Extensive research has shed light on various aspects of cancer progression, including the mechanisms of cell death (apoptosis), the formation of new blood vessels (angiogenesis), the spread of cancer cells to distant sites (metastasis), the transmission of signals within cells (cell signal transduction), the differentiation of cells, and the modulation of growth factors.

Based on this wealth of knowledge, researchers are currently focused on designing molecular targeted therapies that selectively disrupt specific pathways involved in cancer growth. These therapies can involve interventions such as targeting aberrant cell signaling pathways or angiogenesis, as well as blocking the

degradation of key proteins. By selectively impeding the underlying mechanisms driving cancer progression, these molecular targeted therapies offer the potential to inhibit tumor growth with higher precision and efficacy.

When combined with traditional cytotoxic agents, these molecular targeted therapies can synergistically enhance the therapeutic impact on cancer cells. This combination approach not only maximizes the cytotoxic effects but also minimizes the likelihood of drug resistance development. By employing a comprehensive treatment strategy that addresses multiple facets of cancer biology, healthcare professionals aim to improve treatment outcomes and enhance patient survival rates.[6]

Cell cycle phase

The cell cycle is a meticulously controlled and intricately coordinated process that directs the growth and division of cells. It is particularly crucial in eukaryotic cells and can be broadly categorized into two main phases: interphase and mitosis (M phase). Interphase, the longer phase of the cell cycle, can be further divided into three distinct stages known as G1, S, and G2. Each stage plays a vital role in preparing the cell for division and ensuring the accurate replication of genetic material. During G1 phase, the cell grows in size and carries out various metabolic activities, preparing for DNA synthesis. The S phase is dedicated to DNA replication, during which the genetic material is duplicated to ensure each daughter cell receives a complete set of chromosomes. Following DNA replication, the cell enters G2 phase, where it continues to grow and undergoes final preparations before entering mitosis. This complex series of events and regulatory checkpoints ensure that cell division occurs with precision and fidelity, allowing for the proper growth, development, and maintenance of tissues and organisms.

During the G1 phase, the cell focuses on synthesizing RNA and proteins necessary for its growth and preparation for DNA replication in the subsequent S phase. This phase is characterized by an upregulation in the production of mRNA, rRNA, and tRNA, leading to the synthesis of structural proteins and enzyme proteins crucial for cellular functions.

The S phase is a pivotal stage of the cell cycle as it involves DNA replication and the synthesis of chromosomal proteins, such as histones and non-histone proteins. Accurate replication of DNA ensures the faithful transmission of genetic information to the daughter cells during the subsequent stages of cell division, thereby maintaining genetic stability. Consequently, the S phase is a target for many chemotherapeutic drugs aiming to disrupt DNA replication and cell proliferation.

Following DNA replication, the cell enters the G2 phase, where RNA and protein synthesis associated with mitosis take place. Important molecules involved in mitotic regulation, such as microfilaments, tubulin, and key factors required for the proper progression of mitosis, are synthesized during this phase.

The M phase is the culmination of the cell cycle and includes several distinct stages: prophase, metaphase, anaphase, and telophase. During this phase, the replicated chromosomes undergo precise and equal distribution between the two daughter cells. DNA and cellular proteins are segregated, leading to the completion of cell replication.

Upon completion of the M phase, the cell may either enter a new cell cycle or temporarily exit the cell cycle and enter a resting state known as the G0 phase. Cells in the G0 phase can remain quiescent or be reactivated to re-enter the cell cycle under the influence of specific signals or mitogens.

The regulation of the cell cycle is a complex process involving the interplay of various molecular components. Cyclins and cyclin-dependent kinases (CDKs) are key regulators that control the progression of the cell cycle through different checkpoints. Additionally, signaling pathways and feedback mechanisms play crucial roles in coordinating the activities of the cell cycle machinery, ensuring proper cell division and proliferation.

Understanding the intricacies of the cell cycle and its regulatory mechanisms provides insights into the vulnerabilities of cancer cells, leading to the development of targeted therapies aimed at disrupting specific stages of the cell cycle. By selectively targeting aberrant cell cycle control in cancer cells, researchers and healthcare professionals aim to impede tumor growth and improve treatment outcomes for patients..[5]

Mechanism of action

Chemotherapeutic drugs can be classified into four main groups based on their molecular mechanisms: alkylating agents, inhibitors of nucleotide reductase and their anti-metabolites, antibiotics, and anti-tumor plant-derived drugs. The cellular processes that govern cell proliferation and differentiation are intricate and involve a complex interplay of multiple genes, receptors, and signal transduction pathways. Through extensive research in cancer cell biology, scientists have gained valuable insights into various mechanisms, including apoptosis, angiogenesis, metastasis, cell signal transduction, differentiation, and the modulation of growth factors.

Leveraging this knowledge, researchers are actively developing molecular targeted therapies that selectively inhibit specific growth pathways implicated in tumor development. These approaches include targeting cell signaling or angiogenesis, as well as blocking protein degradation, with the ultimate goal of impeding tumor growth and improving treatment outcomes.

Chemotherapy is employed in various treatment settings, including neoadjuvant, adjuvant, combined, and metastatic

scenarios. Neoadjuvant therapy is administered before the primary treatment to prepare the patient for subsequent interventions, while adjuvant therapy involves providing additional treatment alongside the initial therapy to suppress or eliminate hidden cancer cells. Adjuvant therapy has become the standard approach for several types of cancers. In combined modalities, such as chemotherapy combined with radiation, the objective is to shrink the tumor prior to surgery or pursue curative intent. This approach is commonly utilized in cancers affecting areas such as the head and neck, lung, and anal regions.

Therefore, in the realm of cancer treatment, the utilization of multitargeted therapy or combination therapy has demonstrated superiority over single-agent therapy. By employing combination chemotherapy agents with distinct mechanisms of action and nonoverlapping toxicities, the aim is to reduce both resistance and adverse effects. An illustrative example of combination chemotherapy is the curative regimen for testicular cancers, which includes the administration of bleomycin, vinblastine, and cisplatin. Additionally, combination chemotherapy is frequently employed to achieve optimal responses. It appears that by inducing cytotoxicity in both resting and dividing cells, this approach hampers the development of resistant clones.[6]

Indication of chemotherapy[4]

5- Cisplatin, an inorganic molecule, undergoes hydrolysis within cells, producing a reactive platinum complex that inhibits DNA synthesis through cross-link formation and double helix denaturation. It also disrupts DNA function by binding to DNA bases. However, cisplatin can cause side effects such as nephrotoxicity, ototoxicity, nausea/vomiting, peripheral neuropathy, increased liver enzymes, and bone marrow suppression. It is used as the primary treatment for locally advanced head and neck squamous cell carcinoma (HNSCC) with concurrent radiation therapy and as an adjuvant treatment following surgery with radiation therapy. In some cases of metastatic or recurrent HNSCC, cisplatin is utilized as part of induction chemotherapy before definitive treatment.

6- Cetuximab, a chimeric monoclonal antibody, targets and binds to the human epidermal growth factor receptor (EGFR), inhibiting oncogenic signaling pathways. It may also exert its effects through antibody-dependent cell-mediated cytotoxicity. Common side effects of cetuximab include acneiform skin rash, fatigue, diarrhea, and hypomagnesemia. In the treatment of HNSCC, cetuximab is used as a definitive primary treatment with concurrent radiation therapy and as an adjuvant treatment following surgery with radiation therapy. Additionally, cetuximab is employed in the management of metastatic or recurrent HNSCC as a therapeutic option

7- Fluorouracil (5-FU) is an antimetabolite drug that exerts its therapeutic effect by inhibiting the enzyme thymidine synthase, thereby disrupting the process of RNA synthesis. However, the use of 5-FU can be associated with several side effects, including alopecia (hair loss), bone marrow suppression, diarrhea, cardiotoxicity, and hypersensitivity reactions. In the treatment of head and neck squamous cell carcinoma (HNSCC), 5-FU is commonly employed as part of induction chemotherapy, which aims to shrink tumors before the primary treatment. Additionally, 5-FU is utilized in the management of metastatic or recurrent HNSCC, serving as a therapeutic option in those cases. It is important to closely monitor patients receiving 5-FU to ensure proper management of its potential side effects and to optimize treatment outcomes

Docetaxel is a chemotherapeutic agent that exerts its pharmacological effects by binding to microtubules, leading to the inhibition of DNA, RNA, and protein synthesis within cells. However, the use of docetaxel can be accompanied by certain side effects. These include fluid retention, alopecia (hair loss), bone marrow suppression, stomatitis (inflammation of the mouth and lips), and central nervous system toxicity. It is crucial to closely monitor patients undergoing docetaxel treatment to manage these potential adverse reactions effectively. In the treatment of head and neck squamous cell carcinoma (HNSCC), docetaxel is commonly utilized as part of induction chemotherapy, aiming to reduce tumor size before the primary treatment. It is also used in the management of metastatic or recurrent HNSCC. By understanding and addressing the associated side effects, healthcare professionals can optimize the benefits of docetaxel while minimizing its potential risks, ultimately improving treatment outcomes for patients with HNSCC

Nivolumab is a fully human monoclonal antibody of the IgG4 subclass that specifically targets programmed cell death protein 1 (PD-1), a receptor involved in negative regulation of T-cell activation and proliferation. By blocking the PD-1 pathway, nivolumab disrupts the inhibitory signaling, allowing for enhanced antitumor immune responses. However, the use of nivolumab can lead to autoimmune toxicities as a result of the overactivation of the immune system. These toxicities may manifest as colitis (inflammation of the colon), pneumonitis (inflammation of the lungs), thyroiditis (inflammation of the thyroid gland), hepatitis (inflammation of the liver), dermatitis (skin inflammation), and hypophysitis (inflammation of the pituitary gland). Therefore, close monitoring and management of these potential adverse effects are essential during nivolumab treatment.

Pembrolizumab is a fully human monoclonal antibody of the IgG4 subclass that targets programmed cell death protein 1 (PD-1), a receptor involved in regulating T-cell activation and proliferation. By blocking the negative signaling of PD-1, pembrolizumab enhances the immune response against cancer cells. However, the use of pembrolizumab can lead to autoimmune toxicities due to the overactivation of the immune system. These

toxicities may present as colitis (inflammation of the colon), pneumonitis (inflammation of the lungs), thyroiditis (inflammation of the thyroid gland), hepatitis (inflammation of the liver), dermatitis (skin inflammation), and hypophysitis (inflammation of the pituitary gland). Close monitoring and appropriate management of these potential adverse effects are crucial during pembrolizumab treatment.

Classification of chemotherapy

Chemotherapeutic agents can be classified based on their source into two categories. They can originate either from plants (derived from plant extracts) or be synthetically produced.Chemotherapeutic drugs can be further categorized into various subgroups based on their specific mechanisms of action.

Toxicity effect

The administration of chemotherapeutic agents often leads to the occurrence of side effects, which primarily arise from the mechanisms by which these drugs exert their effects. Cytotoxic chemotherapy typically targets DNA and protein expression not only in cancerous cells but also in normal cells within the patient's body. Consequently, a wide range of potential adverse effects can occur. Achieving the right balance between the desired therapeutic effect and minimizing toxicity is a significant challenge in chemotherapy, given that the therapeutic index, which measures this ratio, is often narrow.

Many chemotherapy drugs specifically target rapidly dividing cells, resulting in their rapid impact on various tissues and organs throughout the body. This includes cells in the bone marrow, gastrointestinal (GI) tract, and hair follicles. As a result, common toxicities associated with these agents manifest as myelosuppression (reduced bone marrow function), mucositis (inflammation of the mucous membranes), nausea, vomiting, diarrhea, alopecia (hair loss), fatigue, sterility, infertility, and infusion reactions.

Furthermore, chemotherapy-induced immunosuppression can significantly increase the susceptibility to infections, further complicating the challenges faced by patients undergoing chemotherapy. It is crucial for healthcare providers to carefully monitor and manage these side effects to ensure the well-being and safety of patients receiving chemotherapy. Various supportive measures, such as the use of growth factors, antiemetics, and infection prevention strategies, are employed to mitigate these adverse effects and improve the overall quality of life for patients undergoing chemotherapy. By implementing these strategies, healthcare providers aim to minimize the impact of chemotherapy-related side effects and enhance patients' treatment experience.[6]

An optimal assessment of temporal toxicity in the medical field must fulfill several criteria. Firstly, it should prioritize the patient's needs and preferences, taking into account individual values, while also being practical by relying on objective and easily quantifiable measures. Secondly, it should encompass a comprehensive evaluation. Time toxicity, in our perspective, refers to the burdens associated with the temporal aspects of cancer-directed therapies.

Time toxicity encompasses a broad range of activities and experiences that patients undergoing cancer treatment encounter throughout their healthcare journey. A wide range of activities are involved in the process of cancer treatment and care, encompassing various aspects of healthcare delivery and patient support. These activities span a broad spectrum, ranging from routine procedures such as blood draws and infusion visits to more complex tasks such as medication retrieval and clinic appointments. Patients often find themselves navigating through waiting rooms and occasionally requiring additional healthcare services, such as emergency department visits or hospitalizations.

In certain cases, extended stays in nursing or rehabilitation facilities may be necessary to ensure comprehensive care and support. Additionally, many individuals receive essential services in the comfort of their own homes, including home-based care provided by professionals such as physical therapists and nurses. All of these activities collectively contribute to the overall experience of cancer treatment and care, aiming to address the unique needs and challenges faced by individuals on their journey towards recovery and improved well-being . Additionally, it involves the coordination of care and travel arrangements, such as communicating with insurance companies and organizing transportation to healthcare facilities.

Not only does time toxicity impact patients, but it also affects their care partners who often need to adjust their schedules to align with the demands of the treatment regimen. Furthermore, the time dedicated to treatment and related activities restricts patients from participating in other personal commitments, such as attending family events, as they are bound by the constraints of their chemotherapy schedule.

To comprehensively measure time toxicity, it is essential to consider all these factors, encompassing both planned and unplanned healthcare interactions. Moreover, the assessment should acknowledge the diverse settings in which cancer care is provided. For instance, surgical, critical care, and transplantation interventions are typically intense and singular events. Therefore,

the measurement of time toxicity in such cases should focus on a shorter time frame, such as the 30 days following the intervention, taking into account overnight stays away from home. Various terms, such as home time, days alive and out of the hospital, or hospital-free days, have been used in studies to describe the time spent at home during these periods...[8]

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