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CHEMOTHERAPY FOR ORAL CANCER

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ABSTRACT:

Cancer is a pathological condition characterized by the uncontrolled proliferation of abnormal cells, leading to aggressive malignancies responsible for millions of deaths annually. Advancements in understanding the molecular mechanisms driving disease progression have significantly expanded our knowledge, facilitating the development of novel therapeutic strategies. Over the past few decades, various treatment modalities, including combination therapies, have been introduced and are now widely implemented in cancer management.

Despite growing evidence supporting targeted therapies as the future of cancer treatment, chemotherapy remains a cornerstone of oncological care, particularly in advanced malignancies where surgical intervention or radiation therapy is not feasible. While chemotherapy is associated with significant physical and psychological side effects, it continues to be a primary treatment option due to its efficacy in controlling tumor progression. Over the years, chemotherapeutic agents have played a pivotal role in cancer management, particularly in cases where other treatment modalities are unsuitable. This review provides a concise yet comprehensive analysis of contemporary advancements in chemotherapy, evaluates the current status of approved pharmaceutical agents, and explores the emerging role of targeted therapeutic strategies aimed at enhancing clinical outcomes and survival rates in cancer patients.

KEY WORDS: chemotherapy, oral cancer, side effects.

Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity[1]. The majority of these tumors present as locally advanced cases with poor prognosis. The standard treatment for OSCC includes surgery, often followed by external beam radiotherapy with or without chemotherapy in three specific scenarios: as an adjunct to surgery to enhance loco-regional control in cases with poor prognosis, for patients who cannot tolerate surgery, and for those with recurrent or persistent disease[2].

Chemotherapy refers to the use of anticancer drugs to destroy malignant cells. It plays a pivotal role in the management of recurrent or metastatic oral cancer. Oral chemotherapy offers several benefits, including a painless mode of drug administration, life-saving potential, and improved

quality of life for cancer patients[3]. The decision-making process is influenced by factors such as disease control, anticipated functional outcomes, and cosmetic considerations. Chemotherapy may serve as the primary treatment modality or be combined with radiation therapy. Over the past few decades, the use of chemotherapy has expanded, demonstrating significant improvements in patient outcomes[4,5].

Chemotherapy for oral cancer patients is typically administered in an outpatient setting. Treatment usually involves a combination of drugs to enhance tumor shrinkage, though this also increases the likelihood of side effects. When multiple drugs are used, they are generally administered sequentially every two to three weeks over a period of two to six months, depending on treatment response[6,7]. This article is intended to review the role of chemotherapy in oral cancer, mechanism of actions and its modalities.

Mechanism of Action:

Traditional oral chemotherapeutic agents exert their effects on cancer cells by disrupting cellular division, a complex multi-phase process essential for nucleic acid synthesis, including RNA and DNA, as well as mitosis (nuclear division). These agents are categorized based on their mechanism of action and the specific phase of the cell cycle they target[8].

For instance, the plant-derived alkaloid etoposide primarily acts on the G2 phase, where it inhibits topoisomerase II, thereby preventing the transition to the M phase, during which mitosis normally occurs. Similarly, antimetabolites such as hydroxyurea, mercaptopurine, methotrexate, and thioguanine target the S phase, where they interfere with nucleic acid synthesis. They achieve this either by mimicking purines or pyrimidines or by inhibiting key enzymes crucial for DNA and RNA formation.

Conversely, alkylating agents do not act on a specific phase of the cell cycle. Instead, they introduce alkyl groups into DNA, leading to cross-linking and strand breakage, which ultimately triggers cell death through a process known as alkylation[9].

Additionally, tretinoin, a derivative of vitamin A classified as a retinoid, is also considered a traditional oral chemotherapeutic agent despite not directly targeting the cell cycle. It is predominantly utilized for inducing remission in patients with acute promyelocytic leukemia (APL). While its precise mechanism remains unclear, it is believed to reduce the proliferation of APL cells and subsequently promote apoptosis[10].

Modalities of Chemotherapy

Adjuvant Chemotherapy: Adjuvant chemotherapy, administered after surgery, has not demonstrated significant benefits in recent meta-analyses.[11]

1. **Adjuvant Chemoradiotherapy:** In contrast to adjuvant chemotherapy alone, multiple studies have evaluated the combination of chemotherapy with radiation therapy. This approach, known as adjuvant chemoradiotherapy, is typically administered alongside radiation to enhance its efficacy. Studies suggest that adjuvant chemoradiotherapy is superior to radiation alone, as it reduces recurrence rates.[12]
2. **Primary Chemoradiation:** Primary chemoradiation plays a crucial role in the management of unresectable OSCC. When compared with radiation therapy alone, it has been found to improve survival rates and decrease recurrence[13].
3. **Induction Chemotherapy:** Induction chemotherapy, a combination chemotherapy regimen administered before definitive local therapy, offers several advantages, including a reduction in metastatic recurrence and tumor shrinkage, thereby improving locoregional control.[14]
4. **Neoadjuvant Chemotherapy:** Neoadjuvant chemotherapy has been investigated in oral cancer treatment to reduce surgical margins, lower distant metastasis rates, and improve overall outcomes. Studies utilizing the MACT regimen (5-fluorouracil and cisplatin) have demonstrated a significant improvement in survival rates compared to single-agent or other combination regimens. Recent studies using the TAX323 and TAX324 regimens, which incorporate taxanes along with fluorouracil and cisplatin, have shown improved survival in advanced head and neck OSCC compared to cisplatin and fluorouracil alone. However, these trials were not exclusively designed for OSCC, and questions regarding optimal chemotherapy regimens remain. Overall, the role of MACT in OSCC treatment has failed to show consistent improvements in control rates, necessitating the need for standardized NACT regimens to improve prognosis in oral cancer[15,16].
5. **Metronomic Chemotherapy:** Metronomic chemotherapy involves the administration of low-dose chemotherapeutic drugs at regular intervals, differing from standard platinum-based chemotherapy, which employs cisplatin or carboplatin at a maximum tolerated dose of 100 mg/m² every three to four weeks.

   Metronomic chemotherapy maintains consistent drug levels in the bloodstream, preventing tumor growth by inhibiting angiogenesis, modulating the immune system, and directly targeting tumor cells, progenitors, and stromal cells. Additionally, metronomic chemotherapy has anti-angiogenic effects.

   It is indicated in cases of metastasis, severe side effects from standard chemotherapy, and in cases where surgical therapy for advanced cancer is not feasible. Although metronomic

chemotherapy has advantages such as reduced waiting time, lower cost, and the feasibility of using double or triple drug combinations, its long-term outcomes need further assessment to maximize benefits for oral cancer patients[17-19].

Side Effects of Oral Chemotherapy: Myths vs. Reality

One of the most common misconceptions is that oral chemotherapy has minimal side effects. While some oral agents may be better tolerated than their IV counterparts, they still pose significant risks. Comparative studies have demonstrated that oral chemotherapy can sometimes lead to unique or even more severe side effects. For example, a phase 3 trial by Twelves et al. comparing capecitabine (an oral chemotherapeutic agent) with IV 5-fluorouracil in postoperative colon cancer patients revealed that while capecitabine resulted in fewer overall adverse effects, it was associated with a significantly higher incidence of hand-foot syndrome (60% vs. 9%) and hyperbilirubinemia (50% vs. 20%). These findings underscore the need for careful monitoring and patient education to mitigate risks associated with oral chemotherapy[20].

DISCUSSION AND CONCLUSION:

Surgical resection remains the primary treatment for OSCC. However, in patients with advanced disease and unfavorable prognoses, chemotherapy and radiotherapy play a crucial role.

Large randomized controlled trials (RCTs) have evaluated the effects of various induction chemotherapy regimens across all sites of advanced head and neck cancer. These studies confirmed that induction chemotherapy alone does not significantly benefit oral cancer patients. The role of induction chemotherapy in OSCC remains undefined, and currently, it is not considered a standard treatment for advanced OSCC[21-23].

Chemotherapy alone has been associated with an increase in survival rates in OSCC treatment. Chemoradiotherapy has shown superior outcomes, particularly in advanced cases with poor prognosis and in organ preservation protocols. Currently, cisplatin, carboplatin, 5-fluorouracil, and taxanes are the most commonly used agents.

Recent studies highlight the potential benefits of intra-arterial chemotherapy, which allows for higher drug concentrations at the tumor site while reducing systemic toxicity. The concurrent use of chemotherapy and radiotherapy has demonstrated improved survival rates in patients with head and neck cancer[24]

.However, most clinical trials have combined all head and neck cancer sites, making it difficult to interpret chemotherapy's precise role in OSCC. Further research is required to refine treatment protocols and establish standardized chemotherapy regimens for optimal patient outcomes.

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