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Metronomic Chemotherapy in Oral and Oropharyngeal Cancer

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ABSTRACT

Oral carcinomas have a high incidence rate in the Indian population. The treatment for oral carcinomas consists of a combination of surgery, radiation, and chemotherapy. Low-dose, repeated, and regular drug delivery with no extended drug-free interval characterizes metronomic therapy. In contrast to standard chemotherapy, metronomic therapy offers an alternate treatment option for oral and oropharyngeal cancer.

Key words: Metronomic chemotherapy, Oral cancer, Oropharyngeal cancer

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INTRODUCTION

Metronomic therapy is described as low-dose, repetitive, and consistent administration of drugs with no extended drug-free period. When compared to the Standard Maximum Tolerated Dose (MTD) of chemotherapy, metronomic therapy has comparable efficiency while significantly reducing the occurrence and the harmful effects of the treatment [1].

Oral carcinomas account for a significant incidence rate in Indian population [2]. It is of major concern due to the prevalent oral habits of tobacco chewing, betel quid chewing, smoking, and alcohol consumption [3]. In oral carcinomas, the mode of management is comprised of combination of surgery, radiation, and chemotherapy. Although recent advancements in cancer research and treatment methods have been done, the 5 years survival rate for oral cancer patients has stayed about 50% in recent decades. The recurrence rate is nearly 30-40%despite adequate treatment [4]. Also, conventional chemotherapy, as well as new drugs leads to adverse drug reactions that restrict dosing and also limits the efficacy of anti-neoplastic drugs [5].

Patients who have metastatic, recurring, or advanced cancer, cytotoxic chemotherapy is routinely employed [6]. The use of cisplatin as a single drug increased survival when compared to optimum supportive care alone. Since then, several combinations of chemotherapy with platinum as one of the agents have been used; nevertheless, none of them have been proven to be clearly superior, and overall survival has not increased as the number of agents used has increased [1]. Combination chemotherapy, on the other hand, resulted in higher response rates. Cetuximab when combined with cisplatin and 5 FU improved overall survival compared to cisplatin and 5 FU alone. As a result of this cetuximab was accepted by the Food and Drug Administration for application in recurrent and metastatic cancers [7]. The NCCN and ESMO guidelines recommend it as the category one recommendation for the above-mentioned indication. However, economic and logistical obstacles prevent us from using this combination in India [2].

Recent preclinical investigations have revealed that administering low dosages (one–tenth to one-third of the MTD) of certain antineoplastic drugs called as metronomic chemotherapy, on a regular basis may be beneficial as it enhances the anti angiogenic properties of the drugs. The goal of using metronomic chemotherapy for a longer period of time is to lessen the risk of side effects and to target endothelial cells as well as tumour cells which are at the proliferating stage [5]. As a result, metronomic chemotherapy is defined as antineoplastic medications that are given to patients on a regular basis at comparatively low doses, and does not include a prolonged drug-free period [8].

Following are the features of metronomic chemotherapy: [9].

- Chemotherapy is given often (dose-dense) and without intervals.
- Instead of MTD, use a biologically optimal dose

- Hematopoietic growth factors are not used.
- Preference for medications that are taken orally
- Treatment-related side effects are uncommon.
- Resistance may take longer to develop.

LITERATURE REVIEW

History of metronomic therapy

In the early 1960's after cytotoxic chemotherapeutic agents appeared, metronomic therapy had significant role in cancer treatment. The MTD is the most widely used method for calculating chemotherapy doses in order to achieve the best potential cancer cell death [10]. The MTD chemotherapy was developed as a result of a success of paediatric leukaemia treatment model [11]. MTD chemotherapy, on the other hand, causes significant harm to proliferating tissues like hematopoietic and gastrointestinal epithelial cells. MTD chemotherapy should be given with 3–4 week drug-free period to limit adverse effects and allow the patient to recuperate. The regrowth of cancer cells is unavoidable [12].

Furthermore, due to resistance development, full eradication of cancer cells with MTD chemotherapy is unusual [13]. Cancer cells have various genetic changes and may have undergone genetic evolution which leads to resistance, according to decades of research [14]. Cancer treatment is significantly more complicated as constituents of the tumour microenvironment [15]. This complicates the goal to achieve treatment or long-term management using MTD chemotherapy. Gately et al reported that metronomic chemotherapy inhibit cancer associated angiogenesis and thus help in promotion of tumour regression. While Browder et al stated that metronomic chemotherapeutic drug administration aids in overcoming drug resistance [16]. Also Emmenegger supported this study and reported lower rate of drug toxicity with metronomic chemotherapy [17].

Difference from conventional chemotherapy

While conventional cytotoxic medicines are designed to be used at MTD, metronomic chemotherapy uses doses that are lower than MTD. Unlike conventional therapy, which is normally given at predetermined intervals based on bone marrow recovery, metronomic therapy is given on a continuous basis e.g. weekly, every other day or daily [5].

In metronomic therapy, the drug's plasma concentration is maintained, whereas in conventional therapy, the plasma concentration rises and falls. Conventional therapy targets proliferating cancer cells, whereas metronomic therapy targets cells of the endothelium in tumour's developing vasculature. The goal of conventional cancer treatment is to directly cure cancer by inhibiting or destroying rapidly dividing tumour cells, whereas metronomic chemotherapy is used to control cancer by targeting angiogenesis [5]. Metronomic chemotherapy maintains a low drug level in the blood without causing major toxic side effects, reducing the requirement for supportive care. Toxicity is an issue in traditional therapy since doses are utilized at MTD. Chemotherapy is more efficient against the primary tumour than against metastasis in general. Even when administered in combination schedules at MTD, most cytotoxic drugs can only give palliative care in patients having advanced cancer.

Mechanism of action of metronomic therapy

It is a multi-targeted approach to cancer treatment which affects tumour cells and their microenvironment in both direct and indirect ways. It has the ability to stop tumour angiogenesis, boost anticancer immunity, and induce tumour dormancy.

Antiangiogenic effects: During the primary tumour's growth phase, neoangiogenesis plays a critical role and helps in formation of distant metastatic deposits and suggested as possible target for treatment [18]. In a preclinical investigation, chemotherapeutic drugs were found to have antiangiogenesis effects; however the dose schedule is important in these phenomena [19]. Metronomic chemotherapy was recently discovered to regulate the abnormal tumour vasculature [20]. When provided on a metronomic schedule and cyclophosphamide is the prototype of a chemotherapeutic agent with antiangiogenic properties [21]. Taxanes, camptothecin and vinca alkaloids have been shown to have the similar biological action in a range of cancer types [22]. Antiangiogenic drugs co-administered with chemotherapy have been shown in studies, to operate synergistically in the suppression of tumours and the development of resistance [23].

Immunomodulation: Cancer cells can evade immune surveillance by releasing cytokines and recruiting precancerous immune cells, Myeloid Derived Suppressor Cells (MDSC), and tumour associated macrophage during carcinogenesis and tumour progression [24]. The MTD of several standard chemotherapeutic drugs has been found to have immunomodulatory effects, such as induction of immunogenic cell death [25]. Studies have shown that various agents have the ability to diminish Treg and suppress MDSC using low-dose metronomic chemotherapy [26]. Cell death or signals to promote cell death can be caused by some metronomic agents [27]. All of these actions have the potential to stimulate our immune cells and cause them to fight the tumour. Due to the dynamic nature of the immune system, certain research findings may be questionable and need more clinical confirmation [28].

Cancer stem cell inhibition: Cancer cells have small number of cells that can self-renew and differentiate. Cancer Stem Cells (CSCs) are cells that can be identified by the expression of cell surface markers [29]. Chemo resistance or radio resistance, and hence anticancer treatment failure, have been closely connected to CSCs [30]. Metronomic chemotherapy showed reduced number of CSC's according to few studies [31]. In pancreatic and ovarian cancer orthotropic models, Vives et al reported that MTD chemotherapy followed by

maintenance therapy with gemcitabine and cyclophosphamide successfully eradicated CSCs [32].

Metronomic chemotherapy in oral and oropharyngeal cancers

Metronomic chemotherapy may have impacts on tumour vasculature, tumour immunity, and direct anticancer effect, according to some theories [33]. In head and neck malignancies, celecoxib and methotrexate are both active agents [34]. The most popular metronomic schedule in head and neck malignancies has been celecoxib 200 mg twice daily and oral methotrexate 15 mg/m^2 weekly. The dose of methotrexate chosen was 15 mg/m^2 because it saturates the head and neck squamous cell carcinoma tumour dihydrofolate reductase [35]. Cetuximab, Cisplatin, and 5FU were utilised in the Extreme trial [36]. It was the first time in 30 years that a regimen outperformed platinum based chemotherapy in terms of overall survival [37]. However, the expensive cost of cetuximab prevents it from being used routinely in patients in developing countries [38]. Therapy with oral methotrexate and celecoxib is a viable option for people who do not want to undertake intravenous chemotherapy or who cannot afford cetuximab [39].

Toxicity of metronomic chemotherapy

Metronomic chemotherapy is well tolerated in majority of clinical trials. Furthermore, as evidenced by several clinical trials, it may be a cost effective therapeutic choice [40]. The presence of high grade toxic effects was either unusual or non-existent. Mild nausea and/or vomiting, mild to moderate anaemia, neutropenia, leucopoenia, and lymphopenia, and also low grade tiredness, were the most prevalent adverse effects [41]. Overall, metronomic chemotherapy improves clinical outcomes, including quality of life, while posing low harm. However, the available evidence is insufficient to conclude on the toleration of these drug combinations. Some possible hazards and concerns must be considered while taking it for a prolonged period of time, especially in children. Long-term metronomic treatment can cause cumulative toxicity, which can lead to secondary diseases [5].

Resistance: The emergence of resistance to the treatment regimen used is a major problem in chemotherapy. Because endothelial cells are considered to be genetically stable, anti-angiogenic medication regimens targeting them are unlikely to induce acquired drug resistance. However, certain experimental and clinical research have shown that anti-angiogenic treatment regimens might develop escape mechanisms, supporting the concept that two mechanisms of unconventional resistance can arise: evasive resistance, which is an adaptation to avoid a specific anti-angiogenic impact, and intrinsic or preexisting tolerance [5]. Both evasive and intrinsic resistance can be manifested *via* different strategies in different tumour types. Resistance to metronomic chemotherapy develops through a complicated molecular pathway. The establishment of a resistant phenotype is influenced by a variety of elements and mechanisms. "Reduced vascular dependency" is a significant category of resistance to anti-angiogenic treatment. The resistant tumour develops in the presence of hypoxia and limited nutrition without the development of new tumour capillaries, demonstrating these resistance mechanisms. Blood vessels are damaged and coagulation occurs during anti-angiogenic therapy. As a result, the cells' anticoagulation characteristics might be part of a complicated resistance mechanism. As a result, metronomic chemotherapy might lead to resistance, which needs an assessment of its occurrence and significance [42].

Future Perspective: Majority of people are unaware about the danger of developing oral cancer [43-45]. Well-known cause includes tobacco smoking [46,47]. Metronomic chemotherapy is a new treatment technique to control specific cancers based on evidence from preclinical and clinical research. Even after a decade of clinical research, optimizing a metronomic anticancer therapy remains a challenge. As a result, future cancer research should focus on identifying the appropriate agents to utilize, based on tumour type, calculating the doses of each agent which can be used alone or in combination, and determining when to administer the drugs. New methods are developed which includes a combination of metronomic chemotherapy with traditional chemotherapy, radiation, and/or targeted therapy, and these strategies potentially explore an unlimited number of possible combinations. However, more pharmacogenetic and pharmacoproteomic study on tumour endothelial cells is needed to determine their susceptibility to metronomic chemotherapy and the best medication combination to utilize in the clinic [5].

DISCUSSION

Metronomic therapy is described as low-dose, repetitive, and consistent administration of drugs with no extended drug-free period. When compared to the standard Maximum Tolerated Dose (MTD) of chemotherapy, metronomic therapy has comparable efficiency while significantly reducing the occurrence and the harmful effects of the treatment [1]. Recent preclinical investigations have revealed that administering low dosages (one–tenth to one-third of the MTD) of certain antineoplastic drugs called as metronomic chemotherapy, on a regular basis may be beneficial as it enhances the anti-angiogenic properties of the drugs.

The goal of using metronomic chemotherapy for a longer period of time is to lessen the risk of side effects and to target endothelial cells as well as tumour cells which are at the proliferating stage [5]. While conventional cytotoxic medicines are designed to be used at MTD, metronomic chemotherapy uses doses that are lower than MTD. Unlike conventional therapy, which is normally given at predetermined intervals based on bone marrow recovery, metronomic therapy is given on a continuous basis e.g. weekly, every other day or daily. Metronomic chemotherapy maintains a low drug level in the blood without causing major toxic side effects, reducing the requirement for supportive care. Toxicity is

an issue in traditional therapy since doses are utilized at MTD.

Mechanism of action of metronomic therapy includes a multi targeted approach to cancer treatment which affects tumour cells and their microenvironment in both direct and indirect ways. It has the ability to stop tumour angiogenesis, boost anticancer immunity, and induce tumour dormancy. The most popular metronomic schedule in head and neck malignancies has been celecoxib 200 mg twice daily and oral methotrexate 15 mg/m^2 weekly. The dose of methotrexate chosen was 15 mg/m^2 because it saturates the head and neck squamous cell carcinoma tumour dihydrofolate reductase [35]. Cetuximab, Cisplatin, and 5 FU were utilised in the EXTREME trial [36]. It was the first time in 30 years that a regimen outperformed platinum-based chemotherapy in terms of overall survival [37]. However, the expensive cost of cetuximab prevents it from being used routinely in patients in developing countries [38]. Therapy with oral methotrexate and celecoxib is a viable option for people who do not want to undertake intravenous chemotherapy or who cannot afford cetuximab [39].

CONCLUSION

Oral cancer is linked to a number of risk factors. Despite refraining from established lifestyle or environmental risk factors, many people are diagnosed with oral cancer, where factors such as genetic susceptibility are thought to have a causative role. As a result, it is vital that the general public and doctors are well informed about the risk factors for oral cancer, and dentists should screen for initial signs of oral cancer during routine oral cavity examinations, especially in patients who have a history of recognized risk factors. In contrast to standard chemotherapy, metronomic therapy offers an alternate treatment option. It has a wide range of applications in clinical patient care. To demonstrate its effectiveness, randomized phase III trials comparing it to standard care are necessary.

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