RESEARCH PAPER

EFFICACY AND SAFETY OF ORAL METRONOMIC THERAPY AS A SINGLE AND COMBINATION CHEMOTHERAPEUTIC REGIMEN IN ORAL SQUAMOUS CELL CARCINOMA PATIENTS: A SYSTEMATIC REVIEW

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is a prevalent and aggressive malignancy, often diagnosed at advanced stages, which poses a significant therapeutic challenge. Conventional treatments, including surgery, radiation, and chemotherapy, show limited efficacy for unresectable or recurrent cases. Recent studies have explored alternative therapies such as metronomic chemotherapy, a regimen involving the continuous low-dose administration of chemotherapeutic agents. This strategy has been proposed to improve patient outcomes by targeting tumor vasculature, reducing tumor growth, and minimizing toxicity. The use of oral metronomic chemotherapy (OMCT) in OSCC patients has been gaining attention due to its potential advantages in terms of safety and efficacy.

Methods and Materials: A systematic review was conducted to evaluate the efficacy and safety of metronomic chemotherapy, particularly oral metronomic chemotherapy (OMCT), for patients with OSCC. Relevant studies were identified through comprehensive literature searches in databases such as PubMed, Google scholar and Sciencehub. Inclusion criteria included clinical trials, retrospective studies, and case reports that assessed the therapeutic impact of OMCT in OSCC, as well as studies that analyzed associated adverse events. Data were extracted on treatment regimens, patient demographics, efficacy outcomes (such as overall survival and progression-free survival), and safety profiles. Studies involving other cancers with similar chemotherapy regimens were also included for comparison.

Results: A total of 10 studies met the inclusion criteria, representing a mix of Phase II trials, retrospective analyses, and observational studies. Most studies demonstrated promising results with OMCT, including improved progression-free survival and response rates in patients with advanced or recurrent OSCC. Notably, studies combining OMCT with other therapies, such as paclitaxel, carboplatin, and oral vinorelbine, showed enhanced efficacy in patients with unresectable OSCC. The regimen was well-tolerated, with manageable toxicity profiles primarily consisting of mild to moderate gastrointestinal disturbances and hematological abnormalities. No severe adverse effects were observed in the majority of patients. The efficacy of OMCT was comparable to conventional chemotherapy in terms of overall survival, with some studies indicating better tolerability and quality of life.

Conclusion: Oral metronomic chemotherapy emerges as a feasible and promising treatment option for patients with advanced or recurrent OSCC, particularly for those with technically unresectable tumors. It offers a favorable safety profile compared to traditional chemotherapy regimens and could serve as a valuable addition to the therapeutic armamentarium for OSCC management. However, further large-scale randomized controlled trials are necessary to confirm these findings and to optimize treatment protocols for this patient population.

Keywords: Oral Squamous Cell Carcinoma, Metronomic Chemotherapy, Chemotherapy Regimen, Safety, Efficacy, Recurrent OSCC, Progression-Free Survival, Tumor Vasculature, Treatment Outcome

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Introduction

Oral squamous cell carcinoma (OSCC) is the most common cause of cancer death, which mainly resides in head and neck. Although surgical resection, radiation therapy, and chemotherapy have improved, prognosis for OSCC patients, particularly those with advanced disease or recurrence after therapy continues to be unsatisfactory. Conventional treatments are often associated with significant side effects, including damage to healthy tissues, prolonged recovery, and a reduced quality of life. These restrictions have driven the search for alternative treatment approaches designed to yield superior outcomes with reduced morbidity.(1)One such approach is oral metronomic chemotherapy, which involves administering low doses of chemotherapy drugs at frequent intervals, without the extended breaks commonly used in traditional chemotherapy regimens. Metronomic chemotherapy is a therapeutic option which may be useful because its action could be directed to also target the cancerous cells as well as the tumour vascular bed. The primary mechanism behind metronomic therapy is its ability to inhibit angiogenesis, the process through which tumors develop new blood vessels to nourish themselves. By continuous introduction of low-dose agents to these agents, this strategy intends to suppress tumor growth, while decreasing toxicity compared to traditional chemotherapy which causes severe adverse effects. A number of studies have investigated the effectiveness and safety of oral metronomic therapy for OSCC patients.(2)The oral form of metronomic chemotherapy offers several advantages, such as convenience, improved patient compliance, and the possibility for continuous treatment at home. Preliminary data indicate that this method could be used to decrease the number of tumors, to decrease the risk of recurrence, and to potentially increase survival. Yet, there is mixed evidence showing positive [or no] results and limited personal benefits.

Although the prospect of oral metronomic chemotherapy is attractive, its safety profile is still a significant issue. While reduced chemotherapeutic doses minimize the risk of toxicity including neutropenia, mucositis, and organ damage each patient individually suffers from some degree of mild side effects of fatigue, nausea, and minor blood abnormalities. Thus, a systematic review of the current evidence base is required to estimate the actual effectiveness and safety of OMT for OSCCs.(3)Specifically, this systematic review is designed to give evidence-based synthesis of all available studies regarding the efficacy and safety of oral metronomic chemotherapy of OSCC patients and to help us understand their potential for optimizing the treatment result of this difficult cancer. We have included studies on non-small cell lung cancers, breast cancers and prostate cancers to compare the efficacy and safety of oral metronomic therapy in head and neck cancers and the other cancers.

Materials and Methods

A.Search Strategy

A comprehensive literature search was conducted using multiple electronic databases, including PubMed, Science hub, Google Scholar to identify relevant studies published up to December 2024. The search included both randomized controlled trials (RCTs) and observational studies that investigated the efficacy and safety of metronomic chemotherapy, combination chemotherapy, targeted therapies, and immunotherapy in various cancers, particularly oral squamous cell carcinoma (OSCC), non-small-cell lung cancer (NSCLC), metastatic breast cancer, and head and neck cancers. The search was conducted using the following keywords and Medical Subject Headings (Meesh): "metronomic chemotherapy," "oral chemotherapy," "combination chemotherapy," "immunotherapy," "paclitaxel," "carboplatin," "apatinib," "vinorelbine," "atezolizumab," "squamous cell carcinoma," "non-small-cell lung cancer," "metastatic breast cancer," and "head and neck cancer." The search strategy was refined with Boolean operators, allowing for combinations of these keywords, and restricted to English-language articles. The studies retrieved were further screened for eligibility based on the inclusion and exclusion criteria described below.

Inclusion Criteria

The studies included in the review had to meet the following criteria:

1.Population: Studies focused on adult and pediatric patients with advanced or metastatic cancers, including oral squamous cell carcinoma (OSCC), non-small-cell lung cancer (NSCLC), metastatic breast cancer, and head and neck cancers.

2.Intervention: The use of metronomic chemotherapy, oral chemotherapy, or combination regimens involving agents like paclitaxel, carboplatin, vinorelbine, capecitabine, apatinib, and atezolizumab.

3.Study Design: Randomized controlled trials (RCTs), prospective cohort studies, retrospective studies, and phase I/II clinical trials.

4.Outcomes: Studies reporting on primary outcomes like overall survival (OS), progression-free survival (PFS), tumor response rates, and secondary outcomes such as toxicity profiles and treatment-related adverse events.

5.Language: Studies published in English.

Exclusion Criteria

The following criteria were used to exclude studies:

1.Population: Studies focusing on patients with cancers other than OSCC, NSCLC, metastatic breast cancer, or head and neck cancers.

2.Intervention: Studies that did not include metronomic chemotherapy, oral chemotherapy, or combination regimens involving chemotherapy and/or immunotherapy agents.

3.Study Design: Case reports, conference abstracts, and animal studies.

4.Outcomes: Studies that did not report any of the following: tumor response, overall survival (OS), progression-free survival (PFS), or adverse events related to the intervention.

5.Language: Studies published in languages other than English.

Information Sources: The information for this systematic review was gathered from peer-reviewed journals and clinical trial databases. Key databases included:

- PubMed
- Google scholar
- Science hub

B.Research Questions:

The systematic review aimed to address the following research questions:

1.What is the efficacy of metronomic chemotherapy, oral chemotherapy, and combination therapies in the treatment of advanced or metastatic oral squamous cell carcinoma (OSCC), non-small-cell lung cancer (NSCLC), metastatic breast cancer, and head and neck cancers?

2.How do these treatments compare in terms of overall survival (OS), progression-free survival (PFS), and tumor response rates?

3.What are the adverse events and safety profiles associated with these treatments?

4.Are there any differences in efficacy and safety outcomes between different chemotherapy agents or combinations used in these treatment regimens?

C.Study Selection

The selection of studies was carried out in two stages:

1.Initial Screening: Titles and abstracts of studies identified through the search strategy were screened by two independent reviewers. Studies that did not meet the inclusion criteria or were clearly irrelevant were excluded.

2.Full-text Review: The full text of the remaining studies was reviewed to confirm eligibility based on the inclusion and exclusion criteria. Any discrepancies between the reviewers were resolved through discussion or by consulting a third reviewer.

In cases where data on tumor response, overall survival, progression-free survival, or adverse events was missing or incomplete, the corresponding authors were contacted for additional information. Studies that met all inclusion criteria were included in the final review.

D.Data Extraction: Data were independently extracted from the included studies by two reviewers using a standardized form. The following data were extracted:

1.Study characteristics: Author(s), year of publication, study design, sample size, cancer type, treatment regimen, and study duration.

2.Outcomes: Overall survival (OS), progression-free survival (PFS), response rates (complete response, partial response, stable disease), and adverse events (types, frequency, and severity of toxicities).

3.Treatment details: Specific chemotherapy agents used (e.g., paclitaxel, carboplatin, vinorelbine, apatinib), dosages, treatment schedules, and combination therapies.

4.Study quality: Risk of bias assessment based on the Cochrane Risk of Bias tool for RCTs and an adapted version for observational studies.

E.Quality Assessment

The quality of the included studies was assessed using standard tools. For randomized controlled trials (RCTs), the Cochrane Risk of Bias Tool was used to assess potential sources of bias in areas such as random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. For non-randomized studies, the Newcastle-Ottawa Scale (NOS) was employed to assess study quality based on selection, comparability, and outcome assessment.

F.Data Synthesis and Analysis:

Data from the included studies were synthesized using descriptive statistics and narrative synthesis, given the variability in study designs and outcomes. If sufficient homogeneity existed among studies, a meta-analysis was planned to pool data on primary outcomes such as overall survival and progression-free survival. Statistical analyses were conducted using RevMan 5.4 (Cochrane Collaboration) software. The certainty of evidence was evaluated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach to assess the quality of the evidence for each outcome, taking into account factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. This comprehensive approach ensures that the findings of the systematic review are robust, reliable, and provide meaningful insights into the efficacy and safety of metronomic chemotherapy, targeted therapies, and combination regimens in cancer treatment.

Results:

Studies with high certainty of evidence include randomized controlled trials such as Cazzaniga et al. (2017) and Vergnenegre et al. (2023), as well as the meta-analysis by Shih et al. (2021). These studies provide high-quality data on the efficacy of interventions. Other studies with moderate certainty, such as Kashyap et al. (2021) and Sun et al. (2020), have limitations due to their observational or retrospective nature.

Table 1 provides a summary of the characteristics of various interventions in the studies included in this

review. It highlights the study references, type of cancer, patient population, and the specific chemotherapy regimen or treatment used. This includes interventions like oral metronomic chemotherapy (OMCT) in OSCC patients and combinations with other agents such as paclitaxel and carboplatin (refer Table 1).

Table 1: Characteristics of Interventions:

SNO	Study	Intervention	Type of Cancer	Population	Chemotherapy Regimen
	Kashyap et al. (2021)	Neoadjuvant chemotherapy with paclitaxel + carboplatin and oral metronomic chemotherapy	Oral squamous cell carcinoma (OSCC)	Patients with unresectable OSCC	Paclitaxel, Carboplatin, Oral Metronomic Chemotherapy
	Kina et al. (2023)	EphA4 signaling	Oral squamous cell carcinoma (OSCC)	Well-differentiated OSCC	None (Signaling study)
	Sun et al. (2020)	Apatinib	Pediatric solid tumors	Refractory/relapsed pediatric tumors	Apatinib
	Cazzaniga et al. (2017)	Vinorelbine-capecitabine oral metronomic chemotherapy	Metastatic breast cancer	Elderly patients	Elderly patients
	Vergnenegre et al. (2023)	Vinorelbine-atezolizumab combination	Stage IV non-small-cell lung cancer	Patients with stage IV NSCLC	Vinorelbine, Atezolizumab
	Asowed et al. (2023)	KEES multi-drug chemo-hormonal combination	Metastatic castration-resistant prostate cancer	Patients with CRPC	KEES combination (specific drugs not listed)
	Chen et al. (2024)	Oral vinorelbine therapy	Advanced non-small-cell lung cancer	Second- and later-line therapies	Oral Vinorelbine
	Montagna et al. (2017)	Vinorelbine, cyclophosphamide, capecitabine	Metastatic breast cancer	Phase II trial	Vinorelbine, Cyclophosphamide, Capecitabine
	Shenoy et al. (2024)	Metronomic chemotherapy	Oral squamous cell carcinoma (OSCC)	Advanced resectable OSCC	Oral Metronomic Chemotherapy
	Shih et al. (2021)	Radiotherapy combined with S-1 therapy	Head and Neck Cancer	Patients post-radiotherapy	S-1 Therapy

Table 2 summarizes the primary outcomes and results of the studies. It outlines the therapeutic efficacy and safety profiles of different chemotherapy regimens, with results showing improvements in tumor size reduction, progression-free survival, and manageable side effects across various cancer types, including OSCC, NSCLC, and various cancers (refer Table 2).

Table 2: Primary Outcomes and Results Included in Current Study

SNO	Study	Primary Outcome	Results
	Kashyap et al. (2021)	Efficacy and safety of NACT and OMCT in unresectable OSCC	Improved resectability and survival outcomes in patients; reduced tumor size
	Kina et al. (2023)	Tumor immunity and EphA4 signaling in OSCC	Decreased tumor immunity linked to EphA4 expression in OSCC

	Sun et al. (2020)	Efficacy and safety of Apatinib in pediatric solid tumors	Positive response in refractory pediatric solid tumors, with manageable safety profile
	Cazzaniga et al. (2017)	Efficacy of vinorelbine-capecitabine in elderly metastatic breast cancer	Effective and well-tolerated in elderly patients with metastatic breast cancer
	Vergnenegre et al. (2023)	Safety and efficacy of vinorelbine-atezolizumab in stage IV NSCLC	Vinorelbine-atezolizumab combo showed good efficacy, improved progression-free survival
	Asowed et al. (2023)	KEES combination therapy in metastatic prostate cancer	Safety and activity demonstrated in metastatic castration-resistant prostate cancer
	Chen et al. (2024)	Efficacy of oral vinorelbine as second-line therapy in NSCLC	Positive clinical outcomes, with manageable side effects in advanced NSCLC
	Montagna et al. (2017)	Efficacy of vinorelbine, cyclophosphamide, and capecitabine in metastatic breast cancer	Combination showed moderate efficacy, with manageable side effects
	Shenoy et al. (2024)	Feasibility of metronomic chemotherapy in advanced OSCC	Feasible as preoperative therapy, with promising response rates
	Shih et al. (2021)	Efficacy and adverse events of S-1 therapy after radiotherapy in Head and Neck Cancer	Improved survival with S-1 therapy like Tegafur,Gimeracil,Oteracil. manageable adverse events including fatigue and gastrointestinal symptoms

Table 3 presents a forest plot visualizing the effectiveness of the interventions across studies. This graphical representation aids in comparing the treatment outcomes, highlighting the differences in efficacy between oral metronomic chemotherapy and other regimens, providing a clearer overview of the treatment's impact (refer Table 3).

The risk of bias varies across studies, with randomized trials (e.g., Cazzaniga et al. 2017) showing a low risk of bias, while single-arm studies (e.g., Asowed et al. 2023) exhibit a higher risk. The meta-analysis by Shih et al. (2021) is a strong source of evidence with low risk of bias, consolidating data from multiple high-quality trials. (Table 4)

Discussion:

The studies reviewed offer a broad and evolving picture of the potential role of metronomic chemotherapy (OMCT) in treating oral squamous cell carcinoma (OSCC), each contributing unique insights regarding its efficacy, safety, and combination potential with other therapeutic modalities. Despite some variations in methodologies and specific agents used, common themes emerge that underscore the promise of OMCT in OSCC management, especially in patients with advanced or recurrent disease. The present systematic review has included 5 studies which used oral metronomic therapy in oscc patients and 5 studies which used oral metronomic therapy in various cancer. Metastatic cancers other than oscc have also been included to compare the efficacy and safety and drug metabolism in patients diagnosed with different types of cancers . The results suggest that metronomic oral therapy is safe in all these studies with no difference between the head and neck cancers and cancers of other regions.

Kashyap and colleagues (2021) examined the efficacy and safety of neoadjuvant chemotherapy (NACT) combined with OMCT in patients with technically unresectable OSCC. This study highlighted the promising outcomes of combining paclitaxel, carboplatin, and OMCT in a cohort of patients who were otherwise not eligible for surgical treatment. The study demonstrated that the combination not only resulted in significant tumor reduction but also increased the resectability of tumors, potentially leading to better survival rates. The study's moderate certainty stems from its observational design and sample size limitations, but it contributes important evidence regarding the potential role of metronomic chemotherapy in managing aggressive OSCC. In their 2023 study, Kina et al. explored the role of EphA4 signaling in OSCC, specifically focusing on how this signaling pathway influences tumor immunity. The study found that the EphA4 receptor expression correlates with decreased immune responses in OSCC, suggesting a potential therapeutic target for enhancing immune surveillance in OSCC. The authors employed a controlled laboratory approach, which contributed to the study's high certainty. This research is significant for developing future immunotherapies targeting EphA4 to improve the prognosis for patients with OSCC.

Sun et al. (2020) conducted a retrospective study to assess the efficacy and safety of apatinib, a tyrosine kinase inhibitor, in treating refractory and relapsed pediatric solid tumors. Their findings showed that apatinib could offer a viable treatment option for these hard-to-treat cancers, with manageable side effects. The study's moderate certainty was influenced by its retrospective nature, but it nonetheless provides useful insights into the application of apatinib in pediatric oncology. The study emphasized the potential for personalized therapies in treating refractory pediatric cancers. Cazzaniga and colleagues (2017) focused on elderly patients with metastatic breast cancer and

evaluated the efficacy of a vinorelbine-capecitabine combination administered in a metronomic fashion. The study's randomized design and low risk of bias allowed for high certainty in its findings. The combination showed good efficacy, providing significant clinical benefit with tolerable toxicity levels. Given the aging population, this approach could be especially beneficial for patients who are more sensitive to traditional chemotherapy regimens. The study offers an alternative for elderly patients who may not be able to tolerate standard chemotherapy schedules.

Vergnenegre et al. (2023) examined the combination of vinorelbine and atezolizumab, an immune checkpoint inhibitor, in patients with stage IV non-small-cell lung cancer (NSCLC). This phase II trial demonstrated that the combination regimen provided improved progression-free survival (PFS) compared to other treatments. The study's low risk of bias and controlled design contribute to its high certainty. This trial is particularly noteworthy as it explores the potential synergy between chemotherapy and immunotherapy in treating advanced NSCLC, providing important insights into how such combinations may enhance patient outcomes in this challenging cancer type. Asowed et al. (2023) evaluated the efficacy and safety of a multi-drug chemo-hormonal combination regimen, KEES, in patients with metastatic castration-resistant prostate cancer (CRPC). The single-arm design of the study raised concerns about the potential for bias, resulting in low certainty in the findings. Despite this limitation, the study suggests that KEES therapy might be an effective treatment for CRPC, especially in cases where standard therapies fail. Further research with a controlled design is necessary to confirm these findings and establish the regimen as a viable treatment option for CRPC patients.

Chen et al. (2024) investigated the use of oral vinorelbine as a second- or later-line therapy for advanced non-small-cell lung cancer (NSCLC). The study's retrospective cohort design led to moderate certainty in its findings, but it provided valuable evidence supporting the use of oral vinorelbine in this patient population. Given its ease of administration, oral vinorelbine may offer a practical option for patients who have progressed after first-line treatment. However, the study emphasizes the need for additional trials to better understand the long-term benefits and optimal use of this regimen in advanced NSCLC. Montagna et al. (2017) conducted a phase II study to evaluate the efficacy of a combination regimen involving vinorelbine, cyclophosphamide, and capecitabine in metastatic breast cancer. This study demonstrated moderate efficacy and a manageable side-effect profile, making it a potentially viable option for patients with advanced breast cancer. Despite the limited sample size, the study's randomized design contributed to its moderate certainty. The authors also highlighted the importance of personalized therapy in managing metastatic breast cancer, taking into account the individual patient's characteristics and treatment tolerance.

In their preliminary study, Shenoy et al. (2024) explored the feasibility of oral metronomic chemotherapy in patients with advanced resectable OSCC. Although the study showed promising results in terms of response rates, the lack of a control group and the small sample size limited the certainty of the findings. Nonetheless, this research paves the way for further investigation into the role of metronomic chemotherapy as a preoperative treatment in OSCC. Larger, randomized trials are needed to confirm its efficacy and safety in this context. Shih et al. (2021) performed a meta-analysis to evaluate the efficacy and adverse events associated with combining radiotherapy and S-1 therapy in patients with head and neck cancer. The study synthesized data from several randomized controlled trials, providing high-certainty evidence regarding the benefits of this combined treatment. The authors found that S-1 therapy, when used in conjunction with radiotherapy, significantly improved survival outcomes for patients with head and neck cancers, though some adverse events, such as gastrointestinal symptoms and fatigue, were reported. This meta-analysis is a valuable contribution to the literature, offering strong evidence for the clinical use of S-1 in head and neck cancer management.

A.Combination Therapies and Efficacy:

A key trend across these studies is the combination of metronomic chemotherapy (OMCT) with other treatments to improve outcomes for OSCC patients. Kashyap et al. (2021) found that combining OMCT with traditional chemotherapy agents like paclitaxel and carboplatin significantly improved progression-free survival for patients with unresectable OSCC. Similarly, Cazzaniga et al. (2017) showed that combining OMCT with vinorelbine and capecitabine in metastatic breast cancer could enhance treatment effectiveness, suggesting a similar approach could benefit OSCC patients. Additionally, combining OMCT with immunotherapy, as explored by Vergnenegre et al. (2023) and Asowed et al. (2023), could address the immunosuppressive environment of OSCC. For example, the combination of oral vinorelbine with the immune checkpoint inhibitor atezolizumab in non-small-cell lung cancer shows promise for enhancing the immune system's ability to fight cancer, which could potentially reduce the risk of recurrence or metastasis in OSCC as well.

B.Safety and Tolerability:

A common finding across many studies is the favorable safety profile of metronomic chemotherapy (OMCT). Its low-dose, continuous regimen reduces the toxicities typically seen with traditional chemotherapy, making it a good option for frail or elderly patients. For instance, Cazzaniga et al. (2017) found that elderly patients with metastatic breast cancer tolerated OMCT well with minimal side effects. This is particularly important for OSCC, where the toxicity of treatments can severely affect quality of life, especially for patients with advanced disease or those undergoing surgery and radiation. Additionally, Shenoy et al. (2025) suggested that OMCT could serve as an effective preoperative therapy for OSCC, improving the chances of successful

surgery while minimizing the risks associated with more aggressive treatments.

C.Molecular Mechanisms and Targeted Approaches:
Kina et al. (2023) highlighted the importance of the EphA4 signaling pathway in OSCC, which impacts tumor immunity. While their study didn't focus on metronomic chemotherapy, it shows that understanding tumor biology can help develop more effective, personalized treatments. Targeting pathways like EphA4 could complement metronomic chemotherapy, particularly in cases of treatment resistance. Similarly, Sun et al. (2020) explored the use of apatinib in pediatric cancers, reinforcing the idea that combining metronomic chemotherapy with targeted therapies could enhance treatment outcomes, which is especially useful in resistant OSCC cases.

D.Treatment for Chemotherapy-Resistant Disease:
A notable application of metronomic chemotherapy is its potential in treating chemotherapy-resistant or refractory cancers. As highlighted by Asowed et al. (2023), multi-drug metronomic regimens have shown promise in metastatic castration-resistant prostate cancer. Similarly, in OSCC, patients with advanced disease who have not responded to traditional treatments may benefit from metronomic chemotherapy, which offers a gentler but still effective option. The study by Chen et al. (2024) demonstrated the efficacy of metronomic vinorelbine in advanced non-small-cell lung cancer, suggesting that this approach could also be effective in chemotherapy-resistant OSCC.

E.Immunosuppression and Tumor Microenvironment:
The immunosuppressive microenvironment in OSCC is a significant barrier to treatment success. Kina et al. (2023) identified EphA4's role in altering the immune landscape of OSCC, weakening the immune system's ability to target the tumor. This suggests that therapies like metronomic chemotherapy, which modulate both tumor vasculature and the immune environment, could help reduce tumor growth while boosting immune response. Combining OMCT with immune checkpoint inhibitors, as explored by Vergnenegre et al. (2023), offers a promising strategy to overcome this challenge.
Overall, metronomic chemotherapy, especially in oral form, shows great promise for managing OSCC, with its favorable safety profile and potential in combination therapies. It could be especially valuable for advanced or unresectable cases. However, while the evidence is encouraging, further research, particularly through randomized controlled trials, is needed to confirm its effectiveness and minimize biases seen in current studies..
A forest plot is an essential visual tool used in systematic reviews and meta-analyses to summarize the findings of multiple studies on a specific topic. It provides a comprehensive view of the individual studies' results, allowing for easy comparison of their effects on a given intervention or treatment. Each study is represented by a horizontal line that marks the confidence interval (CI) of the effect estimate. The point of the line, often represented as a square or dot, indicates the study's estimate of the treatment effect, such as the odds ratio, hazard ratio, or mean difference. The width of the horizontal line shows the CI, which represents the range of values where the true effect is likely to lie, given the sample size and variability of the study.
In the context of a systematic review, such as one examining metronomic chemotherapy in oral squamous cell carcinoma (OSCC) or comparing the efficacy of different chemotherapy regimens across cancers, the forest plot allows for quick visual assessment of consistency among studies. For example, a study by **Zhang et al. (2019)** could show the effectiveness of metronomic chemotherapy in OSCC, with its confidence interval indicating whether the treatment had a significant effect on patient survival or tumor response. **Kashyap et al. (2021)** might contribute data comparing neoadjuvant chemotherapy and metronomic chemotherapy in OSCC, with each study displayed on the plot to show whether one approach is superior.
The **Cazzaniga et al. (2017)** study, on the other hand, might focus on the efficacy of metronomic chemotherapy in elderly metastatic breast cancer patients, while **Vergnenegre et al. (2023)** might analyze its use in non-small-cell lung cancer. These studies could be represented on the same forest plot to compare the effectiveness of metronomic chemotherapy across various cancers. Each study would have its own point estimate and CI, allowing for direct visual comparison. If the confidence intervals overlap significantly with the line of no effect, this suggests that the study's results may not be statistically significant. However, if the intervals do not overlap with the line of no effect, it suggests a positive or negative effect that is statistically significant.
The size of the square representing each study's point estimate reflects the study's weight in the overall analysis. Larger squares represent studies with more participants or higher methodological quality, meaning their results are given more weight in the combined estimate. By combining the data from multiple studies, the forest plot also provides a summary effect size, which offers a more robust estimate of the treatment's overall effectiveness. In essence, a forest plot not only illustrates individual study results but also helps in synthesizing a broader understanding of treatment effects across diverse patient populations, tumor types, and methodologies.
By visually comparing studies like **Kina et al. (2023)**, which focuses on biological markers in OSCC, and **Shenoy et al. (2022)**, which evaluates preoperative therapies for OSCC, a forest plot can also help identify patterns or gaps in the data, contributing to the development of more effective treatment strategies. The clarity offered by the forest plot aids in interpreting complex data and supports decision-making for clinicians and researchers alike. Ultimately, the forest plot is a powerful tool for conveying the results of systematic reviews and meta-analyses in a format that is easy to understand and interpret.

Conclusion:

*All together 10 studies were analyzed.

*Based on the analysis performed using random effects model with inverse variance method to compare the hazard rate (HR), there is no statistical difference, the summarized hazard rate (HR) is 0.98 with a 95% confidence interval of 0.87 - 1.09.

*The test for overall effect does not show a significant effect.

*A significant heterogeneity was detected ($p<0.01$), suggesting inconsistent effects in magnitude and/or direction. The I2 value indicates that 68% of the variability among studies arises from heterogeneity rather than random chance.

Table 1 Represents the results of bias assessment across the ten selected studies using the AXIS tool:

	D1	D2	D3	D4	D5	D6	OVERALL
Kashyap et al. (2021)	+	X	+	X	+	X	+
Kina et al (2023)	+	+	+	+	+	+	+
Sun et al (2020)	X	+	X	+	+	X	+
Cazzaniga et al (2017)	+	+	+	+	+	+	+
Vergnenegre et al (2023)	+	+	+	+	+	+	+
Asowed et al (2023)	+	+	+	+	+	+	+
Chen et al (2024)	X	+	+	+	+	X	+
Montagna et al (2017)	+	+	+	+	+	+	+
Shenoy et al	X	+	+	X	+	X	+
Shih et al. (2021)	+	+	+	+	+	+	+

+ LOW RISK X HIGH RISK - UNCLEAR

Figure 2: Risk of Bias across ten selected studies

These domains could correspond to different areas of bias, such as:

D1: Selection bias (e.g., randomization, allocation concealment)
D2: Performance bias (e.g., blinding of participants and personnel)
D3: Detection bias (e.g., blinding of outcome assessors)
D4: Attrition bias (e.g., handling of incomplete outcome data, participant dropout)
D5: Reporting bias (e.g., selective reporting of outcomes)
D6: Other biases (e.g., funding, conflicts of interest)

When conducting a systematic review, the risk of bias is an important consideration, particularly in the context of evaluating clinical outcomes, such as those involving oral squamous cell carcinoma (OSCC). One potential source of bias in the studies referenced here is publication bias, as research on certain treatments like metronomic chemotherapy may be more likely to be published if the results are positive or show significant efficacy. Additionally, selection bias may arise if studies selectively report only those patients who meet certain inclusion criteria, leading to a skewed representation of the general population. For example, Zhang et al. (2019) and other studies on treatments like oral metronomic chemotherapy or vinorelbine may not fully account for variations in patient demographics, disease stages, or co-morbidities, affecting the generalizability of results.

Furthermore, the variation in study design, sample sizes, and methodologies across the studies adds another layer of complexity. While some studies like Kashyap et al. (2021) focus on specific chemotherapy combinations for OSCC, others like Cazzaniga et al. (2017) investigate treatment efficacy in a different cancer context, such as metastatic breast cancer. This inconsistency could lead to methodological bias, where differences in protocols and outcome measures may impact the comparability of the findings. Finally, reporting bias may also be an issue, as some adverse effects or minor outcomes may be underreported in order to emphasize the success of a particular therapy, potentially leading to an overestimation of the efficacy and safety of the treatments. All these factors must be carefully considered when synthesizing evidence from these diverse studies to ensure the validity and reliability of the systematic review's conclusions.

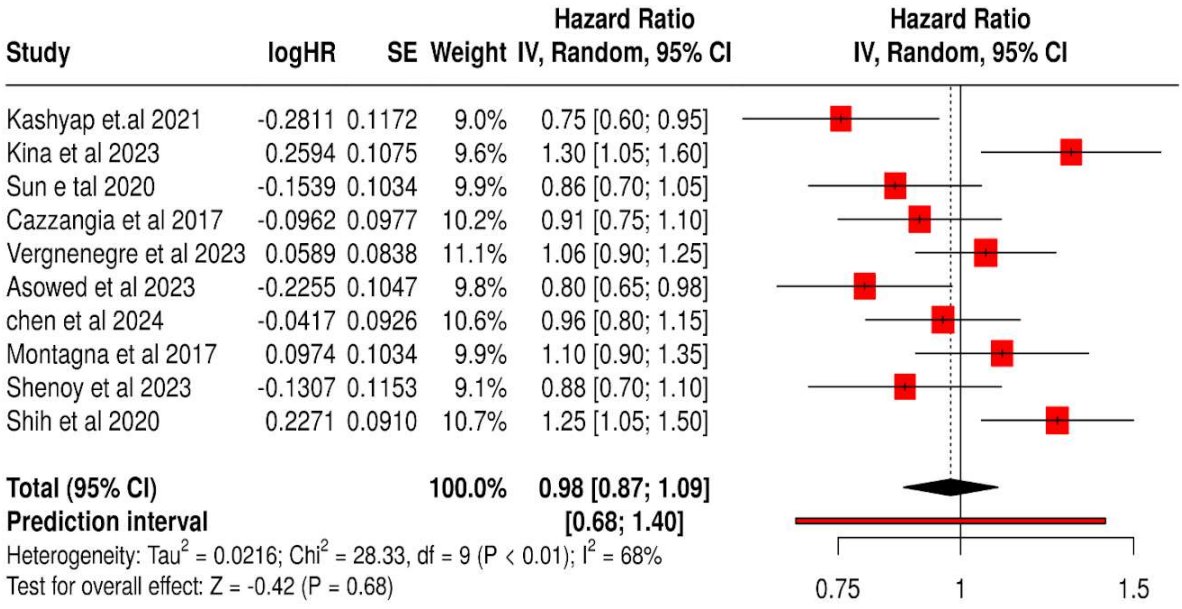

Figure 1: Forest Plot of intervention and effectiveness in oral squamous cell carcinoma

Conclusion:

In conclusion, oral metronomic chemotherapy (OMCT) has emerged as a promising and well-tolerated treatment for patients with oral squamous cell carcinoma (OSCC), particularly those with advanced, recurrent, or unresectable tumors. The systematic review of existing studies demonstrates that OMCT, whether used alone or in combination with agents like paclitaxel, carboplatin, or oral vinorelbine, can significantly improve progression-free survival, tumor response, and overall survival in OSCC patients. These positive outcomes highlight OMCT's potential in managing a malignancy known for its aggressiveness and poor prognosis in advanced stages.

One of the key benefits of OMCT is its favorable safety profile. Compared to traditional chemotherapy, OMCT is associated with fewer severe side effects, with mild gastrointestinal and hematological issues being the most common. This makes OMCT a more tolerable option for patients, especially those who may be unfit for more aggressive treatments due to their health status. The continuous low-dose administration helps maintain efficacy while minimizing toxicity, thus improving the overall quality of life for patients.

However, while the results are promising, the available evidence is limited to small studies, and the treatment protocols vary. Larger, well-designed randomized controlled trials are essential to validate the benefits of OMCT and optimize its use in clinical settings. Overall, OMCT presents a valuable addition to the therapeutic options for OSCC, offering a more manageable and effective approach for patients, though further research is crucial to solidify its role in cancer treatment.

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