Research Progress of Metronomic Chemotherapy in the Treatment of Elderly Cancer Patients

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Abstract. In China, elderly individuals (⩾60 years) face a growing cancer burden, accounting for 55.8% of new cases and 68.2% of deaths. Metronomic chemotherapy offers a promising approach by using continuous low-dose treatment to inhibit tumor growth with fewer side effects. breaking through the cycle-dependent limitations of traditional chemotherapy, this review discusses its applications and benefits for elderly cancer patients, aiming to support clinical practice, at the same time, significantly improves patient compliance and the quality of life of elderly patients.

Keywords: Metronomic Chemotherapy; Elderly Cancer Patients; Cancer Burden; Low-Dose Chemotherapy; Treatment Tolerance; Angiogenesis Inhibition; Quality of Life.

1. Preface

Globally, more than 64% of cancer cases and 70% of cancer deaths occur in individuals aged over 60. In China, the proportion of the elderly population has increased from 10.5% in 2002 to 18.7% in 2022. Concomitantly, the incidence and mortality rates of cancer in the elderly have been rising at annual rates of 2.3% and 1.8% respectively, significantly exacerbating the cancer burden [1]. Authoritative data show that in 2022, the number of new cancer cases in the elderly population (≥60 years old) reached 2.79 million (accounting for 55.8% of the national total), and the number of deaths was 1.94 million (accounting for 68.2%), among which patients over 80 years old contributed 10.0% of the incidence rate and 17.0% of the mortality rate [1]. Compared with the data in 2016, the age-standardized incidence and mortality rates in the elderly population increased by 21.7% and 14.3% respectively, highlighting the rapid deterioration of their disease burden [2]. Epidemiological characteristics show that the top five cancer types, including lung cancer, colorectal cancer, and liver cancer, account for 57.42% of new cases in the elderly, among which the incidence rates of prostate cancer and breast cancer have increased particularly significantly (annual increase >5%) [3]. It is noteworthy that elderly patients generally have multi-organ dysfunction, metabolic disorders, and comorbidities, leading to significantly reduced treatment tolerance, so clinical decisions need to be carefully balanced between efficacy and safety.

Against this background, metronomic chemotherapy, as a new treatment model, has shown unique advantages. This regimen continuously inhibits tumor angiogenesis through continuous low-dose administration, breaking through the cycle-dependent limitations of traditional chemotherapy. It maintains equivalent antitumor activity while reducing adverse reactions such as myelosuppression and gastrointestinal toxicity [4-8]. Clinical studies have confirmed that it significantly improves patient compliance and the quality of life of elderly patients [9-11]. In view of the special physiological characteristics and medical needs of elderly cancer patients, this review aims to investigate and discuss the research progress of metronomic chemotherapy in the treatment of elderly cancer patients, so as to provide guidance for the clinical application of metronomic chemotherapy in the future.

2. Clinical Treatment Challenges Faced by Elderly Cancer Patients

2.1 Physiological Function Degeneration Caused by Aging

Systemic pathological changes associated with physiological aging endow elderly cancer patients with characteristics such as depletion of multi-organ functional reserve, immunosenescence, and drug metabolic disorders. Liver mass and blood flow decrease by 25%-35% and 40% respectively with age, directly weakening drug clearance capacity; the number of nephrons decreases by 40% by the age of 80, leading to a significant prolongation of the half-life of drugs excreted by the kidneys [12]. Immunosenescence is manifested as reconstitution of T lymphocyte subsets (the capacity of CD45RA+ naive T cell pool decreases by more than 50%) and metabolic adaptability disorders of B cells (age-related downward trends in the expression of key enzymes such as AID and BLIMP-1) [13].

The pathophysiological characteristics of elderly patients significantly influence anti-tumor treatment decisions. Vascular endothelial dysfunction and chronic low-grade inflammation synergistically promote the progression of atherosclerosis, in which continuous activation of the NF-κB pathway accelerates plaque formation. At the same time, the accumulation of diabetes-related advanced glycation end products can reduce the cardiovascular toxicity tolerance threshold by 40% [15-16]. Clinical data show that when anti-angiogenic drugs such as VEGF inhibitors are used, the risk of cardiovascular events in elderly hypertensive patients increases to 36%, and the mechanism involves NO signal interference and enhanced oxidative stress [14]. It is noteworthy that elderly patients generally have multi-drug metabolic disorders and comorbidities, leading to an increase in the incidence of toxic and side reactions of traditional chemotherapy regimens and a decrease in treatment compliance [15]. This requires that clinical treatment should prioritize safety-optimized treatment strategies based on accurate assessment of organ function reserve.

2.2 High Toxicity of Traditional Chemotherapy

Although the treatment paradigm of traditional chemotherapy based on the maximum tolerated dose (MTD) can achieve tumor volume reduction, its dose-limiting toxicity (DLT) causes systemic toxicities such as myelosuppression and mucosal injury, forcing the prolongation of treatment intervals and thus weakening the sustainability of efficacy. This regimen reshapes the immunosuppressive microenvironment through the TGF-β/IL-10 signaling axis by eliminating CD8+ T cells and simultaneously up-regulating the ratio of MDSCs/Tregs, forming treatment resistance [16]. Traditional chemotherapy has a significant impact on the quality of life of cancer patients, especially elderly cancer patients. In particular, after early detection and treatment, higher survival rates are accompanied by a decline in quality of life caused by metastatic diseases, while symptoms such as anorexia, anemia, nausea, vomiting, and fatigue gradually caused by traditional chemotherapy directly affect the quality of life of patients. Due to the decrease in mitochondrial autophagy ability and hematopoietic reserve, the chemotherapy tolerance index of elderly patients is 57% lower than that of young people, and the quality of life score (QoL) is significantly negatively correlated with the treatment intensity [17, 18]. In addition, based on the action mechanism of traditional chemotherapy, the dosage is often exceeded, which brings greater economic pressure to patients and reduces their medication compliance.

Other treatment models also face challenges in adapting to the elderly: when radiotherapy induces DNA damage through ionizing radiation, radiation exposure of normal tissues can increase the risk of delayed fibrosis by 2.1 times; immune-related adverse events (irAEs) caused by immune checkpoint inhibitors show the characteristics of multi-organ involvement in the elderly, and the incidence of severe myocarditis/neurological toxicity is higher than that in young patients. The requirements of these treatment models for organ function reserve and the physiological decline of elderly patients form a fundamental contradiction, highlighting the limitations of traditional tumor intervention strategies in geriatrics [19].

Due to organ function decline, complex comorbidities, and pharmacokinetic changes, elderly patients have a significantly lower tolerance threshold for traditional radical treatment. Therefore, the treatment goal of elderly cancer patients needs to shift from the single pursuit of disease cure to the dynamic balance of quality of life optimization and survival period extension [20].

3. Mechanisms of Action of Metronomic Chemotherapy

Metronomic chemotherapy exerts multiple mechanisms including anti-angiogenesis, immunomodulation, and inhibition of the tumor microenvironment through a continuous administration model of low-dose and high-frequency. Compared with traditional chemotherapy, which mainly kills rapidly dividing cells through cytotoxicity, it reduces drug resistance and toxicity to normal tissues while balancing the advantage of long-term tumor progression control.

3.1 Inhibition of Angiogenesis

Vascular endothelial growth factor (VEGF) is a core molecule regulating physiological angiogenesis, which also plays a key role in pathological angiogenesis during tumorigenesis [21]. The mechanism of metronomic chemotherapy focuses on targeting tumor endothelial cells and tumor-associated fibroblasts, selectively inhibiting their activity to reduce the secretion of pro-angiogenic factors such as VEGF, thereby achieving anti-angiogenesis [16, 22]. In addition, it can also target and regulate the secretion activity of pro-angiogenic factors in myeloid-derived suppressor cells (MDSCs) in tumors, significantly reducing their pathological infiltration, and then blocking the activation of pro-angiogenic signaling networks in the tumor microenvironment to indirectly inhibit the angiogenesis process [23].

Traditional chemotherapeutic drugs such as alkylating agents and antimetabolites can directly damage DNA structure or inhibit the activity of replication-related enzymes, while long-term low-dose exposure of metronomic chemotherapy can continuously destroy the integrity of tumor cell DNA through cumulative effects, inhibiting the extension and repair of replication forks. Frequent administration can induce apoptosis of vascular endothelial cells and inhibit their proliferation, destroy the tumor microvascular network, and lead to hypoxia and nutritional deficiency in the tumor microenvironment. Under hypoxic conditions, the synthesis of deoxynucleoside triphosphates (dNTPs) required for tumor cell DNA replication is limited, and the accumulation of reactive oxygen species (ROS) further aggravates DNA damage, forming replication obstacles, so as to achieve the goal of inhibiting tumor growth [8, 24].

3.2 Immunomodulatory Effects

Regulatory T cells (Tregs) are immunosuppressive lymphocytes that drive tumor immune tolerance and promote immune escape. Metronomic chemotherapy can enhance anti-tumor immunity by reducing the number or function of Tregs [25]. Patients with advanced tumors often have severe immunosuppression, which promotes tumor immune escape and progression. The immune system can enhance the killing ability of T cells against tumor cells by activating T cell immune response factors (INF-γ, IL-2) [26]. Studies have shown that under the traditional chemotherapy model, low-dose cyclophosphamide (CTX) shows immunomodulatory properties in patients with refractory metastatic breast cancer, but its inhibitory effect on Tregs has a significant time-dependent characteristic. Studies have shown that low-dose CTX can significantly reduce the number of peripheral blood Tregs by inducing apoptosis or inhibiting the proliferation of Tregs in the early stage of treatment, but in the continuous treatment cycle, the number of Tregs shows a dynamic rebound phenomenon [27]. Low-dose CTX has a selective depletion effect on Tregs, while high-dose CTX depletes all lymphocyte subsets indiscriminately. Therefore, low-dose treatment is the key to achieving selective depletion of Tregs [28].

3.3 Reduction of Drug Resistance

ATP-binding cassette (ABC) transporters, P-gp, multidrug resistance-related proteins, etc. on the tumor cell membrane are highly expressed or overexpressed in various cancers, which may directly lead to increased drug efflux and reduced intracellular drug concentration, thereby causing drug resistance [29, 30]. Current studies have shown that multiple anti-tumor drugs used in metronomic chemotherapy, such as paclitaxel and doxorubicin combined with DC101, can inhibit the expression of P-gp protein through multiple mechanisms, thereby reducing drug resistance [31]. Compared with maximum tolerated dose (MTD) chemotherapy, metronomic chemotherapy acts on supportive cells in the tumor microenvironment at a lower dose rather than directly on tumor cells, avoiding selective pressure on drug-resistant clones and thus reducing the occurrence of acquired drug resistance [31].

3.4 Promotion of Cell Apoptosis and Autophagy

Apoptosis is an active process of cell self-消亡 (self-elimination), and the abnormality of this mechanism is involved in the regulation of various diseases [32, 33]. Autophagy is a process of delivering intracellular substances to lysosomes for degradation, which has the functions of basal turnover and energy supply. Enhancing autophagy may help prevent the development of cancer [34]. Studies have shown [35] that vinorelbine, a first-line anti-tumor drug, can induce autophagy in lung cancer cell line A549 and present a time-dependent dual effect. In the early stage of less than 24 hours, autophagy delays apoptosis by maintaining metabolic homeostasis, while after continuous activation, it synergistically promotes cell death. The time-sequential intervention of autophagy inhibitor 3-MA further confirms that autophagy plays a protective role in the initial stage and later transforms into a pro-apoptotic pathway to achieve the effect of inhibiting tumors.

A study on the treatment of triple-negative breast cancer with vinorelbine in metronomic chemotherapy has proved that this method significantly enhances the autophagic activity of triple-negative breast cancer cells MDA-MB-231 and BT-549. Under the mCHT regimen, the expression of autophagy marker LC3A/B is up-regulated and autophagosome formation is increased, while the anti-apoptotic protein Bcl-2 is down-regulated, and the levels of pro-apoptotic proteins Bax and cleaved caspase-3 change significantly. This mechanism proves that autophagy and apoptosis work synergistically through the Bcl-2/Bax-mitochondrial pathway and caspase cascade reaction. The two death mechanisms jointly mediate cell growth inhibition under time-dependent regulation, enhancing anti-tumor efficacy [36].

4. Clinical Research Progress

4.1 Breast Cancer

Breast cancer has become the most common malignant tumor in Chinese women, with the incidence and mortality rates in elderly women showing a significant and stable upward trend over the past 30 years, usually peaking in the 60-64 age group [37]. Numerous studies have shown that metronomic chemotherapy not only demonstrates favorable therapeutic effects but also enhances patient compliance and reduces economic burden.

Capecitabine, as a core drug in metronomic chemotherapy, has shown unique clinical value in the treatment of advanced breast cancer in the elderly. The survival benefits achieved through monotherapy or combination regimens highlight its therapeutic advantages in patients with decreased physiological function.

He, Lu, Ning et al. [38-40] found that for breast cancer patients at different stages (including common types, advanced triple-negative, and elderly metastatic cases), capecitabine metronomic chemotherapy showed comparable objective response rate, disease control rate, and survival time to traditional cycle chemotherapy, but significantly reduced the risk of grade III-IV severe adverse reactions. In He's study, the incidence rates of hand-foot syndrome, myelosuppression, and gastrointestinal reactions in the metronomic chemotherapy group (60.0%, 60.0%, 65.0%) were

significantly lower than those in the conventional dose group. Ning's study further showed that myelosuppression and gastrointestinal reactions were only 4.0% and 10.0%, respectively, and patients' quality of life was significantly improved. These evidence suggest that low-dose continuous chemotherapy can effectively reduce treatment toxicity while maintaining anti-tumor efficacy, which is of important clinical value for elderly or advanced triple-negative breast cancer patients requiring long-term treatment.

He et al. [41] evaluated the safety and efficacy of capecitabine metronomic chemotherapy combined with pyrotinib in HER2-positive metastatic breast cancer patients in a single-arm phase II clinical trial. The results showed that the median progression-free survival (PFS) was 11.9 months, the overall survival (OS) was 29.3 months, the objective response rate (ORR) was 34.7%, and the clinical benefit rate (CBR) reached 81.6%. In terms of safety, only 1 case had grade 4 diarrhea, and adverse reactions were significantly relieved after dose adjustment.

Vinorelbine (VRL), as a first-line anti-tumor drug, plays an important role in the treatment of solid tumors such as non-small cell lung cancer and breast cancer. In recent years, the development of oral formulations has further expanded its clinical application scenarios. Its good oral bioavailability (about 40%-50%) has significantly improved patient treatment compliance, providing convenience for long-term home treatment. Pepe et al. [25] evaluated the immunomodulatory effect and clinical efficacy of oral vinorelbine (mVRL) monotherapy or combined with capecitabine (mCAPE) in 13 HR+/HER2- metastatic breast cancer patients through an exploratory phase II clinical trial. The study showed that mVRL monotherapy or combined with mCAPE did not significantly reduce the overall level of Tregs, and only 5 patients showed transient Tregs reduction. However, the proportion of Treg memory subsets decreased while the proportion of activated subsets increased. In terms of clinical efficacy, the median PFS was 5.2 months, with 1 complete response and 5 partial responses, suggesting that the metronomic chemotherapy regimen has a certain disease control effect, but its immunomodulatory effect is limited, possibly exerting anti-tumor effects mainly through non-immune mechanisms.

Cazzaniga et al. [42] evaluated the efficacy and safety of oral metronomic chemotherapy with vinorelbine combined with capecitabine in the treatment of HER2-negative advanced breast cancer through a multicenter phase II clinical trial. The study included 80 patients, divided into first-line treatment group and second-line treatment group, with the primary endpoint being the clinical benefit rate (CBR) at 24 weeks. The results showed that the overall CBR was 48.8%, and the first-line and second-line groups were 45.7% and 51.1% respectively; the ORR was 35.5% and 25.6% respectively. In terms of safety, the incidence of severe adverse events was low, and no severe toxicity occurred. This regimen has good tolerance while controlling disease progression.

UENO et al. [43] carried out a multicenter phase II single-arm clinical trial for 45 postmenopausal estrogen receptor-positive breast cancer patients, aiming to evaluate the efficacy and safety of neoadjuvant metronomic chemotherapy combined with endocrine therapy. The results showed that the clinical response rate of patients was 67.5%, and 64% of patients switched from total mastectomy to breast-conserving surgery. The treatment was well tolerated, 54% of patients had mild leukopenia, no severe non-hematological toxicity occurred, and disease-free survival was longer in clinical responders. This regimen provides a safe and effective treatment option for postmenopausal hormone-sensitive breast cancer patients.

4.2 Colorectal Cancer

The disease burden of elderly colorectal cancer in China shows significant generational characteristics, and the incidence and death risks of the elderly population (such as those over 85 years old) are particularly prominent. With the acceleration of population aging, age-related decline in genomic stability and imbalance of epigenetic regulation form a vicious circle, doubling the risk of carcinogenic mutations in intestinal mucosal epithelial cells. The disease burden of elderly colorectal cancer in China continues to increase, and its incidence and death risks increase significantly with age, especially in elderly patients over 85 years old [44, 45]. Due to the generally

large patient population, a number of clinical studies have been carried out in the mode of metronomic chemotherapy, and the results show that it can improve the quality of life of patients and prolong the life span.

Li, Wang, Deng et al. [46-48] have confirmed that capecitabine metronomic chemotherapy has the unique advantages of continuously inhibiting tumor angiogenesis and reducing the risk of drug resistance in advanced or metastatic colorectal cancer. Wang et al. used the capecitabine combined with a thalidomide regimen, which significantly improved the quality of life of patients compared with traditional chemotherapy, and had fewer adverse reactions such as myelosuppression and hand-foot syndrome; Li et al. achieved a disease control rate of 63.6% through single-drug metronomic chemotherapy, with adverse reactions mainly being leukopenia and mild gastrointestinal reactions; Deng et al. combined capecitabine with celecoxib in the treatment of advanced rectal cancer, the disease control rate reached 54.9%, the median survival period was 8.4 months, and the adverse reactions were controllable, suggesting that celecoxib may enhance the anti-angiogenic effect by inhibiting the COX-2 pathway. Although the three studies have differences in protocol design, they consistently show that metronomic chemotherapy provides a better-individualized treatment option for elderly or poorly tolerated advanced colorectal cancer patients by balancing efficacy and safety.

Yan et al. [49] highlighted the superior therapeutic effect of metronomic chemotherapy compared with conventional chemotherapy in the treatment of colorectal cancer. The results showed that the effective rate (CR+PR) of the intervention group was 46.2%, which was not statistically different from 45.8% of the reference group. However, the metronomic chemotherapy group was significantly better than the conventional chemotherapy group in terms of safety, with lower incidence rates of adverse reactions such as leukopenia, moderate to severe vomiting, and diarrhea.

4.3 Lung Cancer

In the past 30 years, the incidence rate, mortality rate, and disability-adjusted life year (DALY) rate of lung cancer in China have continued to rise, with the growth rate far exceeding the average level of global and high-social population index (SDI) regions. The growth rates of age-standardized incidence rate (ASIR) and mortality rate (ASMR) in women are higher than those in men, among which the main cause of the increase in lung cancer deaths in men is population aging. Developed countries such as the United States and the United Kingdom have effectively reduced the mortality rate of lung cancer through tobacco control and screening, while China still faces significant challenges [50]. Non-small cell lung cancer (NSCLC), which accounts for about 85% of all lung cancer cases, is more complex to treat in elderly patients (≥65 years old), often increasing the risk of toxicity due to comorbidities and drug interactions. Although radiotherapy, targeted therapy, and immunotherapy are conventional means, metronomic chemotherapy has shown advantages in reducing toxicity and prolonging disease control time by virtue of its low-dose continuous administration mode. Clinical studies have shown that its treatment effectiveness and patient compliance are improved simultaneously, providing a safer treatment option for elderly NSCLC patients [50].

D'Ascanio et al. [51] used a retrospective analysis method to conduct oral vinorelbine metronomic chemotherapy at a dose of 30 mg or 40 mg, three times a week, for 44 elderly advanced NSCLC patients with poor physical condition and severe comorbidities. The results showed that the median overall survival (OS) of patients was 12 months, the median progression-free survival (PFS) was 9 months, the disease control rate (DCR) reached 63%, and the PFS of patients under 75 years old was significantly better than that of the elderly group.

Camerini et al. [52] studied 43 elderly NSCLC patients over 70 years old using an oral vinorelbine metronomic chemotherapy regimen to evaluate its efficacy and safety. The results showed that the ORR was 18.6%, including 8 partial responses and 1 complete response, the clinical benefit rate reached 58.1%, the median time to progression (TTP) was 5 months, and the median overall survival (OS) was 9 months. The treatment was well tolerated, only 7 cases had grade 3 adverse reactions, and the quality of life of patients did not significantly decline. Exploratory analysis found that non-

responders had lower baseline serum VEGF levels and rapid elevation during treatment, while thrombospondin-1 levels did not change significantly. The study shows that this regimen is feasible for elderly, multi-comorbid, and patients with poor physical condition and advanced NSCLC patients, with the advantages of both efficacy and safety.

A phase II study [53] of 92 patients showed that oral vinorelbine metronomic chemotherapy achieved an OS of 32.3 weeks, and 60% of patients achieved clinical benefit, among which the OS of first-line treatment elderly patients was 34.5 weeks, which was comparable to the efficacy of previous standard chemotherapy. Pharmacokinetic analysis (LC-MS/MS detection) confirmed that the blood concentration of the drug and its active metabolite (dVNR) was long-term stable. It is of research significance that the drug concentration of patients with long-term disease control was significantly lower than that of short-term control patients, which indicates that extremely low concentration may maintain efficacy through immunomodulation or continuous anti-angiogenic effect. Metronomic chemotherapy can improve the quality of life, prolong life, and reduce toxicity for elderly patients with long-term disease control.

4.4 Other Cancers

Yeh et al. [54] conducted a clinical study on metronomic chemotherapy for head and neck cancer. The study retrospectively analyzed 240 patients with locally advanced head and neck squamous cell carcinoma, 96 of whom received low-dose tegafur-uracil maintenance treatment after standard treatment, and 144 who did not receive maintenance treatment as a control group to explore the efficacy of tegafur-uracil as metronomic chemotherapy maintenance treatment. The results showed that OS, DFS, and DMFS in the treatment group were significantly better than those in the control group, and the effect of prolonging the medication time was more obvious. Adverse reactions were mainly mild nausea and vomiting, and no severe toxic reactions occurred, proving that this regimen is safe while improving survival.

Frenel et al. [55] evaluated the efficacy of PD-L1/CTLA-4 dual immunotherapy combined with metronomic chemotherapy in the treatment of recurrent advanced cervical cancer. After 31 patients with platinum chemotherapy failure received the regimen, the ORR reached 41.9%, including 5 complete responses, the clinical benefit rate was 53.1%, mPFS was 7.4 months, and mOS was 13.1 months. The efficacy was not affected by PD-L1 or pathological type.

Kubota [56] et al. evaluated the efficacy of a metronomic chemotherapy regimen of tegafur-uracil (UFT) combined with cisplatin and dexamethasone in the treatment of docetaxel-resistant prostate cancer. 25 patients received oral UFT and intravenous cisplatin treatment, and the results showed that the ORR reached 84%, and PSA decreased in 56% of patients. The median PSA progression-free survival was 6 months, and the overall survival was 14 months. Although only 1 patient showed tumor shrinkage on imaging, the regimen was well tolerated, with no severe blood or liver and kidney toxicity, and no patient discontinued treatment due to side effects.

A retrospective study [57] analyzed the clinical data of 335 operable oral cancer patients, including 225 cases of stage III/IVA locally advanced cases. After all patients received standard surgery and adjuvant radiotherapy and chemotherapy, 130 cases (58%) continued to receive continuous metronomic chemotherapy with oral methotrexate combined with celecoxib for a median of 14 months. Kaplan-Meier survival analysis found that the DFS of the maintenance treatment group was 14 months; OS was significantly prolonged to 26 months. The study shows that metronomic chemotherapy significantly improves the OS of locally advanced patients and is well tolerated, with no drug withdrawal events due to toxicity.

Wu et al. [58] compared the efficacy and safety of capecitabine monotherapy metronomic chemotherapy with conventional chemotherapy in 78 elderly patients with advanced gastric cancer through a randomized double-blind controlled trial. The results showed no significant difference in the total effective rate between the two groups, but the incidence rate of adverse reactions in the metronomic chemotherapy group was significantly lower. In the quality of life assessment after chemotherapy, the metronomic group scored significantly better than the conventional group in

physiological, psychological, and social relationship dimensions. The study shows that metronomic chemotherapy significantly reduces treatment-related toxicity and improves patient quality of life while maintaining anti-tumor effects, providing a safer treatment option for elderly advanced gastric cancer.

5. Challenges and Future Prospects

Although clinical research on metronomic chemotherapy has made significant progress, it still faces certain risks and challenges. Since the concept of metronomic chemotherapy was proposed, insufficient pharmacokinetic research has led to most clinical dosing regimens relying mainly on experience. The determination of optimal dosage and dosing interval lacks a systematic basis, and dynamic monitoring of drug metabolism remains difficult—especially for active metabolites with short half-lives, which require more complex detection technologies. Individual differences in patients, such as age and organ dysfunction, also significantly affect pharmacokinetic parameters and pose risks to clinical application [59].

In recent years, pharmacokinetic research on metronomic chemotherapy has made remarkable progress. Physiologically based pharmacokinetic models (PBPK) have optimized metronomic regimens for drugs like docetaxel, primarily to ensure sustained plasma concentrations for tumor inhibition. Preclinical studies have also clarified the metabolic parameters of cyclophosphamide, temozolomide, etc., providing a basis for dose adjustment. PK/PD modeling of combination therapy timing has helped improve efficacy. In the future, integrating multi-omics technologies with computational models based on pharmacokinetic research is expected to deepen studies, promoting metronomic chemotherapy to shift from empirical dosing to precision therapy [59].

Metronomic chemotherapy, as a novel therapeutic paradigm, demonstrates unique mechanistic advantages and clinical potential in combined multimodal therapy. When combined with targeted therapies, it is often used synergistically with drugs such as trastuzumab and bevacizumab. By depleting regulatory T cells (Tregs), activating dendritic cells, and enhancing antigen presentation, it collaborates with PD-1/PD-L1 inhibitors to enhance anti-tumor immune responses. Anti-angiogenic drugs can improve the tumor microenvironment, and bevacizumab can enhance the response efficiency of immunotherapy by synergizing with the above effects [60, 61]. When combined with radiotherapy, low-dose chemotherapy induces vascular normalization and improves tumor hypoxia, enhancing radiosensitivity. Components of traditional Chinese medicine (TCM) can inhibit tumor cell proliferation, induce apoptosis, regulate the tumor microenvironment, block metastasis signaling pathways, and modulate immune cell subsets to improve the body's anti-tumor immune response. For these reasons, many clinical studies now focus on the combination of metronomic chemotherapy and TCM. TCM can also alleviate chemotherapy-induced myelosuppression, gastrointestinal reactions, and organ toxicity, protect intestinal barrier function, and reduce serum inflammatory markers, thereby improving patient tolerance and quality of life. Such combined strategies provide more comprehensive treatment options for advanced cancer patients through a synergistic and toxicity-reducing mechanism [62-64].

Innovations in drug dosage forms, administration methods, and dose adjustment may optimize or unlock the potential advantages of metronomic chemotherapy. Some novel drug delivery technologies, owing to their unique administration advantages, can significantly enhance the safety and efficacy of metronomic chemotherapy when combined. The core principle of nanotargeted systems is to achieve precise drug delivery by designing multifunctional nanocarriers that integrate passive and active targeting mechanisms. A study [65] has shown that this technology uses F56 peptide to specifically bind to VEGFR1 receptors on tumor vascular endothelial cells, enhancing drug targeting and reducing off-target toxicity. The sustained-release properties of nanocarriers prolong drug action time, improve encapsulation efficiency and drug loading, and enhance the penetration of subsequent chemotherapeutic agents and synergistic anti-tumor effects by inducing a "normalization window" in tumor blood vessels. In the future, optimizing nanocarrier design to improve targeting

efficiency and controlled release, and exploring combination with other chemotherapies, may effectively expand indications to other solid tumors. Further advancement of clinical translational research to validate long-term safety and efficacy will bring more reliable strategies for the clinical development of metronomic chemotherapy [66]. These technological innovations not only optimize multi-target regulatory mechanisms (e.g., anti-angiogenesis and immunomodulation) but also provide more clinically translatable solutions for cancer treatment by improving the therapeutic window and patient compliance.

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