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Advances in Oral Vinorelbine Metronomic Chemotherapy for Non-Small Cell Lung Cancer

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Abstract

Metronomic chemotherapy is a therapeutic strategy that treats tumors through frequent low-dose drug administration. It has many mechanisms including chemotherapy, immunotherapy, and antiangiogenesis, and has the advantages of short therapy interval and slight toxic reaction. Traditional chemotherapy takes the Maximum Tolerated Dose (MTD) as the standard for a drug administration cycle. By contrast, metronomic chemotherapy mainly targets neovascularization of tumors and activates anti-tumor immunity in the body. Oral vinorelbine is an appealing agent, particularly as part of combination regimens containing platinum derivatives, although it can have a role as a single-agent treatment as well. As a tubulin inhibitor, Vinorelbine is regarded as the best option in metronomic chemotherapy for non-small cell lung cancer. Clinical application studies include oral vinorelbine monotherapy and/or combination with platinum-based chemotherapy, combination with radiotherapy, combination with immunotherapy and so on. Its safety profile is generally favorable and its route of administration is generally preferred by patients receiving chemotherapy. Compared to intravenous injection of vinorelbine and other antineoplastic agents, oral vinorelbine has been reported to be advantageous in terms of cost savings. This article clarifies the mechanism and clinical application of metronomic chemotherapy with vinorelbine in advanced non-small cell lung cancer.

Keywords: Metronomic chemotherapy; Vinorelbine; Non-small cell lung cancer (NSCLC); Antiangiogenesis

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Introduction

In 2000, both Browder et al. [1] and Hanahan et al. [2] found in animal experiments that frequent low-dose administration of common cytotoxic drugs can not only kill tumor cells, but also promote the apoptosis of vascular endothelial cells in tumor tissues, and even when tumor cells have been already resistant to the drugs. In 2002, Kerbel et al. [3] from the University of Toronto proposed the new concept of metronomic chemotherapy, which is defined as "the frequent administration of low-dose chemotherapy drugs". In other words, it is designed to administer cytotoxic drugs at low-toxicity doses (generally 1/10 to 1/3 of conventional doses) [4] far lower than MTDs and at higher frequency or continuously (administering once 2 days, or 3 times a week until disease progression or intolerable toxicity), so as to maintain a relatively low but effective blood concentration of the drug (dose accumulation effect) without increasing toxicity additionally. Previously, the anti-tumor effect of metronomic chemotherapy was thought mainly through targeting of proliferated vascular endothelial cells. However, recent studies have revealed some new mechanisms and defined metronomic chemotherapy as a multi-targeted therapy [5].

Comparison between traditional chemotherapy and metronomic chemotherapy

Traditional chemotherapy tries to achieve the anti-tumor efficacy by administering a single dose of cytotoxic drugs at the Maximum Tolerated Dose (MTD) of the human body, and thus has quick effect and can shrink tumors immediately. However, the non-specificity of chemotherapy drugs' cytotoxicity may easily lead to toxic reactions. For this reason, a sufficiently long interval (two to three weeks) is required between two chemotherapy courses in order to avoid irreparable damage by the drugs to normal tissues and let the patients recover from adverse drug reactions. In addition, traditional chemotherapy only kills chemo-sensitive tumor cells; however, tumor cells resistant to chemotherapy remained. During the relatively long interval, due to the reduced

concentrations of cytotoxic drugs, chemo-resistant tumor cells and tumor microenvironment get a "respite", which may lead to recurrence of the disease [6].

Compared to traditional chemotherapy, metronomic chemotherapy has more remarkable long-term effects:

1. The single dose of the latter is far lower than MTD; the blood drug concentration is reduced and the relevant adverse drug reactions are greatly lightened; so, patients' life quality can be improved.

2. Metronomic chemotherapy has multiple anti-tumor mechanisms including antiangiogenesis and immune activation; it may work slowly, but the effect can last longer. It allows long-term administration and is more suitable for patients who have slow tumor growth and the long-term survival and high life quality.

3. Metronomic chemotherapy involves short intervals of administration and targets at chemo-sensitive and –resistant tumor cells as well as endothelial cells and other sustentacular cells in the tumor microenvironment.

Acquired drug resistance is rarely generated in this treatment mode [7]. The reduction of resistant tumor cell clones and the inhibition of anti-tumor immunity may also reduce the probability of disease recurrence. 4) This chemotherapy pattern has good compatibility and allows for combined application with many other treatments [8-11]. In addition, the two chemotherapy patterns would induce different drug-resistant mechanisms. When tumor cells are resistant to a drug that is administrated in traditional chemotherapy, they are still sensitive to the drug in metronomic chemotherapy.

Anti-tumor mechanisms of metronomic chemotherapy

Metronomic chemotherapy, which is a multi-target therapy, has multiple anti-tumor mechanisms, integrating chemotherapy, immunotherapy and Anti angiogenic therapy. Thus, it can realize the synergistic anti-tumor effects, which are described respectively as follows.

Chemotherapeutic Effect Tumor stem cells refer to the cells that have the ability of continuous self-renewal and infinite proliferation and drive the tumor to grow continually, and are regarded as the root cause of resistance to drugs in traditional chemotherapy. More and more evidence suggests that metronomic chemotherapy can kill both tumor cells [12] and tumor stem cells, thus making tumor cell apoptosis last longer. Immunoregulation Regulatory T cells can express cytotoxic lymphocyte-associated antigen-4 (CTLA-4) and inhibit cell-specific immune responses and the anti-tumor immune responses mediated by CD8+lymphocytes, CD4+T helper cells and natural killer cells, and the increase in the number of these cells is associated with tumor progression and lack of responses to the anti-tumor therapy [13,14]. In animal xenograft models, metronomic chemotherapy can increase anti-tumor immune responses by reducing the quantity of Treg cells and inhibiting their functions. Basic research has indicated that the synergistic anti-tumor effect combined metronomic chemotherapy with immune checkpoint inhibitors. Furthermore, metronomic chemotherapy can strengthen the immunogenicity of the tumor cells, improve the cytotoxic activity of immunologic effect or cells such as tumor-specific T cells and γδ T cells, activate the exposure of calreticulin and heat shock proteins, and promote the release of endogenous dangerous signals, thus playing a role in promoting the body's anti-tumor immunity [15]. Anti angiogenic effect metronomic chemotherapy can inhibit the growth of vascular endothelial cells through multiple mechanisms. 1) It can act directly on activated vascular endothelial cells. Research has shown that vascular endothelial cells are far more sensitive to some conventional chemotherapy drugs than bone marrow cells, hair follicle cells and other normal cells and tumor cells. Therefore, activated vascular endothelial cells are more vulnerable at a very low concentration of chemotherapeutic drugs, which has no cytotoxic effect on normal cells or even tumor cells. This is why metronomic chemotherapy brings about much less toxicity than traditional chemotherapy [16]. 2) Metronomic chemotherapy can inhibit the migration of endothelial cells, thereby inhibiting proliferation of tumor endothelial cells and inducing apoptosis of activated endothelial cells [17]. 3) It has been found in both human and animal experiments that metronomic chemotherapy can continuously decrease the number and activity of the endothelial progenitors (CEPs) and thus inhibit angiogenesis in tumors, and by contrast, traditional chemotherapy may lead to a rebound of CEP quantity, rapid tumor growth and drug resistance due to the long intermission of chemotherapy [18]. 4) Metronomic chemotherapy has some effect on the balance between tumor angiogenesis factors and anti-tumor angiogenesis factors. This regimen can not only promote the expression of the endogenous anti-angiogenic factor-thrombospondin-1 (TSP-1) [19], but also weaken the effects of tumor angiogenesis factors in the peripheral blood circulation such as VEGF and PDGF [20,21].

Clinical study on metronomic chemotherapy with oral vinorelbine in non-small cell lung cancer

Lung cancer is the most common cause of cancer deaths in the world. In most cases, NSCLC is diagnosed at an advanced stage; in this situation, palliative chemotherapy is the treatment of choice. Combinations including a platinum derivative in association with a third generation drug (vinorelbine, taxanes, gemcitabine) have proven more effective than monotherapy and currently represent the standard of care for NSCLC [22]. However, such combinations may be too toxic for elderly and unfit patients; in these cases, single-agent chemotherapy represents a suitable alternative. Before the concept of metronomic chemotherapy was proposed, clinicians have carried out low-dose chemotherapy, and many cancer patients benefited from this regimen. Since the concept of metronomic chemotherapy was proposed, there have been more and more relevant studies on metronomic chemotherapy.

Through the comparison of antitumor biological effects (antiangiogenesis, Immunoregulation, and toxicity to tumor cells) between the four kinds of commonly used metronomic drugs for treating non-small cell lung cancer (alkylating agents, tubulin inhibitors, antimetabolites, and camptothecins), it was found that tubulin inhibitors, especially vinorelbine, have the strongest Anti angiogenic effect, and their immunomodulatory effect is no less than the other three [23]. Thus, they are currently the most effective drugs used in metronomic chemotherapy.

Vinorelbine is a semi-synthetic catharanthus alkaloid, which can selectively act on tubulins and result in microtubule formation disorders during mitosis of tumor cells [24]. Metronomic chemotherapy with vinorelbine can reduce the number and activity of CEPs, thereby inhibiting angiogenesis in tumor cells [18], significantly down-regulating the expression of pro-angiogenic genes and up-regulating the expression of anti-angiogenic genes [25], and increase the plasma concentration of thrombospondin TSP-1. What's more,

pharmacokinetics of oral vinorelbine is very stable, convenient to use and suitable for continuous and frequent administration with good patient tolerance and compliance [26]. Therefore, oral vinorelbine is an ideal choice for metronomic chemotherapy in NSCLC. The following describes three application patterns of metronomic vinorelbine in NSCLC.

Vinorelbine as monotherapy: In a Phase I dose-finding study, patients with stage III/IV NSCLC received daily oral vinorelbine at fixed dose levels of 20 to 50 mg/d for 21 days of each 4-week cycle. It showed that a recommended dose of 30 mg/d in cycle 1 with escalation to 40 mg/d from cycle 2, if tolerated. The blood concentrations of vinorelbine after daily metronomic dosing reached lower peaks than intravenous or oral conventional dosing. Blood concentrations were consistent with anti-angiogenic or immune modulating pharmacologic properties of vinorelbine [27]. A study published on BMC Cancer (MOVE trial) reported that 43 III B- IV NSCLC patients above 70 years old (ECOG PS: 0-2), who had not received chemotherapy, were given oral vinorelbine capsules at the dose of 50 mg on the 1st, 3rd, and 5th day of each week until disease progression or intolerable toxicity. The results showed that the objective response rate (ORR) was 18.6%; the disease control rate (DCR) was 58.1%; the Median Progression-Free Survival (mPFS) reached 5 months; the median overall survival (mOS) was 9 months. The majority of the patients showed good drug tolerance; the incidences of various and adverse events were all less than 1%; the most common adverse events were anemia (44%), fatigue (32.4%) and diarrhea (10.5%) [28] the efficacy and safety of this vincribine metronome chemotherapy regimen of 50 mg three times per week were also validated in another study [29]. Recently, D'Ascanio reported that in a prospective phase II not randomized study, 50 elderly patients (≥ 70 years) with stage IV NSCLC, performance status (≥ 2), and/or extensive brain or bone disease were treated with oral metronomic vinorelbine at 30 mg fixed dose three times a week until disease progression. The result showed that overall disease control rate was 32% and 44% in first and subsequent lines, respectively. Median OS and PFS were 7.3 months and 2.7 months, respectively [30]. In addition, there are a number of ongoing clinical studies on the efficacy and safety of metronomic oral vinorelbine in NSCLC patients, such as the ONC-MANILA: evaluation on metronomic oral vinorelbine as first-line maintenance treatment. The study plans to include 120 III B/IV NSCLC patients who are in stable condition after first-line platinum-based chemotherapy. After random grouping, they were given oral vinorelbine at the dose of 50 mg three times a week until disease progression or best supportive care, and the main study endpoint is PFS (NCT02176369) [31].

Oral vinorelbine metronomic chemotherapy in combination with platinum-based chemotherapy: With respect to drug combination, the efficacy of oral vinorelbine in combination with cisplatin in NSCLC has been studied comparatively. In the study, the patients were given vinorelbine at the dose of 40 mg to 70 mg three times a week and cisplatin at the dose of 70 to 85 mg/m^2 (Day 1, 21-day cycle). The objective response rate of the regimen was 37.1%, and the disease control rate was 65.7%. According to the above data, the regimen looks promising currently and more extensive research is required to confirm its effectiveness [32]. In a phase-II study on metronomic oral vinorelbine+cisplatin as first-line treatment of advanced NSCLC, 41 advanced NSCLC patients were included and given metronomic oral vinorelbine at the dose of 60mg three times a week and cisplatin at the dose of 30 mg/m^2 once three weeks. After 4 to 6 cycles, metronomic oral vinorelbine was allowed to be used for maintenance treatment, and would not be withdrawn until PD, intolerable toxicity adverse events or the patients' request for a withdrawal. The results showed that the disease control rate was 65.7%; the median Progress Free Survival (PFS) was 4.2 months; the median overall survival was 12 months. The majority of the patients (77.1%) only experienced grade 1-2 adverse events [33]. The results indicated that metronomic oral vinorelbine+cisplatin is an effective regimen for treating locally advanced or metastatic NSCLC with a manageable safety range.

Oral vinorelbine metronomic chemotherapy in combination with radiotherapy: The disordered new vessels and hypoxic zones in tumors constitute an important factor causing the failure of radiotherapy [34]. The Anti angiogenic effect of metronomic chemotherapy can inhibit tumor angiogenesis, reduce the degree of disorder of the vessels, improve the hypoxic environment in the tumor, and make these tumor cells sensitive to radiotherapy again [35,36]. In addition, due to the combined effect on tumor vessels and oxygen supply status, great attention should be paid to the effective combination of radiotherapy and metronomic chemotherapy. Studies have also shown that low-dose vinorelbine can make tumor cells accumulate in the G2/M phase, induce apoptosis, and strengthen the radio sensitivity of NSCLC, thus having a cell cycle-dependent radiation-enhancing effect [37]. A phase II trial was evaluated the feasibility and risk benefit ratio of concurrent chemoradiotherapy using oral vinorelbine plus cisplatin and concurrent radiotherapy in locally advanced stage III A/B NSCLC. The patients were administrated induction chemotherapy continued to receive cisplatin at 80 mg/m^2 every 3 weeks and oral vinorelbine at 40 mg/m^2 on days 1 and 8 for two cycles concomitantly with chest radiotherapy. Thirty-eight patients out of the 60 enrolled (mean age 57 years) received the concurrent chemo radiation. No complete responses were seen. In the intent-to-treat analysis, the ORRs were 32.1% after induction chemotherapy and 41.1% after concurrent chemoradiotherapy. The median PFS and OS were 9.2 and 20.8 months, respectively. This study showed that concurrent chemoradiotherapy with oral vinorelbine+cisplatin combination had a favorable risk benefit ratio in locally advanced NSCLC [38]. In addition, Krzakowski et al. [39] carried out a study on phase- III NSCLC, in which they tried to work out the standard dose of oral vinorelbine used in combination with radiotherapy. The patients in the first group were solely given vinorelbine, and those in the second group were given vinorelbine and cisplatin. The results showed that the recommended dose of oral vinorelbine used in combination with 60 Gy radiotherapy is 50 mg administrated respectively on the 1st, 3rd, and 5th day of each week (150 mg/week), and the recommended dose of cisplatin is 80 mg/m^2 for every three weeks. The disease control rates in the first and second groups were 42% and 55% respectively, and the experiments showed that oral vinorelbine alone or in combination with cisplatin significantly increased the effectiveness of radiotherapy.

Conclusion

In conclusion, metronomic chemotherapy is a very promising pattern of drug administration, which compared with traditional chemotherapy, is more aligned with the rationale of the emerging molecular targeted therapies as well as the new idea of chronic cancer treatment. In the field of NSCLC treatment, metronomic oral vinorelbine (soft capsules) features multiple functions including chemotherapy, Immunoregulation and antiangiogenesis, and mainly acts on the tumor microenvironment. Metronomic oral vinorelbine

(soft capsules) can achieve a balance between efficacy and toxicity (the efficacy is better than that of traditional chemotherapy, while the toxicity is lower than the latter) and show a long-term disease control capability. Meanwhile, under the assumption that the efficacy of different therapies is the same, patients prefer to choose oral chemotherapy rather than intravenous chemotherapy. Thus, metronomic chemotherapy can improve patients' life quality and compliance while benefiting their survival status, and is conductive to the long-term management of NSCLC. This therapy is suitable for patients who have slow tumor growth and the need to consider long-term survival and life quality as well as elderly patients with poor general condition and other complications, but not suitable for patients with cancer in the rapid proliferative phase. In addition, it can also serve as an option for maintenance treatment with different drug regimens [40-42]. Metronomic oral vinorelbine (soft capsules) also has application prospect in the field of combined treatment, and it can be applied in combination with chemotherapy and radiotherapy. The combined application of metronomic chemotherapy with other therapies such as traditional chemotherapy, targeted therapy, immunotherapy, Anti angiogenic therapy, and radiotherapy is just in the beginning stage, so it is necessary to carry out more large-scale randomized controlled clinical trials to support this theory.

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