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Metronomic Oral Combination of Vinorelbine and Capecitabine in Advanced Breast Cancer: is it Time to be Considered for Daily Clinical Practice?

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Abstract

This commentary summarizes the main mechanisms of action of metronomic chemotherapy (mCHT) aiming to define the criteria for selecting patients for this strategy. mCHT refers to the frequent, regular administration of drug doses designed to maintain a low, but active, range of concentrations of chemotherapeutic drugs during prolonged periods of time without inducing excessive toxicities. Major mechanisms of action, rather than a direct effect on the tumor volume, are inhibition of angiogenesis and stimulation of innate immune response.

The effectiveness of this treatment strategy was confirmed in different trials, reporting percentages of Objective Response Rate of approximately 50% and Clinical Benefit Rate of 77%-80%.

Basing on the patients' characteristics outlined in different trials, the ideal patient for mCHT has HR+ve tumor, indolent disease or bone metastases.

The easy schedule of metronomic chemotherapy, together with the very low incidence of severe toxicities are all valuable advantages to be considered, in particular in countries with limited access to innovative drugs. Studies exploring different areas of application for mCHT are ongoing.

Introduction

In 2014, our group published the first data [1] regarding the use of an all-oral metronomic combination of Vinorelbine (VNR) and Capecitabine (CAPE) in HER2-negative advanced breast cancer patients. The VICTOR-1 trial was a Phase I/II study designed to define the optimal dose of metronomic Vinorelbine (mVNR) in combination with fixed, metronomic doses of CAPE. The Phase II part of the study was subsequently conducted to confirm the toxicity results. Nowadays, several studies evaluates the metronomic administration of VNR [2,3], in order to establish the right dose both as single agent and in combination with different drugs, but no data were available at that moment regarding the combination of a full metronomic regimen. Our results indicated that the recommended dose for future studies of mVNR in combination with fixed doses of CAPE is 40 mg three times per week, without free-break periods.

The most interesting result of VICTOR-1 study was the very low incidence of severe toxicity, even during prolonged treatment: among the 187 cycles administered, the incidence of Grade 3-4 events was below 6%, an amazing finding considering that the same combination of VNR and CAPE administered with a standard, non-metronomic schedule, induced severe leukopenia and neutropenia in more than 40% of the patients [4], requiring in some cases the use of curative (14.8%) or prophylactic (2.8%) G-CSF.

The results provided by VICTOR-1 and other studies led to an increasing attention to the possibility of optimizing chemotherapy administration by reducing the treatment-related toxicities. Metronomic schedules could in fact respond to the greatest needs of metastatic breast cancer patients, namely support and Quality of Life, beyond medical interventions [5].

The present commentary aims to improve patient selection for this strategy, by summarizing the main mechanisms of action of metronomic chemotherapy (mCHT), as well as give some future perspectives for further development of this regimen.

Comments

The development of molecular targeted therapies with highly specific mechanisms of action has raised questions about the paradigm of dosing at the Maximum Tolerated Dose (MTD). Inhibition of the molecular target may in fact occur at dose levels substantially below those producing dose limiting toxicities [6].

Metronomic chemotherapy (mCHT) refers to the frequent, regular administration of drug doses designed to maintain a low, but active, range of concentrations of chemotherapeutic drugs during prolonged periods of time without inducing excessive toxicities [7].

Several preclinical trials reported that some metronomic regimens can have surprisingly potent antitumor effects in comparison to corresponding MTD regimens, and are much less toxic. These results suggest that the efficacy of mCHT may not only depend on a direct cytotoxic action but also on different actions on the tumor microenvironment.

One of the most studied mechanisms is the inhibition of angiogenesis, which is different from conventional anti-angiogenic drugs, that target individual molecules or signaling pathways;

conversely, mCHT acts by inhibiting the production of growth factors at the source. As reported by different Authors [8-10], mCHT reduces tumor endothelial cell proliferation and the correlated angiogenic potential of these cells, increases THBS-1 expression and inhibits CECs, inducing vessels normalization and reduction in tumor perfusion. More recently, Biziota et al. [11] supported the anti-angiogenic effect of metronomic VNR (mVNR) by showing that a protracted low dose is superior to pulsed high-dose administration in inducing anti-angiogenic effects.

Another important mechanism of action of mCHT is the stimulation of the host immune system.

Both innate and adaptive immune responses play an important role in cancer control, but these responses can be compromised by high dose chemotherapy, which triggers host inflammatory immune response and ablates immune surveillance [8]. On the contrary, low continuous doses of drug, such as those administered in metronomic schedules, could lead to stimulation of antitumor immunity and suppression of pro-tumor immune response.

In this context, we have to consider also the role of regulatory T cells (Tregs): they act as one of the major suppressor of anti-tumor immune response. Several preclinical and clinical observations suggest that Tregs can be depleted by some drugs, in particular CTX and VNR [12]. Gè et al. [13] investigated the effect of metronomic low-dose CTX on: Treg numbers, suppressive capacity and proliferation; on endogenous antitumor T-cell responses and on their correlation to clinical outcome in 12 patients with treatment-refractory metastatic breast cancer who received single-agent 50 mg CTX daily. The Authors demonstrated that CTX treatment initially caused a significant reduction in circulating Tregs, even if these latter completely recovered during the treatment due to increased proliferative activity and maintained their suppressive capacity.

Further studies are ongoing to confirm these findings and to verify if other drugs with different mechanisms of action, such as VNR, could improve these results.

mCHT has proved to have other different actions, such as promotion of immunogenic cell death, enhancement of APC through DC, MDSC modulation and enhancement of tumor specific Tcells and γδT cells [14].

The majority of the trials of mCHT have enrolled HR+ve patients: the selection of this kind of patients was mainly due to the frequent presence of indolent disease, but there is also a strong rationale for selecting HR+ve patients, considering that cytotoxic drugs directly suppress ovarian function causing plasma estrogens decline and a corresponding increase in gonadotropins [14].

Some preclinical studies suggest the activation of one mechanism instead of another is strongly dependent on the administered dose.

So far, two questions rise spontaneously: how to determine the right dose for the metronomic schedule and, above all, how to choose the dose which activates the most appropriate mechanism?

The answer to the first question comes from the data published by Shaked et al. [9]: Authors assessed that the determination of Optimal Biological Dose (OBD) ranges of various chemotherapy drugs is possible using CEPs as a marker in the clinic of targeted anti-angiogenic drug activity. They empirically defined OBD as that dose causing maximum reduction in the tumor volume with no or minimal toxicity. This was assessed to be 20 mg/kg CTX daily, 0.33 mg/kg Vinblastine, 9 mg/kg VNR, or 1 mg/kg Cisplatin in the various tumor models used. Authors defined 9 mg/kg VNR as the OBD even though this dose revealed moderate hematologic toxicity by a slight reduction in white blood cells count, in contrast to the 6 mg/kg dose; however, the latter dose was not efficacious. Whether a dose between 6 and 9 mg/kg is the OBD is not known at the moment. The various treatments tested were found to have a significant dose-dependent reduction in viable CEPs, the nadir of which coincided exactly with the previously determined OBD.

It is difficult with the data available at this moment to give an answer to the second question.

Doloff and Waxman [15] demonstrated in their study that important regression of implanted brain tumour xenografts treated with CTX on an intermittent, every 6-day metronomic schedule was accompanied by significant recruitment and activation of innate immune cells. These responses were achieved with little or no anti-angiogenesis. In this context, the schedule of metronomic chemotherapy seems to be critical: it needs to be sufficiently frequent to activate innate anti-tumour immune response, but it also needs to be sufficiently well-spaced in time to minimize damage to the immune cells recruited to the tumour microenvironment. Further, longer intervals between metronomic drug treatments and drug doses that are too low can both contribute to tumour escape or resistance [8].

In our study, the dose of VNR for combination was determined by the old method of the MTD; we don't know if different, lower doses, combined with CAPE are able to differently suppress the mechanism of angiogenesis or to modulate the innate immune response.

The study of Briasoulis et al. [16] failed to specify the optimal dosage of VNR according to the biologic effect promoted: however, considering that antiangiogenic therapy is known to work optimally if endothelial cells are exposed to steady levels of inhibitors and that both VNR and its active metabolite achieved steady state concentrations at the low nanomolar range, it is possible to argue that doses between 30 mg and 40 mg are able to promote anti-angiogenic activity. Regarding the dose of CAPE, different data suggest that 500 mg three times per day are able to decrease both CECs [17] and CEPs [18], so far demonstrating a prevalent anti-angiogenic activity. We don't know at the moment if the combination of the two drugs has superior activity in comparison to both single agent drugs in terms of inhibition of angiogenesis, due to the lack of available data. It is conceivable that VNR, as microtubule-binding agent, plays the major role.

In the last 5 years, data regarding the use of metronomic CHT, mainly in breast and lung cancer, have vertiginously increased [19]. So far, basing on these data, we could now outline the profile of the patients for whom metronomic CHT could be an important option.

Different phase II studies have tested the metronomic administration of oral drugs, mainly Methotrexate (MTX) and/or Cyclophosphamide (CTX) [20,21], or CTX+CAPE, reporting percentages of Clinical Benefit Rate (CBR) of 31%-53% and Objective Response Rate (ORR) of 19%-52%. Most of these studies had small sample sizes and were conducted in heavily pretreated breast cancer patients; in some cases, the schedule chosen could not precisely be defined as metronomic, at least as actually defined, making comparison very difficult.

More recent trials, some of them conducted as single Institution pilot experiences, tested different and more active drugs, mainly VNR and CAPE, due to well-known synergic action of these two drugs

[22,23]. These studies reported percentages of ORR of approximately 50% and CBR of 77%-80%.

The majority of these trials enrolled HR+ve patients, with indolent disease or bone metastases, so far all these disease characteristics could serve as practical guide lines for patients' selection. Metronomic VICTOR combination provides a lot of advantages for the patients: the first, and probably the most important, is that the treatment is full oral, so far patients could take their therapy at home for the whole period, avoiding the need of frequent blood tests, as already demonstrated in the VICTOR-1 trial too; blood tests every 3-4 weeks only is strongly recommended in the clinical practice, with the exception of important organ impairment or clinical conditions requiring more frequent tests. Finally, the unique mechanism of action of metronomic CHT, together with the results obtained with the VICTOR combination, opens different possibilities to the patients living in low-income or medium-income countries, where the advantages provided by the drug fit the local constraints, such as reimbursement, costs, toxicity and lack of infrastructures [24]. The easy schedule, the possibility to deliver the required number of pills for a whole month and thus limiting patients' dependence on hospitals all are value elements to be considered in countries with limited access to innovative drugs.

Which are the future perspectives for the VICTOR combination?

Basing on the two well-known mechanisms of action of mCHT in general, and of VNR in particular, there is a strong rational to test the VICTOR combination in triple-negative breast cancers (TNBC), where inhibition of angiogenesis has a key role, and to investigate the possibility to combine one or both drugs with new anti-PD1/anti-PDL1 agents, considering that mCHT could have a synergic action with these drugs, related to the stimulation of innate immune response well described in different studies.

Our group is currently carrying on an international, randomized study (VICTOR-3) to investigate the role of mVNR, either as single agent or in the VICTOR combination, in TNBC patients after an induction standard-dose CHT, as maintenance therapy. The results of this study, if positive, could open future strategies of disease control in this bad prognosis group of patients.

Randomized, Phase III studies of metronomic *vs.* standard non-metronomic regimens are ongoing too, in order to definitely confirm the favorable results obtained in these large Phase II trials.

We firmly believe that metronomic chemotherapy could represent a turning point in the scenario of breast cancer treatment and we hope that our data could contribute to spread this message.

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