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Mini-review

Metronomic chemotherapy: A relook at its basis and rationale

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ABSTRACT

Metronomic administration of chemotherapy has long been recognized as having a different biological effect from maximal tolerated dose (MTD) administration. Preclinical studies have demonstrated these differences quite elegantly and many clinical trials have also demonstrated reproducible activity albeit small, in varied solid malignancies even in patients who were heavily pretreated. However, the concept of metronomic chemotherapy has been plagued by lack of a clear definition resulting in the published literature that is rather varied and confusing. There is a need for a definition that is mechanism(s)-based allowing metronomics to be distinguished from standard MTD concept. With significant advances made in understanding cancer biology and biotechnology, it is now possible to attain that goal. What is needed is both a concerted effort and adequate funding to work towards it. This is the only way for the oncology community to determine how metronomic chemotherapy fits in the overall cancer management schema.

Introduction

Concepts of cancer therapy have evolved significantly over the decades leading to major strides in survival, even in patients with incurable stages of the disease. It is well established that successful outcome of therapy does not solely depend on taking on the cancer cells, but the microenvironment surrounding them that sustains and shields them from potential damage and death. The battle against cancer started in the 1970's with the use of cytotoxics that are administered at or close to maximal tolerated dose (MTD), typically given in combination regimens comprising agents with non-overlapping toxicities [1,2]. The MTD approach aims to disrupt the mitotic processes of the cancer cells that are typically in over-drive that renders them more sensitive to these drugs than normal quiescent cells. But this strategy is rarely successful in cancers of a complex makeup and it is well established that such cancers make use of the microenvironment to survive.

Two important concepts of cancer therapy have emerged progressively over a long period of time to target the microenvironment [3]: vascular supply of tumor cells that provide the essential nutrients and the immune cell milieu that has learnt to "live" with the destructive force of the cancer cells.

The call by Judah Folkman [4] to target the blood supply of cancer cells in 1971 led to a 30-year journey before the first anti-angiogenic drug called bevacizumab was approved in breast and colorectal cancers. Although the survival benefit conferred was at best modest, the achievement can be considered a landmark as the concept of targeting supporting structures like blood supply was clinically validated.

The development of immunotherapy initially was met with more disappointments than successes. However about 2 years ago immune checkpoint inhibitors were proven to confer significant survival benefit in treatment-refractory complex cancers such as melanomas and renal cancers.

Certain cytotoxics when given in a continuous or more frequent manner without extended rest periods have been found to exert a therapeutic effect on the tumor microenvironment. For instance, it can result in a significant anti-angiogenic effect [5,6]. This strategy came about on a hypothesis that endothelial cell recovery can occur during treatment-free period of conventional scheduling and this could support regrowth of tumor cells and thereby increase the risk

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of emergence of drug-resistant tumor cells [7,8]. A closely spaced or continuous administration of cytotoxics akin to the uninterrupted ticking of a metronome as coined by Hanahan was hypothesized to selectively target the proliferating endothelial cells of cancer and spare the quiescent mature endothelial cells of healthy tissues [9]. Moreover avoidance of mutation and development of resistance is possible, as the proliferating endothelial cells are the main targets, which are genetically more stable. This schedule would necessitate a lower dose of cytotoxics to allow frequent administration. Both Folkman's and Kerbel's group have proven this concept elegantly with their in-vitro and in-vivo experiments [5,6].

Chemotherapy may also have potentially useful partnership with immunotherapy in cancer treatment [10]. Several cytotoxics have been shown in preclinical studies to overcome the tumor immunosuppressive environment in several ways [11,12]. In fact the immunomodulatory properties of cyclophosphamide have been known since 1974 when it was shown to reduce T-cell suppressive activity [13]. It is likely that the cytotoxic and immunomodulatory doses of chemotherapy agents would be different and it is also likely that not all chemotherapy drugs have the same immunomodulatory effects on the tumor microenvironment. Metronomic dosing of chemotherapeutic agents may be able to restore the immune response to a certain degree albeit not fully. It is certainly an attractive mechanism worthy of further exploitation.

A recent meta-analysis of metronomic chemotherapy involving 80 Phase I/II trials, of mainly pre-treated patients with advanced/metastatic breast (26.25%) and prostate (11.25%) cancer showed a response rate of 26% and a mean disease control rate of 56%. Grade 3/4 adverse events as expected were rare (anemia 8%, fatigue 13%) [14]. Hence metronomic chemotherapy appears to be both clinically beneficial and safe.

What is metronomic chemotherapy?

While Hanahan used the analogy of the metronome to describe the closely spaced administration of chemotherapy, there is no universally accepted definition [15]. The oft used definition is schedule-based and refers to a chronic administration of chemotherapy at low, minimally toxic doses on uninterrupted close intervals [16]. Klement and Kamen offered an alternative definition of metronomic chemotherapy as the minimum biologically effective dose of a chemotherapeutic agent, which given at regular dosing regimen with no prolonged drug free interval leads to anti-tumor activity [17]. However, both definitions failed to focus on the alternative mechanisms of action of such schedules, which is the most important distinguishing feature of such an administration. Such a definition would need a robust and reproducible way to measure the anti-angiogenic and immune-related effects of metronomic administration and therein lies the limitation of such a definition. A mechanistic definition is critical to distinguish such a schedule from MTD administration, which we have come to appreciate has a very different biological effect. A mechanistic definition would streamline the literature now abundant with reports of clinical effects of so-called metronomic schedules but some with toxicity profiles that seemed to be more in line with MTD schedules. If a purported metronomic schedule published in the literature reported significant degree of grade 3 or 4 toxicities that necessitated frequent interruptions, there is a need to question whether any efficacy of treatment that resulted is truly a metronomic effect and not a MTD effect. It would benefit the medical and research literati if a more accurate definition be consistently applied in the published literature that we can better appreciate how metronomic chemotherapy can fit into overall scheme of cancer management.

Are there biomarkers available to guide metronomic dosing?

The importance of biomarkers to guide drug development, which should also include drug repurposing or repositioning have been dealt with in excellent reviews [18,19]. Biomarkers to indicate achievement of pharmacodynamic effects are important to determine the optimal metronomic dose (OMD) of cytotoxics. While MTD determination is easily established with routine laboratory tests and clinical assessments, OMD determination faces significant challenges. Amongst the many reported mechanisms of anti-cancer actions of metronomic chemotherapy, two main pharmacodynamic parameters of interest in metronomic chemotherapy are probably worthy of further exploration as biomarkers, namely anti-angiogenic and immune effects. These are arguably the most extensively studied in therapies specific for angiogenesis and immune modulation, albeit not translated into routine clinical use due to lack of validation. Though they are not sufficiently sensitive, specific or reproducible to predict response or survival outcome in routine clinical setting, they may still be useful in the research setting to help derive useful data regarding the metronomic activity of cytotoxic agents of interest to guide the appropriate metronomic dosing.

Many potential biomarkers were studied to demonstrate inhibition of targets of angiogenesis when evaluating anti-angiogenic drugs. They include circulating blood biomarkers (cytokines such as VEGF, angiopoetin or thrombospondin-1/2 and circulating endothelial cells), immunohistochemistry (e.g. VEGF and TSP-2), functional imaging (e.g. DCE-MRI, or DCE-CT) and even single-nucleotide polymorphisms (e.g. VEGF, IL6, IL8, etc) [20–26]. Though changes may occur in tandem with treatment administration, neither the baseline levels nor changes have been shown to consistently correlate with response or survival outcome.

Functional imaging (e.g. DCE-MRI) has been explored quite extensively in several small studies. DCE-MRI is an established technique for evaluation of tumor vasculature and has been utilized in early phase clinical trials of vascular targeting drugs [19,24–26]. DCE-MRI is a technique in which a paramagnetic low molecular weight contrast agent is injected intravenously and monitored, with multiple images over a period of minutes, as it enters the tumor blood vessels and subsequently passes into the extravascular and extracellular space. Vascular parameters can be assessed by T1-weighted and T2-weighted sequences. Quantitative parameters of tumor vascularity derived using DCE-MRI include blood flow, permeability-surface area product, fractional intravascular volume and fractional interstitial volume. However functional imaging is limited by the fact that only one or two representative lesions from one tumor site can be selected for measurement and it is needful therefore to assume that changes in levels in the selected lesion reflect similar changes in other unmeasured lesions during anti-angiogenic treatment. Therefore functional imaging fails to take into account the possible heterogeneity in behavior of the disseminated lesions. This trait may account for the inability of functional imaging to predict for benefit consistently in clinical studies [27].

Metronomic chemotherapy has been reported to affect tumor immune biology in several ways. However, like immune checkpoint inhibitors, it does not uniformly affect tumor immune biology within or across tumor types. As such there is a need to characterize comprehensively the effect of metronomic dosing of cytotoxics on the immunosuppressive and immune stimulatory components that define the inflammatory state of the tumor microenvironment. The significant advances made in the field of high throughput technologies can allow a deeper interrogation of the antibody responses, as well as the magnitude, cytotoxic function and T cell receptor repertoire of T lymphocytes than what has been done in