

# Can Targeted Therapy be Successful without Metronomic Scheduling ?

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**Abstract:** In medical oncology, targeted therapy has emerged over the last decade, as the most promising strategy to fight cancer. In addition, a more complete understanding of tumor heterogeneity and pharmacology of the more conventional anti-cancer agents has led to development of metronomic chemotherapy (MC) (i.e. a more frequent administration of anti-cancer agents at lower doses than the usual maximally tolerated dose because it has been realized that time of exposure to an effective drug concentration is more important than simply the dose/m<sup>2</sup> or kg.). Here, we discuss the nature of the specificity of targeted anti-cancer treatments and conclude that optimizing the schedule is an effective way to improve treatment selectivity.

**Keywords:** Metronomic, targeted therapy, cancer, MTD, chemotherapy.

## INTRODUCTION

The introduction of targeted therapies over the last 20 years has changed the face of medical oncology, raising new hopes of achieving both higher cure rates and decreased toxicity. Indeed, targeted cancer therapies may be more effective and less harmful to normal cells than current treatments by targeting molecules that have higher specificity to cancer cells. Since the end of the 90's, a number of new agents have been approved for the treatment of several malignancies. These such as monoclonal antibodies and kinase inhibitors [1, 2]. Some examples include, Trastuzumab, a humanized monoclonal antibody targeting the HER2/neu receptor, approved for treatment of breast cancer [3]. Bevacizumab, another humanized antibody targeting VEGF-A, is a validated agent in a wide variety of human cancers, including colorectal cancer, metastatic breast cancer, glioblastoma, NSCLC and mRCC [4]. Imatinib, Dasatinib and Nilotinib are tyrosine kinase inhibitors targeting BCR-ABL that are approved for chronic myelogenous leukemia [5]. Gefitinib and Erlotinib target the epidermal growth factor receptor (EGFR) tyrosine kinase and are approved in the U.S. for non small cell lung cancer [6]. The mammalian target of rapamycin (mTor) inhibitors family has been proven to be active on advanced stage renal cancer cell or subependymal giant-cell astrocytoma [7]. Although there is a positive impact of these targeted anti-cancer agents on the outcome of cancer patients, it must be however tempered in regards to toxicities observed in the clinic. Although patients receiving targeted therapies display less frequently the "traditional" toxicities associated with conventional chemotherapy such as alopecia, neutropenia or emesis, they often present with new types of adverse events like skin, vascular, cardiac and

gastrointestinal toxicities, proteinuria, venous thromboembolism and hypothyroidism [4,8,-10]. The occurrence of these side effects highlights that these agents are not as targeted as expected. For instance, Dasatinib has been recently shown to have many unexpected targets [11]. It has been proposed that these novel toxicity profiles might be related to receptor cross-reactivity or the presence of the targeted receptor(s) on the surface of or inside non-cancerous cells [8].

## WHAT IS TARGETED THERAPY?

Targeted therapy is defined as a type of medication that blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and/or tumor growth [12]. For decades, the hallmark of medical treatment for cancer has been intravenous cytotoxic chemotherapy. This definition separates targeted therapy from earlier classic drugs that usually "target" all rapidly dividing cells in the body generally by blocking DNA precursor synthesis, blocking DNA synthesis or repair or the process of mitosis. But in fact, all effective treatments in oncology are intrinsically targeted. At worst, some agents have a number of different targets and are then called "dirty" drugs [13]. Actually, what we usually implicitly mean by targeted therapy is that these treatments have an increased selectivity or specificity towards cancer cells as compared to normal healthy tissues and therefore a better tolerance. Thus, to develop a targeted treatment one needs to increase specificity or increase the differential of sensitivity to a given treatment to maintain efficacy while decreasing toxicity.

## CAN DOSE & SCHEDULE MODIFICATIONS LEAD TO INCREASED TREATMENT SELECTIVITY?

A classical way to increase selectivity relies on improving the targeting by delivering more drug to get to the tumor

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and less to normal tissues. Various delivery systems such as antibody conjugates, liposomes decorated with small molecules directed to membrane proteins, small molecules conjugated with toxins are in clinical trial. This has been extensively reviewed elsewhere [14, 15]. Improvement in targeting may also be obtained by generating compounds with greater selectivity for a given target, which should be a unique molecular feature of cancer cells. Nilotinib for instance is a second generation a TKI which has a greater potency and selectivity for BCR-ABL than imatinib [16]. This affinity and specificity should lead to a better outcome for patients with newly diagnosed chronic myeloid leukemia [17]. An interesting point here is that some of the “older” drugs have a greater affinity and specificity for their respective targets than some of the promiscuous TKIs. For example, methotrexate and deoxycoformycin are spectacularly targeted against their specific enzymes [18, 19] having binding constants much higher than imatinib for bcr-abl [20]. The notion of targeting with the newer generation drugs is that the target itself should be more specific for the malignant cells.

A far more affordable way for clinicians to increase treatment selectivity is illustrated by metronomic chemotherapy (MC). MC is defined as the frequent administration of chemotherapy drugs at doses below the maximal tolerated dose (MTD) and with no prolonged drug-free breaks [21,22]. Perhaps more appropriately, it should be defined as the minimum biologically effective dose of a chemotherapeutic agent, which, when given at a continuous dosing regimen with no prolonged drug-free breaks leads to anti-tumor activity [23]. Historically, chemotherapy was given at the MTD every 2-4 weeks to let the healthy tissue recover from the damaging effects of chemotherapy. The use of MTD dosing, infrequently drastically decreases or almost eliminates the chance for selectivity as the organism is literally saturated with the anticancer agents so that unless there is no target but in cancer cells, side effects will occur. The paradigm is using a maximally tolerated dose (MTD) to a dose limiting toxicity (DLT) simply based upon a single dose and allowing time to recover. This classic model did not consider time as a crucial variable [24, -26]. The underlying paradigm (i.e. the more, the better) suggested that the harder you hit, the better the outcome. However, besides its historical use and the required rest period to recover from high-dose chemotherapy, an increasing number of members of the medical and scientific community agree that there is no mechanistic rationale to support MTD-based chemotherapy administered every 3 weeks as the sole strategy to treat cancer patients.

The emergence of targeted therapy has put daily administration of anti-cancer drugs at center stage [27]. Indeed, small molecules such as Imatinib, Dasatinib, Nilotinib, Gefitinib, Erlotinib or Sunitinib or mTOR inhibitors are given on a daily basis to ensure a uninterrupted exposure of the target to the drug. Similarly, although monoclonal antibodies such as Trastuzumab and Bevacizumab are given on a weekly, fortnightly or even thrice monthly basis, the extended half-life of these compounds (i.e. approximately 20-30 days) ensures continuous exposure of the tumor throughout the course of the treatment.

Interestingly, in the emerging field of MC, changes in dose and schedule cannot be dissociated. Indeed, administering very low doses of chemotherapy every 3 weeks would critically hamper the cytotoxic effects on cancer cells without generating new anticancer effects. Inversely, increasing the frequency of high-dose chemotherapy would have disastrous consequences on the patient's health and both approaches would result in ineffective treatments. In contrast, by simultaneously modulating dose and schedule, (i.e. lowering the dose and using protracted schedule), an increased selectivity may be achieved. That is to say that lowering the dose of anticancer drugs while increasing the frequency of administration has led to the discovery that many conventional anticancer agents had potent anti-angiogenic properties and this may increase the therapeutic efficacy of the agent [28] through both a direct cytotoxic and indirect effect on endothelial cells or other stromal elements of the tumor. [21]. Moreover, it has also been shown that when given frequently at low dose, some anti-cancer drugs can not only target the endothelium but also the immune system by activating or restoring its anti-tumor properties [22]. For example, low dose cyclophosphamide or temozolomide have been shown in a number of trials to decrease the number of circulating and intratumoral Tregs, which are involved in tumor-driven immune evasion [29,30]. Elsewhere low dose vinblastine is not only anti-angiogenic but can also activate dendritic cells [31]. Used with different “dose and schedule”, cyclophosphamide and vinblastine could therefore be regarded as an anti-Treg targeted agent and a targeted dendritic cell activator, respectively as opposed to being conventional anticancer agents when used in MTD-based chemotherapy protocols.

Therefore, modulating the dose & schedule of anticancer agents is a potential way to increase tumor targeting and generate potent anti-cancer effects with lower toxicity.

Not surprisingly, dose and schedule also need to be adjusted when using repositioned drugs (i.e. drugs that were not initially developed as anti-cancer agents but thanks to their potent anti-tumor properties have found new applications in medical oncology). Indeed, as these drugs were initially used for instance in pain management (celecoxib [32]) or in non-malignant conditions such as hypertension (propranolol [33]) or diabetes (metformin [34]), the toxicities that can be accepted are lower than those accepted to treat a life-threatening disease such as cancer. The doses administered for their traditional applications are therefore usually low. However, anti-cancer effects can be obtained by increasing the doses of repositioned drugs while still maintaining a good safety profile, especially when compared with MTD-based chemotherapy. For instance, the non-steroidal anti-inflammatory drug celecoxib, a COX-2 inhibitor, has been shown to have potent anti-angiogenic properties [32] and exert anti-proliferative effects against cancer cells when used alone or in combination with radiotherapy, MC, or high-dose chemotherapy [35].

While dose–efficacy curves of standard anticancer agents are usually closely related to the dose–toxicity curves, this is not always true for targeted therapies as some serious adverse events can occur at relatively low dose and/or in a dose-independent manner. Nevertheless, using lower doses

clearly decreases the risk of higher toxicities and is a pragmatic way of adjusting treatment for a given patient who experiences adverse events. One could thus suggest that part of the tumor specific targeting is related to the use of a low dose, well below the MTD. This may decrease the impact on normal healthy cells as the "normal cells" in a tumor may often be more metabolically active than usual as they were reactive to or recruited by the cancer cell.

Of note, in this context, MTD is not very well adapted and should be replaced by other endpoint in phase I clinical studies, such as the description of a dose administrable over an extended period of time [36] or alternatively the minimum effective dose. By looking at the field of microbiology and the strategies used with antibiotics or antiviral agents to fight bacteria or virus, one can notice that treatments mostly rely on daily effective concentrations above the minimum effective concentrations [37] and not spaced out MTD anti-biotherapy. Of note, the concept of mutant prevention concentration has been introduced which is concentration above which resistance is unlikely to occur [38]. This concept might also be relevant for metronomic scheduling in cancer and doubtlessly deserves additional attention.

## CONCLUSION

The concept of targeted therapy is still a relatively new paradigm in oncology; its commonly accepted main feature is pre-defined selectivity. As mentioned above, targets and selectivity may change according to dosing and schedule. Thus, overall, metronomic scheduling accounts for a part of target therapy selectivity. Therefore, modulating doses and schedule can allow us to better target cancer (or some of its critical component) and increase selectivity.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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