Continuous low-dose anti-angiogenic/metro nomic chemotherapy: from the research laboratory into the oncology clinic

The words ‘side effect’ usually evoke a mixture of fear and anxiety in cancer patients receiving chemotherapy. But, as it turns out, not all side effects are necessarily harmful, or even undesirable. While the collateral damage inflicted upon the dividing bone marrow progenitors, gut mucosal cells or hair follicle cells by DNA damaging or microtubule inhibiting agents is certainly undesirable, the same cannot always be said of the damage inflicted on endothelial cells present in a tumor’s growing neovasculature. A proportion of these cells are dividing at any given time, making them, at least in theory, sensitive to drugs which preferentially damage or destroy cycling cells [1]. Polverini’s group first reported anti-angiogenic effects mediated by conventional cytotoxic anticancer drugs as long ago as 15 years, and since then most common anticancer chemotherapeutic agents, belonging to all major classes, have been shown to be capable of inhibiting angiogenesis [2]. This prompted George Sledge and colleagues recently to suggest the notion of ‘redefining’ chemotherapeutic drugs as anti-angiogenics [3].

What would be the advantage of using chemotherapeutics as possible angiogenesis inhibitors? For a start, the targeting of a normal, terminally differentiated and genetically stable endothelial cell presents the theoretical possibility of avoiding, or at least delaying, the onset of acquired drug resistance which, in part, occurs because of the massive and diverse genetic instabilities present in cancer cells [4]. These genetic instabilities are a major mutational force in the Darwinian evolutionary generation and selection of drug-resistant mutant cancer cells, but they are largely, if not entirely, absent from normal host cells such as bone marrow or endothelial cells [5, 6]. Presumably this explains the fact that myelosuppression remains the same (or worsens) in patients receiving standard chemotherapy [7] even while their tumor cells become progressively resistant to the very same drugs. This raises a conundrum: many cancers are intrinsically resistant to drugs which preferentially damage or destroy cycling at any given time, making them, at least in theory, sensitive to drugs which preferentially damage or destroy cycling cells [1]. Polverini’s group first reported anti-angiogenic effects mediated by conventional cytotoxic anticancer drugs as long ago as 15 years, and since then most common anticancer chemotherapeutic agents, belonging to all major classes, have been shown to be capable of inhibiting angiogenesis [2]. This prompted George Sledge and colleagues recently to suggest the notion of ‘redefining’ chemotherapeutic drugs as anti-angiogenics [3].

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A possible solution to this conundrum was published recently by Judah Folkman’s laboratory [8]. Browder et al. reported that when a drug such as cyclophosphamide was given to tumor-bearing mice at the maximum tolerated dose (MTD), which necessitated breaks at least every 3 weeks to allow for bone marrow recovery, apoptosis of endothelial cells in the tumor microvasculature was observed, but this damage was largely repaired during the rest periods [8]. Hence, little therapeutic benefit could be derived from this transient anti-angiogenic, or anti-vascular effect. However, if the same drug was administered chronically on a once a week schedule—without breaks—at a lower dose (e.g. one third of the MTD), the repair process was compromised and the anti-angiogenic effects of the drug were not lost [8]. Indeed, in a series of remarkable experiments it was reported that mouse tumors which had previously acquired resistance to the drug administered using the conventional MTD schedule, responded dramatically over time to the same drug, when the lower dose, more frequent schedule was started [8]. Reversal of acquired resistance was attributed to shifting the target of the drug to the genetically stable, accessible, drug-sensitive endothelial cell compartment of the tumors [8]. This method of administering chemotherapy was dubbed ‘anti-angiogenic chemotherapy’ by Browder et al. [8] or ‘metronomic’ dosing by Hanahan et al. [9]; the latter term implies regular, frequent administration of drug, which requires lower doses to be used.

Given all the caveats of mouse tumor models, it is intriguing and perhaps reassuring to note that there are actually many clinical precedents for the observations of Browder et al. as summarized recently by Kamen et al. [10], and Gately and Kerbel [11]. For example, significant proportions of breast and ovarian cancer patients (as high as 62.5%) who had stopped responding to MTDs of a taxane given once every 3 weeks, were subsequently found to respond to the same drug once it was switched to a weekly schedule at about one third of the MTD [12–15]. Such weekly schedules using lower drug doses were instituted to minimize the toxicities associated with once-every-3 week MTD taxane protocols. It is not yet known whether the responses observed in these ‘resistant’ patients have an anti-angiogenic basis, or whether such increased response rates will translate into a significant prolongation of survival, as they do in mice [8, 16].

It may be argued that continuous low-dose chemotherapy is scarcely a new concept, and that there is no evidence for a major benefit in survival in humans using such dosing and administration schedules. However, aside from some ongoing clinical trials to evaluate and compare directly continuous low-dose versus standard chemotherapy regimens, truly long-term, regular frequency, low-dose chemotherapy (i.e. without any breaks at all) has been uncommon in adult oncology. In
contrast, there are pediatric malignancies, such as acute lymphoblastic leukemia, where such long-term ‘maintenance’ schedules are used for up to 3 years with significant success, and attempts at shortening these maintenance regimens results in loss of efficacy [17]. In pediatric malignancies, where long-term morbidity is of particular relevance, the motivating force behind the use of such ‘milder’ treatment regimens has been mainly the avoidance of toxicity, but its use has since been bolstered by increased antitumor efficacy and prolongation of survival [10]. Historically, these protocols have been empirically derived and the understanding of the underlying mechanisms is retrospective. With this background in mind, the paper by Colleoni et al., which appears on pages 73–80 of this issue of Annals of Oncology [18], may come to represent an important milestone in the concept of using low-dose metronomic/anti-angiogenic chemotherapy in the clinical setting for treatment of adult, advanced stage, solid tumors. It reports a considerable efficacy in patients treated with this type of therapy, and points out the significant advantages of using this non-toxic protocol, especially for the frail elderly and children.

Colleoni et al. treated a total of 64 women with advanced metastatic cancer using a combination of oral low-dose methotrexate (MTX) and oral cyclophosphamide (CTX). The dose of CTX was 50 mg/day, continuously, while MTX was administered orally at 2.5 mg, twice a day, on days 1 and 2 every week. Fifty of the patients had two or more sites of metastatic disease, and 51 had progressive disease at study entry. All patients had prior chemotherapy, 41 as adjuvant or neoadjuvant therapy, and 52 for metastatic disease. Among 63 evaluable patients there were two complete remissions (CR) and 10 partial remissions (PR) with an overall response rate of 19%. In view of the palliative goal of the treatment in this setting, the investigators felt it was reasonable to consider disease stabilization (i.e. NC, no change for 24 weeks or longer) as an appropriate clinical outcome [18], raising the overall success rate (i.e. CR + PR + NC for at least 24 weeks) to 32%. A total of 26% patients were still responding after 12 months of continuous treatment. Remarkably, this was achieved in the absence of any serious toxicity, or adverse events. Thus, grade ≥2 leukopenia was observed in only 13 patients. Alopecia, nausea/vomiting and mucositis of grade 2 or more was very rare, occurring in 0% to 5% of patients.

Hopefully, these encouraging results will lead to further confirmation of this concept in randomized-controlled clinical trials. As it stands, they add to a growing body of evidence which challenges the dogma that ‘more is better’ when it comes to chemotherapy (8–11, 19–21). As such, host toxicity as a surrogate marker of simultaneous antitumor drug activity needs to be seriously re-evaluated. Colleoni et al. also note the personal and economic costs of their treatment regimen. The low toxicity of the regimen and the oral bioavailability of the drugs make it particularly suitable for outpatient therapy, significantly enhancing the quality of life of the patients. The decrease of hospital admissions for febrile neutropenias, mucositis and necrotizing inflammation of the colon in neutropenic patients is likely to translate into a significant economic benefit, considering the cost of the treatment, which is estimated to be in the range of US$10 per month.

Some new developments may hasten the movement of this type of treatment out of the palliative care field and into the realm of cancer therapeutics. As first reported by Klement et al. [21] and confirmed recently by Bello et al. [22], the effectiveness of continuous low-dose, metronomic, chemotherapy regimens, at least in animal models, can be greatly improved when they are combined with investigational anti-angiogenic, endothelial specific, drugs such as neutralizing monoclonal antibodies to receptors for vascular endothelial cell growth factor (VEGF), which are highly expressed by the activated endothelial cells of newly formed tumor microvasculature. Such combinations can induce remarkable responses including sustained tumor regressions, even of drug-resistant tumors [23], as well as marked prolongation of survival, and can do so in the apparent absence of any serious host toxicity [21, 22]. The direct comparison of combinations of anti-angiogenic agents with either standard-dose or low-dose chemotherapy points out the difficulty in using primary tumor size as an endpoint measurement for clinical trials. As shown by Bello et al. [22], both standard-dose and low-dose combinations may result in equivalent suppression of primary (glioma) tumor, but when survival rates are compared the significance of low toxicity becomes obvious, and the benefit of low-dose chemotherapy is shown. In contrast, the effects of continuous low-dose chemotherapy alone, standard-dose chemotherapy alone or anti-angiogenic therapy alone, may be much less impressive [21, 22].

In view of these results and the report of Colleoni et al., as well as other clinical studies using metronomic-like chemotherapy regimens [10, 11], there is a compelling rationale for the initiation of clinical trials using continuous low-dose chemotherapy regimens of the sort described by Colleoni et al. combined with investigational anti-angiogenic drugs such as VEGF receptor-2-blocking antibodies or small-molecule antagonists. The rationale is that the effects of low-dose chemotherapy on activated endothelial cells might be selectively amplified by using such combinations of drugs, especially when endothelial-specific drugs that target survival mechanisms of such cells are used, as proposed by Klement et al. [21]. Only a limited number of commercially available substitutes for these direct inhibitors of endothelial cells are presently available and drugs such as thalidomide [24] and selective cyclooxygenase-2 (COX-2) inhibitors [25, 26] are being used in this setting. In this regard, Colleoni et al. report preliminary evidence that their continuous low-dose CTX/MTX regimen might indeed involve an anti-angiogenic mechanism, one that could, in the opinion of the authors, be boosted by the addition of a specific anti-endothelial agent. Despite the difficulties associated with efforts to correlate serum or plasma levels of VEGF and the lack of sensitivity of the method, the study reveals a marked drop in VEGF in the serum of these
patients. The median VEGF levels of the subgroup of patients on treatment for at least 2 months decreased with treatment from 315 pg/nl at baseline to 248 pg/nl at 2 months, and 195 pg/nl after 6 months. While intriguing, measuring changes in levels of serum VEGF is not yet accepted as a valid, or reliable, surrogate marker of the angiogenic output of a tumor. To date, there is, unfortunately, no reliable assay to monitor and quantify changes in tumor angiogenesis in vivo—a serious impediment to assessing the effects of putative anti-angiogenic drugs or treatments.

Some significant advances in clinical oncology using standard- or high-dose regimens have been achieved, but such gains seem to have reached a plateau over the past two decades, in part as a result of drug resistance. The shift to alternative targets within the tumor and the use of these targets for the subset of patients who, either because of intrinsic or acquired resistance, are not likely to respond to standard therapy holds promise. The results of Colleoni et al. may herald a gradual shift from standard MTD, or high-dose chemotherapy, to, at least in the chemoresistant population, an alternative therapeutic modality. At present, most of the new molecular targeted therapies such as Herceptin™ or EGF receptor blocking agents such as Iressa or C225 (Cetuximab), as well as anti-angiogenic drugs, e.g. Avastin (the humanized monoclonal antibody to VEGF), are used with standard chemotherapy regimens, which negates their superior safety profiles. As the cancer patient population ages, should these combinations be evaluated in the setting of low-dose, frequent, continuous chemotherapy as well? Perhaps, the time may not be too far off when the term ‘side effect’ for chemotherapy drugs not only loses its dreaded connotation, but takes on a new, and positive, meaning.

Acknowledgements

We thank Cassandra Cheng for her excellent secretarial assistance.

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