Low-Dose Metronomic Chemotherapy: Myth or Truth?

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Cytotoxic anti-proliferative agents are the mainstay of therapy for pediatric and adult cancer. Based on pre-clinical experiments, the log-dose survival curve model for cancer cell kill became the leading model for chemotherapy dose calculation. Conventional cytotoxic drugs were designed for use at maximum tolerated dose (MTD) to treat cancer [1]. This strategy of MTD chemotherapy has led to cure and disease control in a significant number of patients but is associated with significant short-term and long-term complications especially in children. Despite an initially impressive tumor regression or even remission, regrowth or recurrence is quite common in metastatic cancer or in tumors of poor biology [2]. Based on this, it is not surprising that pediatric oncologists have a vested interest in minimizing toxicity while increasing drug efficacy.

Recent studies have shown that cytotoxic drugs used at much lower doses and given more frequently (low-dose metronomic (LDM) chemotherapy) may have the potential for anti-cancer efficacy by way of a secondary alternative mechanism, i.e., inhibition of tumor angiogenesis [3–5]. Interestingly, when one looks back at the history of pediatric cancer therapy, several successful approaches could well be called ‘metronomic chemotherapy’ but instead are known as ‘maintenance therapy’. Pediatric oncologists have shown that daily mercaptopurine and weekly methotrexate is a successful combination in leukemia [6]. Further, the combination of weekly vincristine and low-dose daily cyclophosphamide is effective in neuroblastoma [7] and weekly vincristine is often used in Wilms’ tumor [8].

Two landmark publications by Klement et al. [9] and Browder et al. [10] demonstrated that LDM chemotherapy has an anti-angiogenic effect. Since then a significant number of preclinical studies confirmed the anti-angiogenic effect of LDM chemotherapy, demonstrated increased efficacy when combined with anti-angiogenic agents [11–14], and identified potential surrogate markers of anti-angiogenic activity [15–17].

In this edition of ONKOLOGIE, Sterba and colleagues [18] demonstrate the activity of combining a biodifferentiating agent (retinoic acid) with an ‘anti-angiogenic metronomic chemotherapy regimen’ (temozolomide, etoposide and celecoxib) and confirm the safety of this approach. Interestingly, they report a very significant 64% response rate in this heavily pretreated patient population with relapsed or very high-risk diseases. However, it is difficult to conclude whether this combination is truly anti-angiogenic or biodifferentiating or both. The major drawback of their study is the lack of biomarkers to support the mechanism of action of this apparently effective regimen. This study is similar to a recent report from Kieran et al. [19] who demonstrated that the combination of celecoxib, thalidomide, LDM etoposide and LDM cyclophosphamide is safe and can induce long-term stable disease in very heavily pretreated pediatric patients. In this report Kieran also was unable to validate any biomarkers to support the anti-angiogenic nature of this therapy although the attempt to look at changes in the plasma levels of various proteins involved in angiogenesis was made. Our own experience has shown that a ‘lower’ dose of temozolomide administered regularly or metronomically to a refractory brain tumor patient population can lead to a significant response rate and stable disease. However, this approach can be associated with chronic toxicity such as severe lymphopenia with opportunistic infection and therefore careful patient monitoring is critical [20]. In another of our studies using LDM vinblastine or cyclophosphamide and celecoxib in heavily pretreated patients, we observed impressive durable stable disease with no toxicity [21]. It is important at this time to distinguish between true LDM chemotherapy and a ‘lower’ dose dense chemotherapy and raise the question of designing rational dosing regimens rather than empirically selecting 10–33% of the MTD which is often done [22]. In both LDM and dose dense regimens, a shortened interval between doses and lack of an extended rest peri-

od between cycles is used; hence they can both be considered 'metronomic'. However, while dose dense chemotherapy involves the administration of doses lower than the MTD, the total cumulative dose for a given cycle is greater than what would have been administered in a classical MTD regimen [19]. The target of dose dense therapy remains to be the tumor cell while in LDM chemotherapy regimens, tumor vasculature is postulated to be the target and this is thought to result in an overall anti-tumor effect. Another important distinction is the toxicity of these two types of regimens. While in both cases, the smaller individual doses result in greater tolerability, toxicity is more common and expected in dose dense regimens. On the other hand, in LDM chemotherapy regimens toxicity is either greatly reduced or absent altogether [23, 24]. This issue of toxicity is illustrated in the two examples from our experience cited above.

In similar metronomic chemotherapy studies in adults, the preliminary results are promising, however, more research with larger sample sizes is required to truly establish the efficacy of these investigational therapies. Recently Buckstein et al. confirmed the efficacy of LDM cyclophosphamide and celecoxib in refractory high-grade lymphoma [25] and Young et al. demonstrated that the combination of low-dose cyclophosphamide, weekly vinblastine and rofecoxib is effective in a subset of Hodgkin's disease patients [26]. Garcia and colleagues have recently reported remarkable findings in their interim analysis of a phase II study of low-dose cyclophosphamide and bevacuzimab in recurrent, refractory ovarian cancer [27]. Low-dose cyclophosphamide has also been used with low-dose metrotrexate in the treatment of metastatic breast cancer and some of the responses have been demonstrated [28, 29].

An important component of metronomic therapy remains a challenge for researchers – the validation of a surrogate marker of angiogenesis that can be used to monitor treatment activity and verify if a therapy is truly anti-angiogenic. Such a marker is necessary since this new approach to cancer therapy may not result in rapid tumor regression. To date, none of the plasma markers studied such as VEGF, bFGF and TSP-1 have been successfully validated as being able to monitor the activity of anti-angiogenic metronomic chemotherapy. Current evidence suggests that there appears to be much more hope in studying circulating endothelial cells (CECs) and circulating endothelial progenitors (CEPs) as potential surrogate markers. Recently, Bertolini et al. observed a differential effect of

MTD and LDM cyclophosphamide on CEPs: high-dose cyclophosphamide induced a robust immobilization of CEP resulting in drug resistance while LDM cyclophosphamide resulted in a decrease in the number and viability of CEPs and sustained inhibition of tumor growth [16]. A major challenge in using CECs and CEPs, however, is the standardization of analytical methodologies and this is something that must be addressed particularly if multicenter studies will be conducted. Another challenge is the 're-definition' of valid clinical endpoints that should be incorporated into studies of anti-angiogenic therapies. It is becoming increasingly accepted that the classic RECIST criteria may not apply in the evaluation of these therapies. For the time being, as this approach is being tested in early phase clinical trials meaning that patients with late stage disease and high tumor burdens are being evaluated, the ability of a therapy to induce tumor dormancy which can result in stable disease with good quality of life can and should be regarded as a valid clinical endpoint.

The study of LDM or anti-angiogenic chemotherapy has truly opened up a whole new field for researchers and patients alike. New strategies incorporating this therapy being developed and studied include the concurrent use of LDM chemotherapy and MTD chemotherapy which may lead to even higher rates of remission as demonstrated preclinically by Pietras and Hanahan [30] and as is currently investigated by the Children's Oncology Group for metastatic Ewing's sarcoma. Furthermore, pharmaceutical companies are now interested in developing drugs that can be used metronomically in combination with anti-angiogenic agents.

Based on the available evidence, LDM chemotherapy is far from a myth. There clearly is a great deal of promise in this approach, however, the future success of incorporating it into routine practice requires that a consensus be reached on several major issues including: a clear definition of LDM chemotherapy that related to anti-angiogenesis, the identification of appropriate anti-angiogenic agents to be combined with LDM chemotherapy, the definition of the optimum biological doses of these agents, the validation of biomarkers to monitor treatment activity, the confirmation of long-term safety since due to the chronic nature of administration, the selection of a disease subset that is likely to respond to a particular therapy, and the design of clinical trials and incorporation of new clinical endpoints that can truly speak to the effectiveness of these therapies.

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