Metronomic chemotherapy beyond misconceptions

We read with interest the paper recently published in Haematologica "Metronomic therapy is an effective salvage treatment for heavily pre-treated relapsed/refractory multiple myeloma" by Papanikolaou at al.[1] This paper reports the results of a retrospective analysis of 186 heavily pre-treated relapsed/refractory multiple myeloma patients who were treated on an outpatient ambulatory basis with a so-called "metronomically scheduled drug therapy" developed by the Myeloma Institute of Research and Therapy of the University of Arkansas for Medical Sciences (Little Rock, AR, USA).[2] The treatment regimen consisted of bortezomib and dexamethasone administered on Days 1, 4, 7, 10, 13 and 16 together with 16 days of thalidomide and continuous IV infusion of doxorubicin and cisplatin with or without the addition of the m-TOR inhibitor rapamycin. The authors concluded that metronomic therapy is an effective late salvage treatment in relapsed/refractory multiple myeloma, with a high overall response rate and a favorable toxicity profile. Oddly enough, the authors report that the majority of patients (75%) managed to receive only one cycle of therapy and at the same time they state that half of the patients achieved at least partial remission by IMWG criteria.[1] However, it should be noted that 2 consecutive assessments are required to define response in MM according to the IMWG criteria.[3]

We would like to comment on this article because it contains critical misconceptions about metronomic chemotherapy and treatment efficacy. The term "metronomic" used in this paper is loosely and somewhat arbitrarily accredited to the study therapy. Cancer chemotherapy is conventionally administered in cycles of maximum-tolerated doses (MTD) with the aim of inducing maximum possible apoptosis on cancer cells. However, MTD chemotherapy requires treatment-free intervals to allow recovery of healthy proliferating tissues from toxicities, facilitating at the same time repair of damaged tumor and endothelial cells rendering cancers aggressive and resistant.[4,5] Metronomic chemotherapy stands in the antipode of MTD chemotherapy and its very concept is that of an angiogenesis targeted cancer therapy. It refers to dense, uninterrupted administration of sub-toxic doses of chemotherapy over protracted periods of time, even years, with no prolonged drug-free intervals with the main aim of altering the tumor microenvironment by inhibiting tumor supporting vasculature, inducing tumor dormancy and possibly restoring immune surveillance.[6-8]

The therapy applied in this study was neither chronic nor regularly administered without any breaks. It was actually a variation of the VTD regimen enhanced by continuous administration of doxorubicin and cisplatin over 16 days plus or minus rapamycin. Unfortunately, in this paper the length of each cycle is not clear. The authors acknowledge that therapy was applied off-protocol in the study population and we assume that most likely patients were scheduled to receive treatment every three or four weeks, i.e. with at least one or two drug-free weeks. Although two-thirds of patients received only one cycle of treatment, it would be helpful to know how long the treatment gaps between cycles were in the 25% of patients who managed to receive further courses of therapy. We suggest that researchers should avoid confusing prolonged administration of chemotherapy over days with chronic uninterrupted administration of metronomic chemotherapy,[9,10] and we believe that the suggested schema, although representing an interesting therapeutic option, does not fulfill the criteria of "metronomic therapy" and should not be considered as such.

Another issue with this article is the unfortunate misuse of the term "efficacy". Efficacy of any therapy is only assessed in randomized phase III trials and refers to clinical benefit documented by terms of either improvement in symptoms or prolongation of survival measures such as overall survival (OS), time to progression (TTP), progression free survival (PFS) and, if possible, time to next treatment (TNT).[3,11] Unfortunately, none of these conditions were applied in this retrospective study. Moreover, Kaplan-Meier plots of OS and PFS were almost identical between patients who responded and those who did not respond to treatment according to IMWG criteria (see Papanikolaou et al., Figure 2)[1].

In summary, we agree that relapsed refractory myeloma represents a challenge and there are still unmet medical needs in this setting, However, we suggest that it is prudent not to make loose use of technical medical terms that could lead to misconceptions.

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