Reply to "Metronomic chemotherapy beyond misconceptions" - Haematologica 2013;98(11):e145

In their recent comment on our manuscript "Metronomic therapy is an effective salvage treatment for heavily pre-treated relapsed/refractory multiple myeloma", Drs. Hatzimichael and Briasoulis generally agree with the findings and results of metronomically scheduled chemotherapy for relapsed refractory patients, a challenging group of patients with an unmet medical need. However, the Authors raise some concerns about terminology and definitions, which we would like to clarify.

In the reported retrospective study, responses were evaluated on at least two consecutive assessments for every individual case before the start of a new therapy according to the latest IMWG criteria.[1] This allowed us to not only report response rates, but also time to best response. It should be noted that the term "two consecutive assessments" refers to distinct time points and allows assessment of response even after a single cycle of therapy.

As the Authors correctly point out, the concept of "Metronomic chemotherapy stands in the antipode of MTD (maximum-tolerated dose) chemotherapy and is by concept an angiogenesis targeted cancer therapy". In fact, the antiangiogenic effect forms the foundation of metronomic chemotherapy[2] and it is the only one that has been convincingly demonstrated *ex vivo*.[3-5] For this reason, metronomic chemotherapy is often combined with the anti-VEGF antibody bevacizumab in solid tumors.[6] Metronomic drug treatments have shown promising therapeutic activity using drug administration schedules that range from repeated administration every 6-7 days, to daily or even continuous drug treatment.[2,7] To the best of our knowledge, the duration of the treatment per se does not constitute a defining criterion for the term "metronomic" but rather (as the Authors note) the prolonged administration of sub-toxic doses of chemotherapy aimed at altering the tumor microenvironment by inhibiting the tumor supporting vasculature. As we highlighted in our discussion, the regimen used represents a slightly more intense approach over a shorter period of time compared to other metronomic regimens. However, at a dose of 1-3 mg/m^2 per day for adriamycin and 1-3 mg/m^2 per day for cisplatin, drug dosing was well below the customary MTD doses in myeloma therapy. The same is true for the continuous infusion of these agents in a time period of 16 days. Furthermore, more than 90% of the patients had already been previously treated and relapsed after the combined use of bortezomib and immunomodulatory drugs (IMID) thus making a direct antimyeloma effect of these agents very unlikely. Although mTOR inhibitors failed to show any direct antimyeloma activity,[8] they were included in this regimen because of their anti-angiogenic effect.[9] Thus the mode of administration as well as the selection of drugs aimed at suppressing angiogenesis is, in our opinion, clearly in line with the concept of metronomic therapy.

We agree with the Authors that randomized phase III trials provide the best evidence for the efficacy of a treatment. Traditionally, they are preceded by phase I and phase II prospective trials which are based on either in vitro data, ex vivo data or retrospective series. Depending on the clinical endpoints chosen to demonstrate study efficacy, it is the level of evidence that is changing from the various study types, not the reported efficacy per se.[10] We report 4 of the 6 important clinical endpoints suggested by the US Food and Drug administration for clinical trials in oncology: complete response (CR), overall response rate (ORR), overall survival (OS), progression free survival (PFS).[11] The median OS reported in our series (11 months) compares favorably with the OS reported by Kumar et al. (9 months) in a multicenter international study involving a similar group of patients.[12] Since the use of the term "efficacy" has been mainly linked with prospective trials, which represent a controlled experimental research trial, in our manuscript we mainly used the terms "effective"-"effectiveness" to refer to the benefit of a treatment when used in daily practice,[10] in accordance with the conditions of our retrospective study. We, therefore, feel confident that the metronomically scheduled therapy reported by us is an effective treatment.

Finally, as the Authors correctly point out, and as we discuss in our paper, responses according to IMWG criteria did not correlate with OS or PFS. We and others have shown in the past that it is not necessarily the depth and onset of response, but rather the duration of response which most closely correlates with survival in newly diagnosed,[13,14] as well as relapsed/refractory MM.[15]

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