In Response: We read with interest the reply by Ferretti and colleagues to our recent article in Clinical Cancer Research (1). We show appreciation to the authors for further emphasizing that fractioned and intermittent administration of bisphosphonates represents a new potential therapy targeting the endothelial-tumor-stroma. There is growing scientific evidence that better targeting of the bisphosphonates to cells outside bone could more likely be achieved by more frequent administration of low doses (2, 3). These data are supported by the pharmacokinetic profile of zoledronic acid (ZA). This bisphosphonate is prevalently accumulated into the bone and constantly dismissed in the circulation at very low concentrations by the bone turnover. As a consequence, its circulating plasma levels are low and short lasting. For this reason, repeated pulses of ZA could be useful in the maintenance of active plasma concentrations of ZA. Thus, metronomic (commonly identified as intermittent administration of low doses of anticancer drugs) bisphosphonate administration may lead to significant intracellular accumulation over time in tumor cells.

Although the precise mechanism of this effect is still not well known, it is reasonable to hypothesize that clinical fractionated dosing of ZA may inhibit several antiangiogenic-related cascades at different cellular and molecular levels. It has been shown that ZA may affect angiogenesis (i.e., the formation of new vessels by sprouting of preexisting mature endothelial cells and inhibiting endothelial cell adhesion and migration) but only at higher concentrations (4). On the other hand, we may hypothesize that, at lower concentrations, such as during metronomic administration, ZA could affect vasculogenesis (i.e., the creation of primordial vessels from endothelial progenitor cells derived from bone marrow; ref. 5). The endothelial progenitor cells possess the ability to migrate, colonize, proliferate, and, ultimately, differentiate into endothelial lineage cells appearing to contribute to tumor vessel formation by incorporating into the neoendothelium. (6). The inhibition of endothelial progenitor cell mobilization results in retardation of tumor growth (6). Vascular endothelial growth factor (VEGF) induces the proliferation, differentiation, and chemotaxis of endothelial progenitor cells and is essential for survival of these progenitors (7). It has been shown that circulating endothelial cell levels can be altered by chemotherapeutic and antiangiogenic treatments, such as metronomic chemotherapy or VEGF inhibitors (8). For all these reasons, we could hypothesize that fractioned and intermittent administration of ZA may target directly EPCs. Therefore, based on this stimulating hypothesis, we intend to investigate the effects in humans of ZA therapy on the number and functions of circulating EPCs.

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References
Zoledronic Acid and Angiogenesis
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