To the Editors: In a recent issue of *Clinical Cancer Research*, Santini and co-workers (1) assert that zoledronic acid (ZA) may inhibit several antiangiogenic-related cascades and its metronomic administration could represent a new potential therapy targeting the endothelial-tumor-stroma behavior. We agree with the authors because better targeting of ZA to cells outside bone could more likely be achieved by more frequent administration of low doses. Thus, metronomic ZA administration could lead to significant intracellular accumulation over time in tumor cells (2).

In cervical tumors, the antineoplastic responses due to impaired angiogenesis and reduced vascularity could result in part from the targeting of matrix metalloproteinase (MMP)-9. MMP-9 could mobilize vascular endothelial growth factor (VEGF) and increase its association with VEGF receptor-2. ZA suppresses MMP-9 expression by tissue-infiltrating macrophages and inhibits its activity, reducing association of VEGF with its receptor on angiogenic endothelial cells (3). In mice, a combinatorial regimen involving a MMP inhibitor along with metronomic chemotherapy produced regression and survival benefit against large end-stage pancreatic tumors. On the other hand, ZA can also directly inhibit proliferation of the angiogenic endothelial cells. Bisphosphonates, however, have been used in animal models at high doses, which are not comparable with the clinical dosing regimens used for the treatment of cancer patients with skeletal metastases (4).

With regard to the ability of ZA to inhibit MMP-9, it is worthwhile noting that MMP-9 is involved in mobilization of circulating endothelial progenitor cells and hematopoietic stem cells from the bone marrow. MMP-9 induced in bone marrow cells causes the conversion of Kit ligand from a membrane-bound, adhesion/survival-promoting molecule to a soluble survival/motogenic molecule, releasing soluble Kit ligand and permitting the transfer of endothelial and hematopoietic stem cells from the quiescent to proliferative niche (5). Release of soluble Kit ligand by MMP-9 enables bone marrow repopulating cells to translocate to a permissive vascular niche, favoring differentiation and reconstitution of the stem/progenitor cell pool. The mobilization of both hematopoietic stem cells and VEGF receptor-2–expressing circulating endothelial progenitor cells to the circulation occurs in response to VEGF and is MMP-9 dependent (5). MMPs and the VEGF/VEGF receptor-2 system are responsible not only for the formation of the dense vascular network but also for the recruitment and infiltration of bone marrow–derived macrophages. Depleting tumor-associated macrophages and tumor-associated dendritic cells, however, does not eliminate other stromal sources of proangiogenic mediators (i.e., mast cells, neutrophils, fibroblasts, other dendritic cell subsets, and possibly pericytes). For this reason, tumor-associated macrophage depletion remains an adjuvant treatment that has to be combined with chemotherapy or radiotherapy.

References


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