Cancer Chemother Pharmacol (2006) 58: 284
DOI 10.1007/s00280-005-0154-9

LETTER TO THE EDITOR

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Reply to letter to the editors (K Altundag et al.)

Received: 30 September 2005 / Accepted: 1 November 2005 / Published online: 6 December 2005

The authors would like to thank Dr. Altundag and colleagues for their interest in our paper "Phase I/II dose escalation study of angiotensin 1–7 [A(1–7)] administered before and after chemotherapy in patients with newly diagnosed breast cancer (Cancer Chemother Pharmacol 12:1–10, 2005). We agree with Dr. Altundag that micrometastases, disseminated before or around the time of surgical therapy may contribute to subsequent metastatic disease. However, we do not agree that angiotensin 1–7 [A(1–7)] is likely to contribute to proliferation of metastatic disease. Indeed, we have directly assessed the response of primary breast cancer as well as endometrial adenocarcinoma, colonic adenocarcinoma, and ovarian adenocarcinoma cells to A(1–7) in clonogenic assays and found A(1–7) to effectively eliminate survival of these cells. Gallagher and Tallant have also shown inhibition of lung cancer cell growth by A(1–7). The studies referred to by Greco et al. [4] on cell proliferation of human cultured breast epithelial cells relate to angiotensin II type 1 receptor responses. At least three receptors bind to angiotensin peptides with substantial differences in affinities for specific peptide sequences. Angiotensin II is the primary ligand for AT1 and AT2, while A(1–7) is the primary ligand for MAS, especially at physiological concentrations. Gallagher and Tallant [2] showed that A(1–7) inhibited proliferation of lung cancer cells through inhibition of the ERK 1 and ERK2 pathways via MAS.

Our studies, as well as those of others, show that A(1–7) in concentrations appropriate for human therapeutics does not principally interact with the AII type 1 receptor [3, 6, 8]. Rather, the MAS receptor appears to be a primary target of A(1–7) [7]. Importantly, studies have shown that expression and interaction of A(1–7) with MAS results in inhibition of the angiotensin type 1 receptor [1, 5]. Further, Tallant and Clark [9] reported that the effects of A(1–7) on vascular growth may result, in part, from inhibition of vascular smooth muscle cell growth. This action of A(1–7) is mediated through inhibition of ERK1 and ERK2 pathways. We agree with Dr. Altundag and colleagues that A(1–7) may be an important attenuator of cytopenias following antineoplastic chemotherapy resulting from hematopoetic progenitor cell responses in the bone marrow. Further elucidation of these complex biological responses should come from continued clinical studies.

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