Plerixafor inhibits myeloid cell recruitment and improves the radiocurability of cervical cancer

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Abstract
Background: There is an important need to improve the effectiveness of radio-chemotherapy (RTCT) for cervical cancer. These tumors recruit myeloid cells from the bone marrow via the CXCL12/CXCR4 pathway, which in turn influence vascular function and radiotherapy response. The objective of this study was to explore combined treatment with Plerixafor (a CXCL12/CXCR4 inhibitor) and standard RTCT on primary tumor control and the development of metastases, using xenografts derived directly from patients with cervical cancer.

Methods: Two primary xenografts (OCICx13 and OCICx20) were grown in the cervices of immune deficient mice. These tumor models have been shown to mirror the clinical and biological behavior of cervical cancer in patients. To simulate clinical treatment, image-guided radiotherapy (30 Gy in 15 daily fractions) and concurrent weekly cisplatin (4 mg/kg) were administered, with or without Plerixafor (5 mg/kg/day). The primary endpoints were tumor growth delay, the frequency of lymph node metastases and animal survival. Chemokine expression and neutrophil recruitment were evaluated by immunohistochemistry. Acute gut toxicity was assessed using the crypt cell assay. Blood and normal organs were examined for late toxicity.

Results: The combination of RTCT and Plerixafor produced substantial tumor growth delay, reduced metastases and improved survival compared to standard RTCT alone in both tumor models. There was a reduction in chemokine signaling (CXCL12/CXCR4) and myeloid cell infiltration (GCSF, CD11b) with combination treatment compared to RTCT alone. There was no effect of Plerixafor on acute GI toxicity, nor were there changes in blood counts or organ morphology to indicate increased late hematological or normal tissue toxicity.

Conclusion: This preclinical study demonstrates that the addition of Plerixafor to standard RTCT for cervical cancer improves local tumor control and reduced metastases with no increase in toxicity. Plerixafor is commercially available for other indications, which will facilitate translation of these findings to phase I/II clinical studies.