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Combining AMD3100 with chemo-radiotherapy for treatment of cervical cancers

We have used human cervical cancer xenografts grown orthotopically in the cervix of mice to assess the effects of hypoxia on lymph-node metastases and to examine the efficacy of chemo-radiotherapy. We have been particularly interested in the chemokine receptor CXCR4 since it is upregulated by hypoxia and expression of its ligand CXCL12 (SDF1) may be increased following radiation treatment. The clinically-available drug AMD3100 (Plerixafor) blocks the CXCR4/CXCL12 interaction and treatment of xenograft-bearing animals with this drug reduces lymph-node metastases. A small animal imager/irradiator was used to treat the orthotopic tumors with 2 Gy fractions (5 days/week), combined with weekly cisplatin with or without the addition of AMD3100. Interestingly, AMD3100 treatment throughout the course of the chemo-radiotherapy was found to enhance the tumor response as well as reducing lymph-node metastases. The mechanism of this effect was currently unknown but may relate to reduced angiogenesis. When acute toxicity to the normal intestine was assessed using a gut clone assay following single radiation doses given with and without cisplatin and/or AMD 3100, there was no evidence of increased damage associated with the AMD3100 treatment. These results suggest that it may be beneficial to add AMD3100 to standard chemo-radiotherapy for treatment of cervical cancers, particularly for patients whose tumors contain significant regions of hypoxia, since such patients have been found to have increased propensity for metastatic failure following chemo-radiotherapy. This emphasizes the need to assess levels of hypoxia in the tumors by imaging prior to selection of patients for such studies.

Biography

Richard P Hill obtained his BA in Physics at St John's College, Oxford and his PhD in Radiation Biology at St. Bartholomew's Hospital Medical College in London, UK. He is currently a Member of the Senior Scientific Staff of Ontario Cancer Institute/Princess Margaret Cancer Centre, which is part of the University Health Network in Toronto, Canada. He has published over 250 scientific papers and is the Co-Editor of the *'Basic Science of Oncology'*; a book that is widely used in basic courses for oncology trainees and is currently in its fifth edition.

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