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Correspondence

Lack of correlation of P-glycoprotein expression with response to MIC chemotherapy in oesophageal cancer

Darnton *et al*[1] reported the lack of P-glycoprotein (P-gp) expression with response to mitomycin, ifosfamide, and cisplatin (MIC) chemotherapy in oesophageal squamous cell cancer. These cancers responded to chemotherapy better than oesophageal adenocarcinomas did; the latter expressed the MDR-1 (multidrug resistent) gene.

Oesophageal cancer is the most common cancer among South African black men,[2] with more than 96% being squamous cell carcinomas. As the disease is often diagnosed late, prognosis is usually poor even with the availability of all known treatments (median survival ranges from 2.5–6 months).[3] Brachytherapy alone is one of the recent methods that has been introduced in the palliation of advanced disease. Studies from the department of radiation oncology of our institution have shown that median survival improved to seven months following brachytherapy. The majority of the treated patients are dysphagia-free with death often due to disseminated malignancy (Sur *et al*, unpublished data).

Since 1994, it has been our policy to treat oesophageal cancers diagnosed early (albeit few) with preoperative brachytherapy followed by total oesophagectomy. Interesting radiation changes have been demonstrated in the oesophageal wall, the centre of the tumour, and lymph nodes.[4] Using immunohistochemistry we measured P-gp expression in the tumour cells and adjacent stratified squamous mucosa in the pre-radiation biopsies of early oesophageal squamous cell cancers and in the post-brachytherapy resection specimens from eight patients. Monoclonal antibody to P-gp (clone JSB-1, Novocastra Laboratories, Newcastle upon Tyne, UK) was used in the modified sandwich technique on formalin fixed, paraffin wax embedded sections. P-gp was not expressed in either pre- or post-brachytherapy tissue specimens (after brachytherapy of 20 Gy) in any of the eight cases. These findings, together with those of Darnton *et al*,[1] indicate that P-gp expression is of no value in predicting the responsiveness of the tumour to chemotherapy or radiotherapy in squamous cell cancers. It is therefore likely that there may be alternative factors associated with drug resistance in squamous cell carcinoma.

The MDR-1 gene does, however, have some value in predicting the response to treatment in adenocarcinomas. This has been demonstrated clinically in breast carcinomas (patients who express the gene have poor survival),[5] renal cell carcinomas,[6] cancer of the urinary bladder,[7] colorectal malignancies,[8] gastric,[9] and ovarian carcinomas.[10]

Unlike chemotherapy, radiotherapy effects cell death by the formation of free radicals. This involves interaction with other atoms or molecules, particularly water, to produce free radicals that are able to diffuse and damage the critical targets. These include the DNA in the chromosome (most critical target) and the nuclear membrane. Studies have shown that about two-thirds of *x* ray damage by high voltage ionisation is caused to the DNA by the hydroxyl free radical. In contrast, P-gp acts as an ATP dependent drug efflux pump that transports drugs associated with multidrug resistance out of the cell before cytotoxic effects occur. It is therefore unlikely that the expression of P-gp (the MDR-1 gene product) could have any bearing on responsiveness of the tumours to radiation.

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Dr Darnton and colleagues comment:
Drs Sur and colleagues report that eight squamous cell carcinomas of the oesophagus did not express P-gp before or after radiotherapy. Their finding is in agreement with our study in which 26 of 27 squamous cell carcinomas were negative for P-gp before and after MIC chemotherapy. Sur *et al* point out that, because of the mechanism of cell death induced by radiotherapy, expression of P-gp is not expected to be related to resistance of tumours to radiotherapy unless it correlated with p53 mutation. In our chemotherapy treatment study, although lack of P-gp expression was significantly associated with a good response of squamous cell carcinomas of the oesophagus to treatment, we described too few positive cases to determine the effects of P-gp expression in that histology. Solid conclusions can only be drawn when larger numbers of cases (probably more than 100) have been systematically studied. We feel that Sur *et al* are drawing conclusions beyond the limited scope of their data.

Notices

Royal College of Pathologists Symposia 1997

Wednesday 2 July The myeloproliferative disorders: pathogenesis and clinical management

Wednesday 9 July Prescription for the media: practical media skills for the medical profession*

Wednesday 16 July Update on genitourinary infections

Thursday 25 September Practical problems for a coroner's pathologist: how to cope

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Fees: fellows/members £75; trainees/retired £45; non-members £100 (*£75).

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For further information contact Prof. Dr. M Altwegg, Department of Microbiology, University of Zurich, Gloriastrasse 30, CH-8028 Zürich, Switzerland. (Fax: +41 (1) 252 8107.)