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Cigarette Smoking is a Risk Factor for Bleomycin-induced Pulmonary Toxicity

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To ASSESS late pulmonary toxicity after bleomycin administration, we measured the vital capacity (VC), total lung capacity (TLC) and single breath diffusion capacity (KCO) on a single occasion in 71 patients who had completed treatment for testicular germ cell tumour.

All patients had a haemoglobin concentration (Hb) of > 11 g/dl and the 44 treated with bleomycin received a median dose of 360 mg (range 90–630 mg). Their median age at time of testing was 32 years (range 17–60) and the median time from treatment completion was 28 months. No patient had other evidence of pulmonary toxicity.

Multiple regression techniques were used to estimate the simultaneous effects of bleomycin dose, time since treatment, disease stage, smoking and anaesthesia on the various measures of lung function. The information obtained on current smoking, having ever smoked and average number of cigarettes smoked was highly correlated. Analysis of variance techniques were used to estimate the difference in lung function between those who never received bleomycin, those patients less than 2 years post-treatment and those more than 2 years post-treatment.

Bleomycin-treated smokers had significantly worse VC and TLC values than non-smokers ($P = 0.021$ and $P = 0.016$, respectively), and a significant improvement ($P = 0.049$) in VC occurred in those tested more than 2 years post-bleomycin. There was a suggestion that a slower recovery rate occurred in smokers ($P = 0.067$, test for interaction). When patients treated with bleomycin were compared with those not so treated (controls), the same pattern of improvement of lung function with time was seen and the poorer performance of smokers confirmed. Bleomycin-treated smokers also suffered a much greater drop in KCO compared with non-smokers within the first 2 years, but this difference in KCO disappeared for patients treated more than 2 years previously. None of the other patient characteristics examined had a significant effect on lung function measurements.

Impaired pulmonary function measurements in patients surviving overt bleomycin pneumonitis can be reversed completely in 2 years [1]. However, bleomycin-treated cigarette smokers have formed the majority of patients with persistent abnormalities of lung function in other studies of teratoma patients [2, 3, 4].

Alveolar macrophages from cigarette smokers release hydrogen peroxide both spontaneously and when incubated with bleomycin, a finding not seen in macrophages from non-smokers [5]. These findings may partly explain the association between smoking and impaired pulmonary function seen in this and other studies.

Our findings provide additional evidence that smoking is an important risk factor for bleomycin-induced pulmonary toxicity. The significance of this finding is increased by the absence of abnormalities in these tests of lung function in young cigarette smokers [6, 7].

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Overcoming Tumour Radiation Resistance Resulting from Acute Hypoxia

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IN RESPONSE to our editorial entitled "Overcoming tumour radiation resistance resulting from acute hypoxia" [1], Senan writes that in our article we discuss the induction of acute hypoxia in tumours as a means of exploiting hypoxic cytotoxins,

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but we fail to discuss the implications of a possible increase in metastatic potential of tumour cells which have recovered from hypoxic exposure [2].

Unfortunately, Senan has somewhat misinterpreted our comments. Our editorial was an attempt, based on experimental results, to suggest possible ways in which radio-resistant acutely hypoxic cells may be eliminated. Such hypoxic cells have now been shown to normally occur in tumours [3]. The methods suggested were either to use certain drugs to actually prevent acute hypoxia from happening; to employ treatments which can directly kill these cells or sensitise them to radiation; or finally make these acutely hypoxic cells chronically hypoxic and then attack them with hypoxic cell cytotoxins which preferentially kill such cells. If, with this latter treatment, some of the hypoxic cells are not killed by the cytotoxin, then it is possible that they may become re-oxygenated or remain hypoxic. The ultimate fate of these surviving cells will depend on what treatment was used to make the tumour hypoxic in the first instance. If the hypoxia was induced by agents that damage tumour vasculature, then the resulting hypoxia could last for 24 h or longer [4], thus any cell surviving subsequent treatment with the hypoxic cell cytotoxin could remain hypoxic long enough to have the potential to interfere with any conventional therapy likely to be used against the aerobic population. However, physiological modifiers of tumour blood flow result in hypoxia lasting only a few hours [4]. With hydralazine, for example, which is the agent we use to illustrate our proposal, tumour blood flow is substantially reduced and results in full radiobiological hypoxia which lasts for less than 2 h [5]. This is more than sufficient time to enhance the action of hypoxic cell cytotoxins like hyperthermia [5] and bioreductive drugs [6] and, therefore, physiological modifiers of tumour blood flow are probably the best way to induce chronic hypoxia in tumours.

It has been shown experimentally that prolonged exposure of tumour cells to hypoxia [7] or acidosis and glucose starvation [8] may increase their metastatic potential when they are subsequently incubated in normal aerobic conditions, but the exposure times to these adverse conditions were for 18–24 h. Moreover, one study suggested that at least 6–12 h exposure under hypoxic conditions was necessary before any increase in metastatic potential was seen [9]. This is not an acute exposure as Senan suggests and it is far longer than the chronic conditions we recommend, so although long-term hypoxia followed by reoxygenation may lead to an increase in metastasis, it has no relevance to our proposals.

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Overcoming Tumour Radiation Resistance Resulting from Acute Hypoxia

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IN DISCUSSING the induction of acute hypoxia in tumours as a means of exploiting hypoxic cytotoxins, Horsman and Overgaard [1] have mentioned both the lack of consistent reduction in blood flow by the currently available agents and the often prolonged period (greater than 24 h) of resulting reduction in blood flow. They fail, however, to discuss the implications of a possible increase in metastatic potential of tumour cells which have recovered from hypoxic exposure.

Following a period of *in vitro* reoxygenation, cells isolated from the hypoxic regions of murine tumours (identified by proximity to functional vasculature) have been shown to have an increased lung colonisation ability [2]. In addition, a 24–48 h recovery from acidosis or glucose starvation has been shown to result in a marked (30-fold) increase in metastatic ability [3]. The changes in metastatic potential associated with cells cycle position were between 0.5- and 2-fold following hypoxic exposure, and cannot account for this finding [3]. All three conditions (hypoxia, acidosis and glucose starvation) have been shown to introduce a class of stress proteins [4] which may confer a survival advantage in adverse conditions, including the metastatic process.

These findings are relevant as resumption of blood flow following the induction of acute hypoxia will allow tumour cells access to blood vessels. With highly selective hypoxic cytotoxins such as SR-4233 and E09 currently undergoing clinical trials, the option of inducing acute hypoxia in an attempt to increase tumour cell kill must be approached with caution.

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