Review Article

Pulmonary toxicity of antineoplastic agents: Anaesthetic and postoperative implications

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Agents commonly used in the treatment of neoplastic diseases may impair pulmonary function, and a wide spectrum of agents are currently implicated as toxic to the pulmonary system. Agents most commonly implicated are bleomycin, carmustine, busulfan, methotrexate, and thoracic radiotherapy. Less commonly implicated agents include mitomycin, procarbazine, melphalan, chlorambucil, and cyclophosphamide. Therapeutic interactions at time of operation and postoperatively may exacerbate existing pulmonary damage. It is imperative for the physicians treating patients receiving antineoplastic therapy to recognize potentially dangerous therapeutic interactions, and adjust the therapeutic regimen accordingly. Concentrations of inspired oxygen must be maintained as low as is safely possible. Intraoperative monitoring of arterial and mixed venous oxygen tensions will enable the clinician to adjust inspired oxygen concentrations to the lowest possible level while maintaining adequate oxygen tensions to the tissues. A systematic review of antineoplastic agents currently implicated, drug-oxygen interactions, and a review of the pathophysiology are presented.

Key words

PHARMACOLOGY CHEMOTHERAPEUTIC AGENTS: pulmonary toxicity, COMPLICATIONS: oxygen toxicity, pulmonary fibrosis.

The detection and recognition of pulmonary pathology are of paramount importance to the preoperative evaluation of the patient scheduled for surgery and anaesthesia. One of the prices paid for chemical and radiotherapeutic treatment of neoplastic and collagen vascular disease is damage to the vulnerable tissues of the pulmonary system. The appearance of pulmonary fibrosis secondary to antineoplastic therapy may be insidious in onset and may progress, with fatal results. Exacerbations of recognized or occult pulmonary fibrosis may occur as a result of therapeutic use of fortified inspired oxygen concentrations during anaesthesia and in the immediate postoperative period. Therefore, it is imperative to recognize the wide spectrum of agents that are currently implicated as potentially toxic to lung tissues. Chemotherapeutic agents currently implicated as pulmonary-toxic are considerably greater in number than may be generally appreciated by the clinical practitioner (Table). It is of interest to systematically review the toxic effects on the pulmonary system secondary to antineoplastic interventions. Mechanisms, pathophysiology, and drug interactions are reviewed.

Clinical presentation

The clinical picture of interstitial pneumonitis progressing to pulmonary fibrosis is remarkably consistent for pulmonary toxicity attributable to the spectrum of antineoplastic agents. The characteristic clinical constellation consists of dyspnoea, non-productive cough, basilar rales, and fever. The development of these symptoms may be insidious and generally precedes the appearance of radiographic changes.¹

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TABLE Summary of available data on pulmonary toxicity of commonly used antineoplastic agents.

Agent	Incidence	Latency	Potentiation by		References
			Oxygen	Thoracic Radiotherapy	
Busulfan	10%	1-10 yrs	—	yes	5, 6, 7, 8
Bleomycin	40%	variable	yes	yes	11, 15, 33, 41, 42
Carmustine	20-50%	1-36 mos.	—	—	2, 9, 18-22
Chlorambucil	rare	6-22 mos.	—	—	3, 4
Cyclophosphamide	rare	acute	yes	possible	8, 29, 30
Dactinomycin	NR	NR	—	yes	17
Doxarubicin	NR	1-3 mos.	—	yes	17
Melphalan	rare	1-48 mos.	—	—	3, 4
Methotrexate	7%	2 wks-18 yrs.	—	—	24-26
Mitomycin	5%	3-7 wks.	yes	—	16, 28
Procarbazine	rare	1-2 days	—	—	27

NR = not reported.

The earliest detection of pulmonary fibrosis may be achieved through the serial evaluation of pulmonary function. Sequential measurement of carbon monoxide diffusion capacity (DLCO) may indicate the presence of occult pulmonary changes.² Arterial hypoxaemia is commonly found, and spirometry reveals decreased lung volumes compatible with restrictive lung disease.³ Radiographic changes typically appear as bilateral diffuse interstitial infiltrates, more prominent at the bases, with patchy areas of consolidation. Alveolar and interstitial reaction and pleural effusion may be found. Once radiographic signs are noted, however, the process has often progressed irreversibly.

Regression or amelioration of the toxic pulmonary pathology may occur with immediate cessation of therapy at the earliest signs of toxicity. Steroid therapy has been found to be effective in some cases.^{16, 17, 23, 26}

The appearance of pulmonary infiltrates may be the result of the malignant process, incidental pathology, infectious processes, or complications of antineoplastic therapy. Alveolar cell carcinoma, metastatic carcinoma, leukaemia, and lymphoma may present with pulmonary infiltrates. Lymphangitic carcinomatosis, miliary metastatic disease, and diffuse bronchiolo-alveolar metastatic disease are the most common metastatic processes that present as diffuse pulmonary infiltrates. Lipid embolization to the lungs may result from lymphangiographic procedures, and occur acutely following the angiogram. Volume overload and pulmonary oedema may present with diffuse pulmonary infiltrates; leukoagglutinin reaction, pul-

monary haemorrhage, and infectious processes must be considered.⁴⁰

Patients receiving antineoplastic therapy may have coincidental parenchymal and airway disease complicating the clinical picture. Presentation may therefore be highly variable, contingent upon individual drug regimen, incidental disease, and coincidental pathology. Lung biopsy, sputum cultures, and cytologies may therefore provide the most definitive diagnostic modalities.

Alkylating agents

Busulfan (Myleran) therapy is associated with pulmonary toxicity, manifested by dyspnoea or cough, changes on chest x-ray, or serial pulmonary function tests. The appearance of clinical signs is often insidious. The prognosis for pulmonary fibrosis associated with this compound is exceptionally poor, with expectations for survival ranging from one month to two years.⁴ Thoracic radiotherapy prior to treatment with busulfan may predispose to pulmonary toxicity, while radiotherapy after cessation of busulfan can lead to accelerated radiation pneumonitis.⁵⁻⁸

Cyclophosphamide (Cytoxan) may result in toxicity with a clinical picture quite similar to that caused by busulfan. Toxic changes due to cyclophosphamide, however, tend to be more acute. Clinical evidence suggests that enriched inspired oxygen may have an additive effect in the development of broncho-pulmonary dysplasia.⁸

The simultaneous administration of cyclophosphamide and carmustine was reported to result in the development of pulmonary toxicity in nine pa-

tients.^{2,9} A similar synergism has been reported with the simultaneous administration of cyclophosphamide and bleomycin in the treatment regimen for diffuse histiocytic lymphoma,¹⁰ and rapidly fatal interstitial toxicity has been reported in one patient treated with cyclophosphamide and doxorubicin.⁴

Chlorambucil (Leukeran) and *Melphalan* (Alkeran) have been shown to cause pulmonary toxicity on rare occasions.^{3,4}

Antibiotics

Pulmonary toxicity associated with *bleomycin sulfate* (Blenoxane) remains the dose-limiting factor in the therapeutic administration of this agent. There is a two to ten per cent mortality associated with toxicity due to this agent.^{1,11} The patient population most at risk for the development of pulmonary fibrosis is 65 years of age and older, those with pre-existing pulmonary pathology, and those receiving adjuvant thoracic radiotherapy.¹¹⁻¹³

The threshold dose level for the development of pulmonary disease is in the range of 200 to 250 mg/M², and the development of disease may be seen with significantly lower cumulative doses in the presence of adjuvant radiotherapy. The enhanced pulmonary toxicity from simultaneous or sequential administration of bleomycin and thoracic radiotherapy has only recently been recognized as a significant clinical entity.^{11,14} A review of published clinical studies in which bleomycin and thoracic radiotherapy were administered concomitantly demonstrated a ten per cent mortality associated with the development of pulmonary fibrosis. The therapeutic index may be further reduced if agents with known pulmonary toxic potential are used in adjuvant therapy.¹⁵

Mitomycin (Mutamycin) is known to cause pulmonary toxicity, and fatal progression of pulmonary fibrosis is known to occur. This reaction is responsive to steroid therapy.¹⁶

Doxorubicin (Adriamycin) and *Dactinomycin* (Actinomycin D) are not known to result in direct pulmonary toxicity. However, these agents have been shown to potentiate and reactivate pneumonitis secondary to thoracic radiotherapy.¹⁷

Nitrosoureas

Carmustine (BCNU) has a high propensity for causing pulmonary toxicity.¹⁸ The incidence of pulmonary toxicity associated with this drug is dose

related. Symptoms may begin as early as one month and as late as one year after the initiation of therapy. Factors which together favour the development of pulmonary toxicity include pre-existing lung disease secondary to tobacco use and environmental/occupational exposure, cumulative BCNU dose, number of treatment cycles, thrombocyte and leukocyte nadir during the first treatment cycle, and patient age.²

Sequential measurement of pulmonary diffusion capacity for carbon monoxide (DLCO) may detect subclinical pulmonary pathology.^{2,22} Changes in diffusion values may be appreciated before changes are noted on x-ray examination, and on occasion, diffusion changes may precede the appearance of cough and dyspnoea characteristic of pulmonary fibrosis.¹⁹⁻²¹

Pulmonary fibrosis can develop rapidly accompanied by progressive radiological changes and diminished arterial pO₂ values.²² Radiologic changes may include diffuse "fibrosis and stranding" to "nodular densities," or may eventually have the appearance of "shock lung," pulmonary oedema, or adult respiratory distress syndrome.

Semustine (methyl-CCNU) and *lomustine* (CCNU) are far less frequently toxic to the lungs. The incidence of pulmonary toxicity with cumulative doses of *chlorozotocin* and *PCNU*, structurally similar to *carmustine*, is unknown.¹⁸

Antimetabolites

Pulmonary toxicity from *methotrexate* is accompanied by eosinophilia,²³⁻²⁵ which is consistent with hypersensitivity reaction. Steroids may provide improvement in clinical symptoms and chest x-ray within 24 hours of therapy.^{23,26}

Cytarabine (Ara-C) has been implicated in the production of a direct pulmonary toxic picture consisting of interstitial and intra-alveolar exudation. Incidence of pulmonary toxicity with this agent is at this time unclear.⁴

Miscellaneous drugs

Procarbazine (Matulane) has been used for some time in the treatment of Hodgkin's disease, melanoma, and multiple myeloma. It has only been recently reported that this drug can result in pulmonary changes thought to be responsive to steroid therapy. However, fatal pulmonary fibrosis directly attributed to procarbazine has been reported.²⁷

Oxygen toxicity

The possible synergistic effects of high inspired oxygen concentrations with bleomycin,^{15,41-45} mitomycin,²⁸ or cyclophosphamide^{29,30} must be borne in mind. A series of 17 patients, ages 15 to 54 years, was analyzed for survival as a function of age, bleomycin dosage, interval between bleomycin treatment and surgery, preoperative vital capacity, operative duration, DLCO, and FiO_2 concentration. Only differences in FiO_2 were found to correlate significantly with outcome. Mean FiO_2 was 0.24 for the surviving cohort, and 0.39 for the non-surviving cohort. No deaths were reported in those who received FiO_2 less than 0.26, and none survived who received FiO_2 greater than 0.34. It is of interest to note that the surviving cohort received significantly less crystalloid intraoperatively than the non-surviving cohort, perhaps inferring that fluid management might influence survivability.¹⁵

In a series of 20 patients undergoing treatment with mitomycin and thoracic radiotherapy for squamous cell carcinoma of the oesophagus, it was noted that two patients who received FiO_2 concentrations greater than 0.50 developed pulmonary infiltrates. Those receiving FiO_2 concentrations below 0.30 were without pulmonary complications.²⁸

Pathophysiology

The mechanism of pulmonary toxicity associated with use of these agents is at this time uncertain. As previously noted, some agents are known to result in dose-dependent toxic reaction, while others demonstrate no such predictable dose-dependency. Direct cytotoxicity probably represents the most common mechanism for pulmonary toxicity.

One proposed mechanism for bleomycin toxicity involves the production of superoxide and other free radical moieties which then cleave nuclear DNA.¹¹ Theoretically, the production of these highly oxidizing radicals might be increased by the inspiration of fortified concentrations of oxygen. The additive toxic effects associated with ionizing thoracic radiotherapy might be explained by the additional production of free-radicals. The toxic effects of these free-radicals may compromise production of surfactant⁸ and damage the delicate alveolar structure, resulting in histopathologic changes that progress to fibrosis.

Superoxide radicals are produced during normal

metabolism by all living aerobic cells. These anions are important both as oxidizing and as reducing agents in the metabolism of a variety of biological substrates. Superoxide exerts its toxic effect through the production of other moieties, e.g., hydroxyl radical and carbonate radical,³⁴ and these reactive species are capable of initiating the production of free-radical chain reactions. The structure of sensitive chemical compounds such as nucleic acids, lipoproteins, nucleoproteins and lipids may be altered. Extensive cellular damage may therefore result if the precursor anion, superoxide, were not eliminated by superoxide dismutase.^{35,36} Further, there is evidence that superoxide dismutase may afford protection against the cellular damage caused by free-radical formation due to gamma-irradiation.³⁷ Any exogenous process or agent which might denature or decrease activity of this protective enzyme system might well effect the cellular damage observed in vulnerable lung tissues.

An allergic or immunologic mechanism may explain the development of pulmonary fibrosis in some patients. As previously stated, eosinophilia has been reported with procarbazine and methotrexate-induced pulmonary toxicity. Steroid responsiveness suggests the possibility of an immunologic mechanism.

The microscopic appearance of lung tissue reveals thick alveolar septa with collagen deposition and mononuclear infiltration. A moderate increase in type II pneumocytes has been noted in the alveolar septa.¹⁶ Cuboidal metaplasia and cellular atypia may also be noted.^{11,28} Interstitial and intra-alveolar exudates may organize and progress to fibrosis. The microscopic picture reflects the phase of the disease process, and no montage of microscopic findings is specific for any single drug.⁴

Anaesthetic implications

At this time, it is unclear whether fortified oxygen concentrations themselves predispose to drug-induced pulmonary toxicity, or under what combination of circumstances fibrosis may occur, e.g., duration of exposure, hydration status, or temporal relationship to thoracic radiotherapy. On the basis of the available data,³¹⁻³³ it seems prudent to reduce the concentration of inspired oxygen to the lowest level consistent with safe anaesthetic practice. In contradistinction to patient populations

not receiving antineoplastic therapy, the marginal risk to marginal benefit ratio of enhancing inspired oxygen concentrations is clearly in favour of increased risk. A "target" PaO_2 should be selected as safe or appropriate for an individual patient, and the inspired oxygen is then titrated to yield this desired oxygen tension. Intraoperative monitoring is the key to safe administration of oxygen to these patients. Arterial blood gas analysis should be monitored by indwelling arterial cannulae or by intermittent sampling techniques. Transcutaneous oxygen monitoring devices may be useful in other patients, but may not afford the accuracy or reliability required in patients receiving low inspired oxygen concentrations. The niroscope may provide a suitable tissue-level oxygen monitoring capability when it is available, but until it is available, mixed venous blood sampling may be required to monitor the adequacy of peripheral oxygen consumption and delivery.

The judicious use of positive end-expiratory pressure (PEEP) may increase oxygenation and minimize the need for supplemental oxygen. Maximization of oxygen exchange may be accomplished through rigorous chest physiotherapy, pulmonary toilet, and rigorous treatment of atelectasis, oedema, and infection. Avoidance of general anaesthesia may be appropriate if the circumstances permit another technique. The "routine" use of supplemental oxygen therapy postoperatively should be avoided.

Summary

In conclusion, one must consider the possibility of occult pulmonary dysfunction in patients treated with a wide spectrum of antineoplastic agents.^{38,39} Symptomatology consisting of cough, low-grade fever, and dyspnoea may indicate the presence of occult disease. Basilar rales will be detected long before changes are noticed on radiograph. Serial evaluation of pulmonary function and carbon monoxide diffusion may not only indicate the severity of disease, but may provide the first evidence of disease.

If pulmonary disease due to antineoplastic therapy is suspected, it is crucial to plan the anaesthetic management to minimize further lung injury. Inspired oxygen tensions of less than 30 per cent appear to present a significantly smaller likelihood of contributing to pulmonary fibrosis than do

oxygen tensions greater than 50 per cent.^{15,28,31-33} The judicious use of intraoperative PEEP to enhance oxygenation and the postoperative use of rigorous chest physiotherapy to treat ventilation-perfusion abnormalities may be preferable to the use of enriched inspired oxygen concentrations. Appropriate monitors must be selected to ensure adequate oxygen supply and delivery while maintaining inspired oxygen concentrations at the lowest possible level. Arterial blood gas analysis and mixed venous blood gas analysis will permit careful titration of inspired gas composition. Awareness of the potential for occult pulmonary pathology and the potential hazard presented from the use of supra-physiologic concentrations of oxygen should influence the choice of anaesthetic technique, and should discourage the use of "routine" postoperative oxygen supplementation.

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Résumé

Les agents couramment employés dans le traitement des maladies néoplasiques peuvent nuire à la fonction pulmonaire et effectivement, on a démontré des effets pulmonaires toxiques pour plusieurs d'entre eux.

Les substances les plus communément impliquées sont la bléomycine, la carmustine, le busulfan, le méthotrexate et la radiothérapie du thorax. Les agents moins souvent incriminés sont la mitomycine, la procabazine, le melphalan, le chlorambucil et la cyclophosphamide. Les interactions thérapeutiques au moment de l'intervention chirurgicale ou dans la période post-opératoire peuvent aggraver une maladie pulmonaire pré-existante. Il est très important pour les médecins traitant les patients recevant des antinéoplasiques de reconnaître ces interactions potentiellement dangereuses et d'ajuster la thérapeutique en tenant compte de ces médicaments.

Les concentrations d'oxygène doivent être maintenues aussi basses que possible, tout en assurant la sécurité du malade. Le monitoring per-opératoire de la pO₂ artérielle et veineuse aide le clinicien à ajuster la concentration d'O₂ inspiré à la valeur la plus basse possible tout en maintenant des pO₂ tissulaires adéquates.

Une revue systématique de la pathophysiologie de ces interactions avec l'oxygène est présentée ainsi que le répertoire des divers agents impliqués.