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PULMONARY TOXICITY OF CYTOTOXIC AND IMMUNOSUPPRESSIVE AGENTS

A review

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Abstract

Cytotoxic agents may cause interstitial or eosinophilic pneumonitis, alveolar proteinosis, pulmonary venous occlusive disease, pulmonary fibrosis, pneumothorax, or pulmonary oedema. These agents may also potentiate lung injury caused by radiotherapy or high oxygen fractions in inspired air. Clinical and roentgenological features of lung damage induced by cytotoxic drugs are usually non-specific, and differential diagnoses include progression of the malignant disease and a plethora of opportunistic infections. Monitoring of blood gases and carbon monoxide transfer factor may facilitate early detection of drug induced lung injury. Fiberoptic bronchoscopy, bronchoalveolar lavage, transbronchial biopsy, or open lung biopsy may be necessary for reliable diagnosis. Early detection of lung damage and immediate withdrawal of the responsible agent(s) are essential. Steroids may be of therapeutic value in some patients.

Key words: Cytotoxic drugs, immunosuppressive drugs, pulmonary toxicity.

An increasing number of cancer patients are cured or rendered disease-free for prolonged time periods by means of modern chemotherapy. As more patients have been exposed to cytotoxic agents, the number of reports concerning toxicity have been growing at a fast rate. Pulmonary tissue is particularly vulnerable. Several cytotoxic and immunosuppressive agents can cause desquamative interstitial pneumonitis, usual interstitial pneumonitis, eosinophilic preumonitis pulmonary alveolar proteinosis, pulmonary venous occlusive disease, pulmonary fibrosis, spontaneous pneumothorax, and pulmonary oedema. Knowledge of risk factors, diagnosis, clinical course, and adequate treatment will reduce the hazards of pulmonary toxicity.

Drugs may cause pulmonary disease due to toxicity, allergy, or idiosyncrasy. Dose-related toxic effects have been demonstrated for chlorambucil (1), busulphan (1), carmustine (2), lomustine (3), bleomycin (4, 5), and peplomycin (6). Allergic mechanisms may mediate pulmonary damage caused by cyclophosphamide (7–9), methotrexate (10, 11), procarbazine (12, 13), and bleomycin (5, 14, 15). The occasional pulmonary toxic effect of low-dose bleomycin has been explained by idiosyncrasy (16), possibly due to genetically determined impaired drug metabolism as seen in laboratory animals (17).

Pathogenesis

The dynamics of pulmonary toxicity have been investigated in longitudinal studies of bleomycin action on laboratory animals (18). Initially, damage to capillary endothelium affects permeability, and causes interstitial oedema. Subsequently, swelling and necrosis of type I pneumocytes occur. Denuding of the alveolar epithelium allows passage of fluid and plasma proteins into the alveolar sacs, producing hyaline membranes. The flattened type I pneumocytes, normally lining most of the alveoli, are replaced by cuboidal cells as regenerative proliferation of type II pneumocytes proceeds. Eventually proliferation of fibroblasts occurs, leading to pulmonary fibrosis.

Free radical formation and lipid peroxidation of phospholipid membranes may play a role in the action of cyclophosphamide (19), bleomycin (19) and mitomycin (20) on the pulmonary endothelial cells. Even the venous endothelium may be affected. Pulmonary venous occlusive disease due to vasculitis and intimal fibrosis, produc-

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ing pulmonary hypertension, has been observed subsequently to mitomycin and bleomycin therapy (21).

Peripheral eosinophilia has been observed alongside pneumonitis caused by bleomycin (14), procarbazine (12, 13), and methotrexate (11, 22), suggesting an allergic etiology. Correspondingly, bleomycin may produce type IV like hypersensitivity in mice (23), and a functionally active thymus seems essential in mice developing pulmonary toxicity from bleomycin (24) and peplomycin (25). Methotrexate may produce granulomas with multinucleated giant cells, hilar adenopathy, and migratory pulmonary infiltrates as seen in allergy (10, 26, 27). However, retreatment with methotrexate seldom results in recurring pneumonitis (27).

In rare cases bleomycin elicits an anaphylactoid reaction with acute pulmonary oedema (5), fulminant angiooedema (14) and eosinophilia in blood and bronchoalveolar lavage fluid (15, 28, 29). A similar reaction to cyclophosphamide has been reported (8). Enteric protein loss, caused by the toxic action of cytosine arabinoside, results in hypoproteinemia which is causally related to the appearence of non-cardiogenic pulmonary oedema (30). Intrathecal administration of methotrexate may cause pulmonary oedema, possibly of neurogenic origin (31). Mitomycin-induced haemolytic-uremic syndrome occasionally produces alveolar haemorrhagic oedema (32–35).

Spontaneous pneumothorax is a serious aggravation of interstitial pulmonary disease, and has been observed after treatment with bleomycin (36–38), carmustine (39), and intensive combination chemotherapy (40, 41). It is probably conditioned by distortion of the alveolar architecture with subpleural fibrosis and cyst formation.

A few cases of pulmonary alveolar proteinosis caused by busulphan and carmustine have been reported (42–45). Drug-induced deficiency of the macrophage activity in pulmonary alveoli possibly explains the observed accumulation of homogenous, proteinaceous material in the alveolar spaces in these patients (42).

Histopathology

Inflammation of lung parenchyma is generally termed pneumonitis. Parenchymal disease of the lung may be classified as alveolar, interstitial or vascular according to location, and further subdivided on a descriptive basis (46). Pulmonary alveolar proteinosis and desquamative interstitial pneumonitis refer to alveolar accumulation of proteinaceous material and discharged histiocytes respectively. Usual interstitial pneumonitis and eosinophilic pneumonitis refer to interstitial inflammation with primarily fibroblasts and eosinophils respectively. Venous occlusive disease and vasculitis represent vascular lesions. Often there are lesions in all three anatomical compartments at the same time and histological overlap is not uncommon.

Desquamation, proliferation, and metaplasia of the alveolar epithelium, which are common features of desquamative interstitial pneumonitis and usual interstitial pneumonitis, are the most striking histopathological effects of alkylating agents (47–50), nitrosoureas (51–53), and antitumor antibiotics (54, 55) according to lung biopsy and autopsy. However, fibrinous exudation, hyaline membranes, and interstitial fibrosis occur in most cases, and are diagnostic of usual interstitial pneumonitis (46). Desquamative interstitial pneumonitis may represent an early stage of usual interstitial pneumonitis with a more favourable prognosis due to considerable less fibrosis. Pulmonary fibrosis is the final common pathway of pulmonary alveolar proteinosis, usual interstitial pneumonitis and venous occlusive disease.

Distortion of the cellular repair mechanism probably causes epithelial dysplasia by interfering with the reparative proliferation of type II pneumocytes (18). The atypical epithelial proliferation is a characteristic ultrastructural finding in pulmonary toxicity induced by bleomycin (55), melphalan (48), busulphan (56), and nitrosoureas (57, 58). Bizarre epithelial giant cells with large hyperchromatic nuclei can be seen in sputum smears from patients treated with busulphan (59), and have been suggested to represent a precancerous state (50, 59). Secondary lung cancer appearing 5 years following busulphan therapy has been reported (60). Pulmonary ossification and alveolar calcification have been associated with busulphan toxicity (61).

A shift from early infiltration with polymorphonuclear granulocytes to late infiltration with lymphocytes has been demonstrated with bleomycin (62, 63). Peripheral eosinophilia and eosinophilic infiltrates, as in eosinophilic pneumonitis, characterize the pneumonitis induced by methotrexate (22, 26, 64), procarbazine (13, 65, 66), and occasionally bleomycin (14, 15), and suggest an allergic etiology. Fibroblast proliferation and interstitial fibrosis are particularly prevailing in pneumonitis produced by alkylating agents (3, 47, 48, 53, 67–69), and the antibiotic agents bleomycin (55, 70, 71), peplomycin (6) and mitomycin (72).

Clinical features

Dry cough, progressive dyspnoe, and cyanosis are the presenting symptoms of drug-induced pneumonitis. The onset is insidious, and appears most often during therapy, but may be delayed by 1–3 months after completed therapy with carmustine (44, 51), bleomycin (1), mitomycin (73), and neocarzinostatin (74, 75). Late-onset pulmonary fibrosis has been reported after a latency period of 33–57 months past completion of cyclophosphamide therapy (76). At auscultation crepitant rales can be heard over the lung bases. The progressing ventilatory defect is usually irreversible, and potentially lethal. However, the antimetabolites methotrexate, mercaptopurine, and azathioprine principally produce reversible pulmonary toxicity (22, 27, 77–79).

Acute or subacute non-cardiogenic pulmonary oedema

may follow the administration of bleomycin (5), cyclophosphamide (8, 80), ifosfamide (8), cytosine arabinoside (30), and methotrexate (31, 81, 82). Within minutes (80) to several hours (82) respiratory distress occurs with chest tightness, dyspnoe, cyanosis, distended neck veins, discharge of frothy sputum, widespread pulmonary crepitations, and rhonchi. Subsequently severe hypotension may develop (80). Patients with mitomycin induced hemolytic-uremic syndrome may develop lethal hemorrhagic alveolar oedema months after concluded therapy (54).

Pulmonary alveolar proteinosis is characterized by slowly progressing dyspnoe, weakness, and productive cough with white and thick sputum (43). All four reported cases expired in respiratory distress (42–45). Pleurisy and pleuritic pain have been recorded as a complication to methotrexate therapy in 4% of patients with trophoblast tumours (83).

Roentgenological features

Interstitial infiltrates produce diffuse, reticular densities on the chest roentgenogram, while alveolar infiltrates appear as nodular patches. The initial roentgenological changes comprise interstitial infiltrates on both lung fields, predominantly in the lower areas. Fine, linear shadowing in the subpleural areas may be seen already one week after initiation of bleomycin therapy (84), and up to three weeks before clinical presentation (85). Advanced cases produce widespread interstitial and alveolar infiltration, sometimes even lobar consolidation (86). Earlier reports of busulphan toxicity described a nodular appearance on chest roentgenograms due to intraalveolar fibrinous oedema (56, 87), which is probably identical to pulmonary alveolar proteinosis.

In rare cases the roentgenogram may appear indistinguishable from pulmonary metastases. Carmustine-induced pneumonitis may produce roentgenological changes similar to lymphangiosis carcinomatosa (88), characterized by coarse linear infiltrates. On the other hand, bleomycin has been reported to produce nodular densities mimicking haematogenous tumour spread (89). Computed axial tomographic scanning is probably more sensitive to bleomycin-induced pneumonitis than conventional chest roentgenogram, but does not always discriminate between fibrotic lesions and metastatic nodules (90).

Pulmonary function test

Pneumonitis produces a restrictive ventilatory defect with hypoxia, hypocapnea, and a chronic respiratory alkalosis caused by diffusion limitation and hyperventilation. The restrictive defect is easily quantified by arterial blood gas analyses. Worsening hypoxia during exercise is typical, and correlates with the amount of pulmonary fibrosis. Both alveolar volume and vital capacity decrease and remain low for 18–24 weeks in patients with symptoms of bleomycin-induced pneumonitis, before they slowly return to normal (91). The vital capacity is reported to be inversely related to the total dose of bleomycin (92).

The transfer factor of the lung for carbon monoxide reflects the diffusing capacity of the alveolar capillary membrane, the reaction rate of binding carbon monoxide to oxyhemoglobin, and the pulmonary capillary blood volume (93). Adjustment of the transfer factor to the actual haemoglobin level is essential to avoid bias due to anemia (92). Significant reductions in the transfer factor have been recorded prior to physical signs and roentgenological findings during treatment with alkylating agents (88, 94), antimetabolites (27, 95), and antitumor antibiotics (96, 97). The transfer factor decreases by more than 50% in symptomatic pneumonitis caused by mitomycin (98), and neocarzinostatin (74). Empirical data justifies cessation of bleomycin therapy to avoid manifest pneumonitis, if the transfer factor is reduced by more than 60% (96). Increasing doses of bleomycin and peplomycin produce a linear decrement of transfer factor (6, 96), which may be significantly reduced already after 60–90 mg bleomycin (96, 97).

Both pulmonary capillary blood volume and diffusing capacity decrease during bleomycin therapy, the former returning to normal at withdrawal of therapy, while the latter remains decreased for at least 42 weeks (91). Thus, a transient vascular damage seems to precede a prolonged impairment of gas-exchange. Van Barneveld et al. (99) have introduced a risk score based on alveolar volume, vital capacity, pulmonary capillary blood volume, and creatinin clearence, which predicts bleomycin-induced pneumonitis with 88% sensitivity and 81% specificity.

Alkylating agents

Several alkylating agents may produce damage to lung tissue. The most common pulmonary lesion is usual interstitial pneumonitis. Melphalan and busulphan are associated with pronounced atypical epithelial proliferation of distal airways (48, 59). Acute pulmonary oedema has been observed after the administration of cyclophosphamide and ifosfamide (7, 8).

Only isolated case reports of pulmonary toxicity are available for cyclophosphamide, ifosfamide, melphalan, chlorambucil, lomustine, semustine, and chlorozotocin (Table 1). These drugs produce pulmonary lesions infrequently, but once established the lesions are potentially lethal. The incidence of clinically evident pneumonitis, caused by busulphan, was 5% in a combined material of 117 patients (56, 68, 94, 113). In three prospective carmustine trials the overall incidence of drug-related pneumonitis was 33% and the lethality was 24% (2, 51, 114).

No relationships have been established between dose or duration of therapy and lung toxicity for cyclophosphamide, ifosfamide, and chlorozotocin. Most cases of chlorambucil toxicity appear after at least 6 months' therapy with no less than 2000 mg accumulated dose (1). The

Table 1

Synopsis of pulmonary toxicity produced by the alkylating agents cyclophosphamide (CYC), ifosfamide (IPH), melphalan (MPL), chlorambucil (CHL), busulphan (BUS), carmustine (BCNU), lomustine (CCNU), and chlorozotocin (CTN)

Drug	Lesion	Risk factors	Course	Incidence	Lethality	References
CYC	UIP	Anesthesia, radiotherapy, other cytotoxics	Reversible	19 cases	4 cases	47, 76, 80, 100–106
	PO		Reversible	2 cases		8, 80
IPH	PO	Previous CYC	Irreversible	1 case	1 case	8
MPL	UIP		Irreversible	4 cases	3 cases	48, 107, 108
CHL	UIP	Total dose >2g	Often irreversible	9 cases	6 cases	49, 67, 109–112
BUS	UIP	Total dose >500 mg, radiotherapy	Often irreversible	5%		56, 68, 94, 113
	PAP		Irreversible	2 cases	2 cases	42, 43
BCNU	UIP	Total dose >1 500 mg/m^2, radiotherapy, anesthesia, smoking, lung disease, other cytotoxics	Reversible	33%	24%	2, 51, 114
	PAP		Irreversible	2 cases	2 cases	44, 45
CCNU	UIP	Total dose >1 100 mg/m^2, radiotherapy, CYC therapy	Irreversible	5 cases	5 cases	3, 52, 58, 115
MCCNU	UIP	Total dose >4 000 mg/m^2	Reversible	1 case		53
CTN	UIP		Reversible	2 cases		69

PAP = pulmonary alveolar proteinoses, PO = pulmonary oedema, UIP = usual interstitial pneumonitis.

Table 2

Synopsis of pulmonary toxicity produced by the antimetabolites methotrexate (MTX) cytosine arabinoside (ARA-C), mercaptopurine (6-MP), azathioprine (AZA), and the immunosuppressive agent cyclosporin A(CyA)

Drug	Lesion	Risk factors	Course	Incidence	Lethality	References
MTX	EP	Adrenalectomy	Reversible	3–8%		19, 64, 117
	PO	Intrathecal injection pleuritis	Reversible	5 cases 4%	3 cases	81, 82, 118 83
ARA-C	PO	High dose regimen, severe diarrohea	Reversible	22%	6%	124
6-MP	DIP		Reversible	7 cases		77, 119, 120
AZA	DIP		Reversible	2 cases		78, 79
CyA	PAP	Total body irradiation, marrow transplantation, acute leukemia	Irreversible	5/29	5/29	125

PO = pulmonary oedema, DIP = desquamative interstitial pneumonitis, EP = eosinophilic pneumonitis, PAP = pulmonary alveolar proteinoses

least dose of busulphan to produce pneumonitis is about 500 mg (1). The pulmonary toxicity of the nitrosoureas seems to be dose-related, and usually emerges above total doses of 1 500 mg/m^2 carmustine (2), and 1 100 mg/m^2 lomustine (3). However, severe pulmonary fibrosis was seen in one patient who only received 800 mg lomustine (116).

Pulmonary insufficiency due to severe restrictive disease is the most likely outcome of toxicity produced by melphalan, chlorambucil, and busulphan, despite cessation of drug therapy. Clinical recovery has been seen in about 50% of cases of cyclophosphamide-induced pneumonitis, provided withdrawal of drug therapy (1). All the described cases of cytotoxic-induced pulmonary alveolar proteinosis have followed a progressive course which led to death from respiratory failure (42–45).

Antimetabolites and immunosuppressive agents

Desquamative interstitial pneumonitis and eosinophilic pneumonitis may result from therapy with methotrexate, mercaptopurine, and azathioprine (Table 2). Clinical, roentgenological, and morphological evidence of pulmonary toxicity was found among 8% of adults receiving

Table 3

Synopsis of pulmonary toxicity produced by the antimitotic agents vinblastine (VBL), vindesine (VDS), and teniposide (VM-26)

Drug	Lesion	Risk factor	Course	Incidence	Lethality	References
VBL	DIP	Mitomycin	Reversible	2 cases	1 case	127
VDS	DIP	Mitomycin	Reversible	5 cases		128
VM-26	UIP	Radiotherapy? Carmustine?		1 case		129

DIP = desquamative interstitial pneumonitis, UIP = usual interstitial pneumonitis.

methotrexate for various malignancies (64), while 3% of adolescents receiving high-dose methotrexate for osteogenic sarcoma developed restrictive lung disease (117). Seven cases of desquamative interstitial pneumonitis related to mercaptopurine monotherapy or mercaptopurine containing regimens have been reported (77, 119, 120), and two similar cases have been reported in the course of azathioprine therapy (78, 79).

The symptoms fade after withdrawal of the drugs, and may last for 40–45 days past cessation of methotrexate therapy (22, 27). Continued methotrexate administration may delay the recovery for 360 days (27), although rapid resolution during 10–40 days usually occurs despite continuation of the drug (22). Leucovorin rescue does not seem to protect pulmonary tissue (121). Pulmonary fibrosis is uncommon with methotrexate, and only 10 cases have been reported (10, 11, 26, 122). Four of them have died from respiratory failure. Methotrexate-induced pneumonitis is neither related to dose nor way of administration (117, 123).

Both cytosine arabinoside and methotrexate are known to cause non-cardiogenic pulmonary oedema (30, 31, 81, 82, 118, 124). The incidence of cytosine arabinoside-induced pulmonary oedema is clearly linked to dose, and reaches about 20% in high-dose schedules (124). Only five cases of pulmonary oedema are reported following methotrexate therapy, and all of them received methotrexate intrathecally (31, 81, 82, 118).

Interstitial pneumonitis is often seen in leukemia patients receiving allogenic marrow transplants. Progression to lethal respiratory failure is seen in two-thirds of the patients (125, 126). The etiology is multifactorial, including pulmonary leukostasis, total body irradiation, graft-versus-host disease, and prophylactic immunosuppressive chemotherapy. In contrast to the insidious pneumonitis following methotrexate prophylaxis, cyclosporin A is associated with a fulminant course of pulmonary alveolar proteinosis starting within 30 days of therapy, and circulatory crisis, with a 100% death rate (125), suggesting a causal relationship to cyclosporin A.

Antimitotic agents

Pulmonary toxicity caused by the antimitotic agents vinblastine, vindesine, and teniposide is uncommon and probably elicited by interaction with other cytotoxic agents (Table 3). Symptoms of acute respiratory failure appear 30 min to 5 h after injections of vinblastine and vindesine respectively, and fade within days with symptomatic treatment (127, 128). Chest roentgenograms show alveolar infiltrates. Vinblastine and vindesine were combined with mitomycin in seven cases of acute respiratory distress (127, 128). Two of these patients later developed a restrictive ventilatory defect consistent with mitomycin toxicity. Subacute pneumonitis related to teniposide monotherapy was seen in one case 5 months after completing a course of 115 mg/m^2 carmustine (129). However, there was no evidence of pulmonary fibrosis due to carmustine toxicity.

Antitumor antibiotics

The antitumor antibiotics bleomycin, peplomycin, mitomycin, and neocarzinostatin have been reported to cause usual interstitial pneumonitis in man (Table 4). Doxorubicin and dactinomycin do not produce pulmonary toxicity per se, but seem to potentiate radiation pneumonitis (135–137). Braun et al. (138) have suggested that dactinomycin produces longstanding radiosensitizing effects on lung parenchyma.

In two large series of bleomycin-treated patients the incidence of pulmonary toxicity steeply increased at ages above 70 years and total doses exceeding 450–500 mg (4, 5). A reduction of the single bleomycin dose from 15 mg/m^2 to 5 mg/m^2 by i.v. bolus injection has been shown to reduce the pulmonary toxicity in combination chemotherapy regimens (1). Single doses of 5 mg/m^2 peplomycin seem to be more tolerable than 10–15 mg/m^2 in a dose-escalation study (6). Dose-dependent toxicity has neither been observed in mitomycin nor neocarzinostatin therapy. Pulmonary symptoms may appear after a single dose of 20 mg/m^2 mitomycin (73).

Continuous infusion produces less pulmonary complications than intermittent administration of bleomycin in controlled mice experiments (139, 140). Corresponding controlled studies in man have not been performed. However, in a non-randomized trial a lower incidence of bleomycin-induced pneumonitis was reported with intravenous infusion than with intramuscular injections (86), and unexpectedly low incidences have been reported with

Table 4

Synopsis of pulmonary toxicity produced by the cytotoxic antibiotics bleomycin (BLM), peplomycin (PEP), mitomycin (MMC), neocarzinostatin (NCS), doxorubicin (DOX), actinomycin D(ACT), and the non-classified cotytoxic procarbazine (PCB)

Drug	Lesion	Risk factor	Course	Incidence	Lethality	References
BLM	UIP	Total dose >450 mg age >70 years, IV bolus injection, anesthesia, overhydration, radiotherapy, renal dysfunction, emphysema, other cytotoxics	Reversible in early stages	3–7%	6–63%	4, 5, 130, 131, 143, 146
	EP		Reversible	4 cases	1 case	14, 15
	PO	Malignant lymphoma	Reversible	1%	12.5%	5
PEP	UIP	>10 mg/m^2 IV bolus injection		11 cases	3 cases	6, 132
MMC	UIP	Anesthesia, vinblastine,	Reversible	3–12%	0–33%	72, 73, 133, 134
	PO	blood transfusions		5 cases	3 cases	32–35
NCS	PV		Reversible	2 cases	1 case	74, 75
DOX	RP	Irradiation		1 case		135
ACT	RP	Irradiation		3 cases		136–138
PCB	EP	Reversible		0.8%		12

EP = eosinophilic pneumonitis, PO = pulmonary oedema, PV = pulmonary vasculitis, RP = radiation pneumonitis, UIP = usual interstitial pneumonitis.

infusion regimens against head and neck carcinomas and non-Hodgkin's lymphomas (141, 142).

Emphysema seems to predispose patients to pulmonary toxic effects of bleomycin (143). Smoking habit do not influence the toxicity rate (84). In a retrospective study of 275 patients who had received bleomycin, renal dysfunction was found to be the most important risk factor in patients developing bleomycin-induced pneumonitis (144).

Two small series of patients receiving mitomycin monotherapy revealed an incidence of 3–12% clinically evident pneumonitis (133, 134). According to DeLena et al. (145) 40% of bleomycin-treated patients experienced pulmonary symptoms, but only 0.5% proved to be causally related to bleomycin. In larger series the incidence of clinically evident pneumonitis from bleomycin is 3–7% (4, 5), excluding those above 70 years of age.

The pneumonitis ends fatally in 6–63% of affected cases with bleomycin toxicity (130, 131), and 0–33% of affected cases with mitomycin toxicity (72, 73). The wide ranges reflect great uncertainties in quantifying lethality due to lack of conformity in diagnostic criteria and patient selection. In advanced cases with established fibrosis the outcome is usually death from progressive restrictive disease or spontaneous pneumothorax.

In a broad rewiev of 2079 patients acute pulmonary oedema occurred in 1% following the first or second dose of bleomycin (5). The death rate was 12.5%. All but one affected patient had malignant lymphoma, suggesting a predisposition among these patients. No fatal complications have been reported after an initial test dose of 1–2 mg bleomycin. Haemolytic-uremic syndrome produced by mitomycin may cause pulmonary oedema due to pathological increase in capillary permeability (35). Serum lactate dehydrogenase levels rise during development of haemolytic-uremic syndrome, and may prove to be useful in monitoring mitomycin toxicity (34).

Interactions

All pulmonary toxic agents compromize the air-blood barrier, and may act synergistically. Toxic effects are seen at much lower doses than expected when nitrosoureas are combined with cyclophosphamide (3, 115). Pulmonary toxicity from vinca-alkaloids are only seen in conjunction with mitomycin (127, 128, 147). Experimental studies indicate an increased fibrinogenous response to bleomycin when combined with vincristine or cyclophosphamide (148, 149). Clinical studies reveal an increased incidence of bleomycin pulmonary toxicity at relatively low total doses when combined with cyclophosphamide, vincristine, and doxorubicin (1, 150). Decreased renal function resulting from cisplatinum therapy increases the risk of bleomycin-induced pneumonitis (151).

Fractionated lung irradiation in excess of 18–20 Gy may cause pneumonitis (152). Pulmonary tolerance to whole-body irradiation combined with high-dose cyclophosphamide treatment is less, with serious or even lethal lung

Table 5

Postoperative complications and risk factors in patients treated with bleomycin

References	n	Operation type	Total dose bleomycin	Preoperative		Surgery hours	FiO_2 at surgery	Pulmonary damage
				$\%T_{LCO}$	(%FVC)			
Goldiner & Schweizer (146)	5	4AS 1TT	426±181 mg	59±3	(81±7)	5.9 (2.0–7.3)	39±0.1	5 lethal
	12	10AS 2TT	276±24 mg	63±3	(83±37)	5.7 (2.0–7.1)	24±0.3	None
Rubery & Lindop (166)	1	AS	750 mg	84	(91)	1.5	33	No
	1	AS	600 mg	92	(99)	1.5	33	No
Douglas & Coppin (167)	13	AS	296 mg (150–480)			4.6 (1.3–8.5)	35	None
	1	AS	300 mg	48		1.6	70	Reversible
				107*		6.3	25	No
Hulbert et al. (168)	1	AS	360 mg			9.5	40	Lethal
Lamantia et al. (169)	13	AS/TT	394±6 mg	Normal		6.1±0.7	41±4	None
Allen et al. (170)	3	AS/TT	534±8 mg	Normal		6.6±0.9	24±1	None
	1	TT			(95)	2.8	21	No
					(70)*	5.0	24	No

*reoperated.
AS = abdominal surgery, TT = thoracotomy, FiO_2 = inspiratory O_2 fraction, T_{LCO} = Co transfer factor, FVC = forced vital capacity.

damage occurring at dose levels exceeding 12–14 Gy (153). High-dose cyclophosphamide sensitizes the lungs to radiation fibrosis twice as much as low-dose cyclophosphamide (154). Mutual sensitation of lung parenchyma is brought about by radiotherapy and chemotherapy including either cyclophosphamide (76, 106, 154, 155) or busulphan (156), regardless of sequence order. Low doses of nitrosoureas have been associated with pneumonitis when combined with radiotherapy (57, 115). Doxorubicin and dactinomycin seem to increase the pulmonary toxicity of irradiation (135, 138). Simultaneous administration of bleomycin and pulmonary irradiation increases the risk of fatal pneumonitis (157), and lowers the threshold of maximally tolerable doses (158). Sequential treatment produces less risk both experimentally (159, 160) and clinically (161).

Blood transfusions have elicited acute and lethal pulmonary oedema in three mitomycin-treated patients with latent haemolytic-uremic syndrome and aggravated the ventilatory defect in two other patients (33, 34), possibly due to immunological activation of intravascular coagulation. Heparinization before transfusions may give some protection (35).

Epithelial and endothelial lesions have been observed in human lung after 14 h exposure to 70% oxygen (162). The pulmonary toxic effect of cyclophosphamide is amplified by oxygen ventilation both experimentally (163) and clinically (164). An acute and lethal aggravation of carmustine-induced pneumonitis was reported after 5 h ventilation of 90% oxygen (51). Postoperative ventilatory support at high oxygen concentration was reported to produce fatal respiratory failure in mitomycin-treated patients, whereas less than 30% oxygen in the inspiration gases was tolerable (165).

The interaction between bleomycin and anaesthesia has been widely studied (Table 5). Goldiner & Schweizer (146) observed lethal postoperative pulmonary failure in 5 patients receiving 35–40% oxygen perioperatively, while the postoperative period was uneventful in 12 patients receiving 22–26% oxygen. Overhydration with crystalloid fluids and preoperative restrictive lung disease may have contributed to the fatal complications. Other potential risk factors are duration of surgery, the surgical trauma, and the accumulated bleomycin dose. Patients with normal pulmonary function have been reported to tolerate 41% oxygen and approximately 8 ml/kg crystalloid fluid replacement without any postoperative complication due to interaction with bleomycin (169).

Hyperoxia probably potentiates the inflammatory phase of bleomycin pulmonary toxicity. When organization has taken place, potentiation no longer occurs, and in hamsters an indifferent phase is reached in 1–2 months (171). The human lung may be sensitized for at least 12 months (146).

Differential diagnosis

Immunocompromised cancer patients who develop clinical, roentgenological, and laboratory evidence of pulmonary disease while receiving cytotoxic agents raise complex diagnostic problems. Basically, the attending clinician must differentiate between lung metastases, a plethora of opportunistic infections, lung embolies, collagenosis, allergy, or lung damage induced by cytotoxics

and other drugs. Interstitial pneumonitis has also been causally related to some antibacterial agents, anticonvulsants, analgesics, diuretics and antiarrhythmics (19).

Fiberoptic bronchoscopy supplemented by bronchoalveolar lavage for biochemical, microbial, and cytological analyses and by transbronchial biopsy for histopathological evaluation, carries a risk of major complications of less than 1% (172), and is a central procedure in the investigation of these patients. Lavage is particularly valuable for the demonstration of malignant cells, infectious agents, or alveolar proteinosis. The diagnostic accuracy of transbronchial biopsy in chronic infiltrative lung disease was only 37%, compared to at least 90% for open lung biopsy (173). In critically ill patients open lung biopsy is the procedure of choice (172). Fifty per cent of immunocompromised patients who had nonspecific transbronchial biopsies, had potentially treatable diseases diagnosed at open lung biopsy (174).

Defects of humoral and cellular immunity frequently occur in the course of haematologic neoplasia or during aggressive chemotherapy. Immunocompromised patients are at particular risk of developing interstitial infiltrates in the lung. Infectious disease constituted 50% of the specific diagnoses obtained by open-lung biopsy in a retrospective analysis of 87 immunocompromised patients, and the protozoe Pneumocystis carinii accounted for 44% of the opportunistic agents (175). Other less frequent opportunistic agents are Mycobacteria, Aspergillus, Candida, Nocardia, and Cytomegalovirus (175).

Immunofluorescent staining of induced sputum using monoclonal antibodies (176) or microscopy of silver stained material from bronchoalveolar lavage, bronchial brushings, or transbronchial biopsy will demonstrate the protozoe in most patients with P. carinii pneumonitis (177, 178). The infection is progressive and usually fatal if left untreated. Trimethoprim-sulphmethoxazol is effective in the prevention (179) or treatment (178) of P. carinii pneumonitis in severely immunocompromised patients.

Treatment

Pulmonary toxicity is best controlled by cessation of the causative chemotherapy regimen. Early stages of bleomycin-induced pneumonitis have reversed clinically and roentgenologically after withdrawal of bleomycin (89, 90, 145). The symptoms produced by methotrexate may resolve despite continuation of the treatment (22, 27). However, the recovery is speeded up by corticosteroids, so that normal blood gases may be restored within 8–10 days (10).

Corticosteroids may provide some protection when given concomitant with cyclophosphamide (8, 102) or melphalan (108). However, the effect on clinically established usual interstitial pneumonitis is poor. Corticosteroids have been reported useful in treatment of pneumonitis caused by chlorambucil (49), carmustine (57, 114, 180), and busulphan (1, 87, 181), and may stop the inflammatory process secondary to bleomycin (182–184), mitomycin (33, 73), and neocarzinostatin (74, 75). The application of corticosteroids seems useful in early stages of pneumonitis before fibrosis develop.

Eosinophilic pneumonitis caused by methotrexate, procarbazine, and bleomycin is sensitive to corticosteroids (10, 15, 66). Peripheral eosinophilia in bleomycin-treated patients indicates an allergic response, but cannot predict the responsiveness to steroids (29). In a prospective study of 287 patients receiving combination therapy including bleomycin it was demonstrated that even severe usual interstitial pneumonitis may improve from corticosteroid therapy, although the improvement required daily administration of 60–100 mg prednisone for several months (36).

Conclusion

Consideration of various differential diagnoses is essential when facing concomitant lung disease in a cancer patient, due to the divergent therapeutic consequences. Clinical findings, lung function tests, and radiological signs are often non-specific. Fiberoptic bronchoscopy with bronchoalveolar lavage supplemented with cytology and appropriate microbiologic investigations are essential to exclude opportunistic infections or neoplastic lung involvement. Transbronchial biopsy provides a relatively safe and useful sampling technique of lung specimen under local anaesthesia. Percutaneous or open-lung biopsy may also be necessary for reliable diagnosis.

Pulmonary drug toxicity remains an exclusion diagnosis. The probable causative agent(s) must be withdrawn. Corticosteroids may be effective, but cannot reverse established lung fibrosis. Early detection of pulmonary toxicity is the only way to reduce illness and death from these serious and sporadic complications to antineoplastic and immunosuppressive drug treatment.

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