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CORRESPONDENCE

Management of interleukin-2-induced severe bronchoconstriction

To the Editors:

The immunostimulatory cytokine, interleukin (IL)-2, is used for the treatment of patients with cancers, such as metastatic renal cell carcinoma and melanoma [1, 2]. The toxicity of IL-2 has been well described, including hypotension, a capillary leak syndrome including pulmonary oedema, thrombocytopenia and renal dysfunction [1, 3–5]. Interestingly in a rare case, IL-2 administration, especially its inhalation, was reported to cause bronchoconstriction [3, 4, 6]. However, little is known about the risk factors and management of IL-2-induced bronchoconstriction. We conducted a study to elucidate the clinical characteristics of patients developing IL-2-induced bronchoconstriction and to examine how to manage this condition.

The study subjects included 18 patients with malignant cutaneous haemangioendothelioma (10 males and 8 females). Most of them were elderly with a mean (range) age of 72.3 (52–95) yrs, and all had lesions on the face and head. All patients received IL-2 immunotherapy plus radiotherapy. IL-2 was administered intralesionally in four patients and intravenously in one. The remaining 13 patients received IL-2 both intralesionally and intravenously. IL-2 was usually given 2–3 times a week. Total doses of intralesional IL-2 were $1.2–56 \times 10^6$ U (average, 13.8×10^6 U) and intravenous IL-2 were $8–60 \times 10^6$ U (average, 32.8×10^6 U).

During therapy, three patients developed severe cough, dyspnoea and chest tightness. The clinical characteristics of these three patients are shown in table 1. Intralesional administration of IL-2 was performed in two of these patients, while the third patient was given IL-2 intravenously. Chest auscultation showed a diffuse wheeze. Pulmonary function tests revealed obstructive impairment with no abnormal opacities on chest radiograph. Inhalation of the bronchodilator salbutamol, a short-acting β_2-agonist (SABA), showed a small increase in forced expiratory volume in one second (FEV_1 <10%) with little symptomatic improvement (table 1). All patients developing bronchoconstriction had a history of asthma, but they were mild-intermittent asthmatics not needing regular medication, such as inhaled corticosteroids (ICS). Bronchoconstriction typically occurred 6–8 h after IL-2 administration, and continued overnight, regardless of the administration route (fig. 1). Inhalation of a SABA before IL-2 administration did not prevent the bronchoconstriction. Pre-treatment with ICS (fluticasone propionate 200–400 μg *b.i.d*) alone or a long-acting β_2-agonist (LABA; salmeterol 50 μg *b.i.d*) alone, which were given 1 day before IL-2 administration, decreased an IL-2-induced fall in FEV_1 by <30%. However, pre-treatment with ICS plus a LABA (fluticasone propionate 200–400 μg, salmeterol 50 μg *b.i.d*) markedly reduced the decline in FEV_1 by 70–80% with symptomatic improvement (fig. 1). The serum levels of IL-4, IL-5, eosinophilic cationic protein or the plasma levels of thromboxane-B_2 did not increase after IL-2 administration.

Bronchoconstriction has been reported as an adverse effect of IL-2 in several studies, but in the majority, IL-2 was administered by inhalation [6]. Our study demonstrated that the intravenous and even intralesional administration of IL-2 caused bronchoconstriction. Notably, IL-2-induced bronchoconstriction occurred exclusively in patients with a history of bronchial asthma, suggesting that asthmatics are more susceptible to bronchoconstriction induced by IL-2 therapy. IL-2-induced bronchoconstriction usually appeared 6–8 h after IL-2 administration with a 40–55% decrease of baseline FEV_1 that lasted overnight. To date, there has been only one case report studying the treatment of IL-2-induced bronchoconstriction [6], in which pre-treatment with a SABA successfully prevented bronchoconstriction induced by inhaled IL-2 therapy in a case of metastatic lung tumours of renal cell carcinoma. However, the present study showed that SABA

TABLE 1 Characteristics of patients developing bronchoconstriction by interleukin (IL)-2 therapy

Patient	Sex	Age yrs	History of asthma	IL-2 administration	IgE U·mL^{-1}	PC_{20} mg·mL^{-1}	FEV_1 L		
							Baseline	After IL-2 therapy	Post-inhalation of bronchodilator
1	M	69	Yes	Intralesional + *i.v.*	104	2.1	2.12	0.91	1.00
2	F	67	Yes	Intralesional	86	ND	1.88	0.98	1.02
3	M	59	Yes	Intralesional + *i.v.*	44	2.6	2.54	1.41	1.50

Ig: immunoglobulin; PC_{20}: methacholine concentration causing a 20% fall in forced expiratory volume in one second (FEV_1); M: male; F: female; ND: not done.

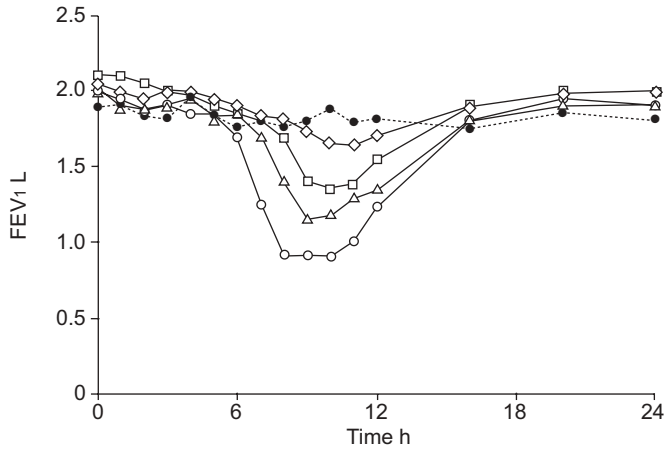

FIGURE 1. Changes in forced expiratory volume in one second (FEV_1) during interleukin (IL)-2 therapy. Vehicle (●) or IL-2 (○) were injected intravenously into patient 1. Changes in FEV_1 after pre-treatment with inhaled corticosteroid (△) or a long-acting β_2-agonist (□) alone, or in combination (◇) are shown.

pre-medication failed to prevent the bronchoconstriction. The different route of IL-2 administration may partly explain this discrepancy. Inhalation of IL-2 was reported to develop bronchoconstriction very shortly after administration [6], while bronchoconstriction induced by intralesional and intravenous injection started 6–8 h after therapy and continued overnight. Thus, a SABA is unlikely to prevent the latter bronchoconstriction because of its short-acting effect. Interestingly, pre-treatment with LABA or ICS alone induced only a small increase in an IL-2-reduced FEV_1, but ICS in combination with a LABA markedly decreased a fall in FEV_1 with symptomatic improvement. These results suggest that, in addition to a long-acting bronchodilator, anti-inflammatory drugs were required for preventing IL-2-induced bronchoconstriction.

In summary, our study showed that interleukin-2 administration, even intralesionally, induced severe bronchoconstriction in patients with malignant cutaneous haemangioendothelioma. Bronchoconstriction occurred exclusively in patients with a history of bronchial asthma; therefore, attention must be directed to interleukin-2-induced bronchoconstriction, especially in patients with a history of asthma. Once it occurred, interleukin-2-induced bronchoconstriction did not respond well to bronchodilators, and pre-treatment with inhaled corticosteroids in combination with a long-acting β_2-agonist successfully prevented this condition.

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STATEMENT OF INTEREST

None declared.

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