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Editorial Office Notes:

RES-17-736

EDITORIAL

Endobronchial Drug Delivery – Expanding techniques and possibilities in Interventional Pulmonology

Key Words: Lung cancer, Bronchoscopy and interventional techniques, Neoadjuvant therapy

Malignant involvement of central airways is common in NSCLC, occurring in an estimated 20% of patients with Non-Small Cell lung cancer (NSCLC) and frequently portends a poor prognosis. Therapeutic bronchoscopy is recommended in patients with symptomatic malignant airway obstruction for improvement in dyspnea, cough, hemoptysis and overall quality of life.(1) Registry data suggests a high rate of success in relieving symptoms, though success is potentially lower in patients with primary lung cancer.(2)

While central airway obstruction may cause major symptom burden, successful management with therapeutic bronchoscopy allows similar survival outcomes to those seen in patients with advanced NSCLC without central airway obstruction (CAO).(3) Hence active management of endobronchial disease should be sought wherever possible. Numerous bronchoscopic techniques have been reported to achieve successful palliation of malignant airway obstruction. Despite the significant physiologic compromise frequently present in patients with CAO, complication rates for bronchoscopic intervention are low.(4)

Bronchoscopic injection of cytotoxic agents directly into airway tumor, also termed endobronchial intratumoral chemotherapy (EITC), has been reported for management of central airway tumor. In NSCLC this has previously been used both for palliation of bronchial obstruction,(5, 6) as well as with neoadjuvant intent in patients with Stage III disease.(7, 8) Convex-probe endobronchial ultrasound-guided

transbronchial needle injection (EBUS-TBNI) has also been utilized for direct injection of chemotherapeutic agents into extraluminal primary tumors or mediastinal lymph nodes.(9-11)

The advantages of intratumoral chemotherapy (as discussed in abstract for) are likely intuitive, and include (i) precise delivery of cancer drugs to and within the tumor, achieving (ii) dramatically higher intratumor drug concentrations than possible by systemic drug delivery, with (iii) virtually none of the toxic side effects associated with conventional systemic chemotherapy.(12) Furthermore, supporting a role in neo-adjuvant intent therapy for EITC, sustained treatment effect may be possible given the ability to deliver chemotherapy to the entire tumour, and the persistence of chemotherapy within tissue. This is in clear contrast to traditional mechanical debulking technqiues (eg. laser, cryoresection), where unresected tumor remains unaffected and improvements are frequently short-lived.(5)

In this edition of *Respirology,* Tsukada & colleagues report use of a micro-needle infusion catheter to administer paclitaxel into bronchial mucosal tissue.(13) Technical feasibility of the Blowfish® Transbronchial Micro-Infusion Catheter had previously been reported by the same group.(14) In the current study the authors demonstrate, in a porcine model, the feasibility and safety of bronchoscopic delivery of Paclitaxel, with achievement of tissue levels in resected bronchial wall segments well in excess of therapeutic concentration, without significant local injury. Systemic absorption was minimal – peak plasma levels were greater than an order of magnitude lower that that associated with systemic administration, and were undetectable by 5 days, while tissue levels remained in excess of therapeutic levels even beyond 20 days. These are very promising results.

Prior studies have confirmed safety/feasibility, and confirmed clinical responses to EITC, however this study is the first *in vivo* report establishing the pharmacokinetics of Paclitaxel in bronchial tissue. In establishing the safety and stability of Paclitaxel delivered by the Blowfish® device, Tsukada & colleagues

have confirmed the potential of EITC to become a front-line intervention in bronchoscopic management of CAO. These results also create a platform for future clinical studies – as the authors identify, injection of paclitaxel in this study was into normal bronchial mucosa of study animals. The results of the subsequent study (NCT02066103), examining the safety and feasibility of intratumoral injection of paclitaxel into the bronchial wall of patients with malignant CAO, will be of significant interest.

Utility of this technique in an emergent setting remains unclear – such scenarios are still more likely to require intervention achieving immediate effect (e.g. laser, cryotherapy) however EITC may be an important component of multi-modality therapy in optimizing the magnitude and durability of any responses to therapeutic bronchoscopy.

Findings reported by Tsukada & colleagues confirming consistent and sustained tissue concentrations are perhaps most intriguing as they suggest significant potential for neo-adjuvant intent EITC. Similar to a number of recent developments in Interventional Pulmonology (IP), this report does more than advance the current IP literature; it establishes potentially novel therapeutic applications of bronchoscopy, which serves to grow the IP field exponentially faster still.

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