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EDITORIAL

Photodynamic therapy: where do we go from here?

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Photodynamic therapy (PDT) involves the use of photosensitising agents that are selectively retained within tumour cells. The agents remain inactive until exposed to light of the proper wavelength. When activated by light, these compounds generate toxic oxygen radicals that result in tumour necrosis. In the current issue of the *European Respiratory Journal*, MOGHISSI *et al.* [1] have provided an exhaustive review of PDT and lung cancer. PDT appears to be a therapeutic technique, with a low toxicity profile and photosensitising agents, such as sodium porfimer, that have been approved by the Food and Drug Administration and European Agencies for the photodynamic treatment of early and late stage lung cancer.

However, despite 2 decades of basic research and clinical experience, only a few centres have regular experience of PDT. Furthermore, several issues remain as yet unresolved, such as the best indications of PDT, the use of photosensitising agents other than sodium porfimer, or the comparison of PDT and other endobronchial therapies, such as electrocautery, Neodymium-doped Yttrium Aluminum Garnet (Nd YAG) Laser, cryotherapy, or even endobronchial brachytherapy.

These endobronchial treatments have all been proposed in the treatment of late obstructing lung cancers. In this palliative setting, these therapies provide a substantial improvement in respiratory symptoms. Choosing a technique from the different available endobronchial treatments remains a matter of clinical experience, equipment, toxicity and cost-effectiveness. Despite a good palliation index, PDT appears to be prohibitively expensive when compared with treatments such as electrocautery or cryotherapy. Furthermore, skin photosensitivity lasts 4–6 weeks, implying that precautions must be taken to avoid exposure of skin and eyes to direct sunlight or bright indoor light during this period. This may interfere with the quality of life of these patients with a very limited life expectancy. Hence, PDT is probably preferred in interventional bronchoscopy units accustomed to this method, whereas other units use less expensive and easier to perform treatments, such as electocautery or cryotherapy.

The use of PDT in early stage lung cancer appears more encouraging. Thus, the natural history of early stage lung cancer, the risk of multifocal synchronous or metachronous lesions and above all, the need for conservative treatments in patients with a limited pulmonary reserve are justifications for endobronchial treatments. Among these endobronchial treatments, PDT is the most extensively studied technique. A recently published paper studying the level of evidence and benefit made a recommendation of grade B for PDT, whereas electrocautery, brachytherapy and cryotherapy were graded C [2]. The authors of the latter study did not recommend Nd YAG Laser treatment. It must be stressed that a randomised comparison of these techniques has not been performed.

Despite endobronchial treatment, some early preinvasive lesions will progress to invasive lung cancer. A recent study including nine patients with carcinoma *in situ* (CIS) indicated that about a half of these lesions evolve into invasive lung cancer during 6 months of follow-up [3]. Nevertheless, not all patients received an endobronchial treatment. Another study reported on 35 CIS treated with cryotherapy [4]. The complete response rate at 1 yr was 91%. Local recurrence was observed within 4 yrs in 28% of patients. In the latter study, the progression-free interval curve shows a 5-yr rate of ~50%. This progression rate fully explains that patients need repeated endobronchial treatments and often multiple sessions of all available endobronchial treatments. PDT, cryotherapy and, up to a certain point, electrocautery can be repeated a number of times, unlike brachytherapy. This feature allows physicians to repeatedly treat tumours and control their growth in cases of progression or persistence.

Aside from their therapeutic properties, photosensitisers have been tested for the photodetection of early lung cancer and preinvasive bronchial lesions. It should be noticed that some of these studies led to the discovery of natural autofluorescence of normal bronchial mucosa and later to the advent of autofluorescence bronchoscopy (AFB) [5, 6]. Early stage cancers and bronchial preinvasive lesions are now easily and more frequently diagnosed, emphasising the need for effective therapeutic techniques. Photosensitisers used for PDT might improve the targeting of lesions diagnosed during AFB. Thus, a fluorescence bronchoscopy performed after sodium porfimer injection discloses bronchial lesions with a fluorescent red appearance allowing a better definition of tumour margins and the target lesion to be illuminated. However, there is still a risk of false-positive aspects in the bronchial tree and only biopsy-proven lesions should be considered.

Skin photosensitivity remains one of the biggest challenges of PDT and photodetection. Ideally, inhaled photosensitising agents with a reduced systemic biodisponibility and a reduced skin retention are clearly needed. Several new agents have been tested with some limitations and there is still a great deal of room for improvement [7, 8]. Future developments include a new, wider choice of wavelength to affect depth of penetration, improved dosimetry systems and better light delivery producing more consistent and homogenous light delivery.

Photodynamic diagnosis and therapy have exciting potential in lung cancer management, especially in early stage lesions. The authors believe that it is not the beginning of the end for photodynamic therapy, rather the end of the beginning.

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