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EDITORIAL REVIEW

Non-specific immunotherapy with bacille Calmette–Guérin (BCG)

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In the past two decades, the most successful immunotherapy in man probably consisted of non-specific immunotherapy with BCG for superficial bladder cancer. This intravesical therapy was first introduced by Morales in 1976 [1].

Superficial papillary bladder cancer is not, in most cases, a lethal disease but it is characterized by a high percentage of recurrences (60–80%) and a much lower percentage of progression to invasive, potentially lethal bladder cancer (15%) [2]. The initial therapy for this disease is surgery, and adjuvant intravesical chemotherapy has been used to reduce recurrences and prevent progression. The latter, however, has not been successful, as shown in multiple randomized clinical trials [3].

Zbar *et al*. formulated the conditions for which BCG in an optimal situation could work against malignant tumours [4]. These meant that: (i) direct contact between tumour cells and BCG is mandatory; (ii) an adequate dose of BCG is necessary; (iii) BCG will work only when the tumour burden is limited; (iv) not only the tumour but also lymph node metastases draining from the parent organ may disappear.

Morales projected the conditions of Zbar *et al*. to superficial bladder cancer, where it was easy to bring BCG in a watery solution through the urethra into the bladder, directly in contact with tumour cells. BCG turned out to be superior to any of the known chemotherapeutic drugs. In some selected series, it seems that BCG is able to prevent progression to invasive bladder cancer [5]. However, a number of problems remain despite intensive research during the past 20 years.

Urologists still do not know whether there is an optimal strain of BCG. All the known BCG strains are derived from the original strain found by Calmette and Guérin. This product was the result of an attempt to find an attenuated strain of a highly virulent bovine tuberculosis strain that was to serve as a vaccine against human tuberculosis. By prolonged culture the bovine tubercular strain lost its virulence and its pathogenic characteristics but its immunogenic properties remained unaffected [6].

It took Calmette and Guérin 13 years of culture with 230 consecutive transplants to tame the bacterium. During this period mutation and genetic drift had taken place. After exporting the strain all over the world the genetic drift must have gone further, resulting in different therapeutic results and immunogenic properties [7]. In relation to bladder cancer, few studies have been performed to compare the effects of different strains [8]. Aside from the question as to which strain is superior, the optimal dose and instillation regimen of BCG are also still unknown.

However, the most intriguing problem that remains is that we do not know exactly how BCG works. There is a cascade of immunological events which depends upon the host, dose and regimen and which can lead to immunostimulation, as well as to inhibition, of immune reactions [9]. In the case of superficial bladder cancer, the immune response is translated into the urinary secretion of cytokines such as interferon-alpha (IFN-α), IFN-γ and IL-2. Although not yet tested in large series of patients, the level of cytokines secreted seems to be related to the clinical outcome for patients with superficial bladder tumours [10].

The authors Luo *et al*. in this issue of *Clinical and Experimental Immunology* [11] take a major step forwards in the use and understanding of how BCG works in human bladder cancer. As Calmette and Guérin had done, they altered the genetic properties of tubercle bacilli but this time by using recombinant BCG (rb-BCG) and incorporating the human IFNα 2B gene. Such genetic modification may lead to a greater clinical efficacy and fewer side-effects of BCG immunotherapy, although this has yet to be established. Luo *et al*. then elegantly showed that this rb-BCG incorporating the human IFNα 2B gene induced increased production of both recombinant human IFN-α (rh-IFN-α) and IFN-γ, compared with wild-type BCG. This production was inhibited upon antibody neutralization of rh-IFN-α, indicating that the genetic alteration was responsible for the increased immunostimulation. Both *in vitro* and with peripheral blood mononuclear cells from 10 patients, the authors showed an immune response to rb-BCG which was also more rapid than that to wild-type BCG.

This work is important for two reasons. First, it may lead to a better understanding of how BCG exerts its anti-tumour effect in bladder cancer, and second, it may be a step towards developing a BCG product with higher efficacy and lower toxicity for patients than the wild types of BCG. Further work is required to translate Luo *et al*.'s studies to a clinical setting.

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