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A new hope

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Immuno-oncology uses the body's inherent immune system to combat malignancy. It is one of the most promising new avenues of treatment for the millions of people worldwide who are experiencing cancer. For many years, the immune system has been known to play an important role in the regulation of cancer. Patients who are immunosuppressed experience a higher incidence of malignancy, and the incidence of spontaneous remission in a variety of cancers is approximately 1 in every 60,000 to 100,000 cases[1,2]. Possibly the earliest example of immunotherapy is noted in the Ebers Papyrus (*ca.* 1550 BCE), attributed to the legendary Egyptian physician Imhotep (*ca.* 2600 BCE). In it, the recommended treatment for swellings (tumours) is the application of a poultice, followed by an incision. Such a treatment would lead to an infection at the site of the tumour and regression[3].

In 1891, an American surgeon, William B. Coley, first attempted to harness the immune system for treating cancer[4,5]. After noting responses in cancer patients who developed erysipelas, Coley injected heat-inactivated bacteria ("Coley toxins") directly into tumours and achieved a significant number of regressions and durable complete responses in his patients[6]. However, because of a number of factors, including failure to follow appropriate scientific protocols, inconsistent results, severe side effects, and the development of radiation therapy and chemotherapy, Coley's techniques gradually disappeared from clinical practice. However, in 1976, his strategy resurfaced when bacillus Calmette–Guérin was found to be effective in the treatment of superficial bladder cancer[7].

In the decades that followed, progress in immunotherapy remained quite slow, with only the approvals for two nonspecific immunostimulatory cytokines: interleukin 2 and interferon. Both were associated with limited efficacy and significant toxicity. However, long-term remissions or cures were noted in melanoma and renal cancer. Interferon alfa was approved in 1986 for hairy cell leukemia, chronic myelogenous leukemia, follicular non-Hodgkin lymphoma, melanoma, and AIDS-related Kaposi sarcoma. Interleukin 2 was approved for the treatment of renal cancer in 1991 and for melanoma in 1998. Immunotherapy began to change with the description of PD-1[8,9] and the isolation of CTLA-4 and determination of its function[10,11]—two watershed events that allowed for the development of checkpoint inhibitors. However, it would be 14 years before the first phase III clinical trials definitively showed the benefits of those agents, allowing for their approval by regulatory bodies[12].

At approximately the same time, Carl June and colleagues used a chimeric antigen receptor T cell strategy to produce a complete and durable remission in a pediatric patient with treatment-refractory chronic lymphocytic leukemia after adoptive transfer of construct-transduced autologous T cells[13]. Immuno-oncology had entered the 21st century.

In 2013, *Science* declared cancer immunotherapy to be the "Breakthrough of the Year"[14]. Since that time, the field of immuno-oncology has grown rapidly, now being used in the treatment of a wide range of malignancies. Its impact is being felt by all specialists involved in the management of patients with cancer, and the benefits to those patients have been nothing short of extraordinary.

The introduction of immunotherapy into Canada has not been without its challenges: Patients with hitherto untreatable and incurable cancers are now routinely being offered treatment, straining already-limited resources and treatment beds. For example, before 2010, almost all patients with stage IV melanoma were not offered systemic therapy. Now almost all are receiving some form of treatment, which, in some cases, is bringing their disease under control for a long period of time. The impact is even greater in the more common tumours such as lung cancers. With those successes in the metastatic setting, immunotherapy has now moved into the adjuvant setting, putting additional strain on resources[15–18].

From my personal perspective as a melanoma specialist, the combinations of new metastatic and adjuvant therapies have roughly quadrupled my workload since about 2010. The side effect profile of some of the immunotherapy therapies are quite favourable[19]. As a result, patients who would never have been considered for systemic therapy now have that option. In cancer clinics, a number of otherwise healthy patients in their late 80s and early 90s are receiving immunotherapy and achieving control of their disease. The cost of the new treatments has also placed a strain on Canada's ability to fund them. A disconnect is evident between immunotherapies approved by Health Canada and those that are funded by health payers. With some therapies priced in the hundreds of thousands of dollars, difficult decisions will have to be made with respect to the groups of patients that will receive treatment.

In this *Clinical Oncology* supplement dedicated to immuno-oncology, we have gathered some of the leading experts in Canada to discuss the many issues that physicians face daily in this new therapeutic field. The supplement presents an overview of the mechanism of action of this new class of drugs; the impact these agents are having

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in a variety of cancers, including melanoma, lung cancer, genitourinary tumours, and hematologic malignancies; management of the novel side effects attending the use of immunotherapy; promising new treatments, including chimeric antigen receptor T cells; and future directions in the field. I hope that the supplement will provide an excellent overview of the current state of the art in this exciting new area of cancer therapy.

CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and I declare the following interests: I have received fees as an advisory board member for Bristol–Myers Squibb, Novartis, and Sanofi Genzyme.

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