TITLE: Building the fourth pillar: the state of cancer immunotherapy in 2019

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ABSTRACT

The past decade saw great excitement over cancer immunotherapy, particularly with the discovery being heralded as a “game changer”.¹ In 2013, *Science* magazine dubbed immunotherapy the “breakthrough of the year”,² and in 2018, the *Nobel prize in physiology and medicine* was awarded for contributions to the field.³ Throughout the 2010s, unprecedented clinical results were seen with chimeric antigen receptor (CAR) T-cell therapy,^{4–6} and the first FDA approvals were obtained for CAR T-cell products,⁷ oncolytic viruses,⁸ and checkpoint blockade.⁹ Despite rapid advances, cancer immunotherapy progress has not been without its hurdles. New toxicities and high costs continue to challenge the field, alongside uncertainties regarding the durability of responses and widespread applicability of these therapies across different tumour types.^{10,11} Now, at the close of the decade, we provide a brief overview of the history and current state of immunotherapy; we summarize the major successes, the promising research and therapeutic pathways, and the barriers currently faced by the field, reflecting on how this treatment has truly “changed the game”.

INTRODUCTION

The notion that the immune system can fight cancer proved to be one of the most contentious ideas within the field of oncology throughout the 20th century.^{12,13} William Coley is often credited as the “father of immunotherapy” for his breakthrough studies showing that induction of an immune response by administration of killed bacterial toxins could, in select cases, promote tumour regression.¹⁴ Coley’s discoveries came at a time when in depth knowledge of the cellular mechanisms of the immune system was virtually absent.¹⁵ As such, the nascent field of immunotherapy was characterized by radical fluctuations between acceptance and dismissal of the role of the immune system in controlling cancer.^{12,13,16} In 1959, Thomas and Burnet proposed the theory of immunosurveillance, which posited that the immune system is constantly recognizing and eliminating incipient neoplasms^{17,18} This notion was supported by mouse models demonstrating rejection of syngeneic tumours. However, it lacked a comprehensive mechanistic explanation prior to the understanding of T-cell mediated immunity in 1974.^{19,20} Even at this point, ambiguity existed regarding what was actually being recognized by the immune system. Only in the late 1980s²¹ and early 1990s²² were the first descriptions of *bona fide* tumour antigens in humans established²³. This paved the way for the modern understanding that while the immune system does indeed perform a function of immunosurveillance, clinical cancer can arise through mutations in tumour cells which reduce the immunogenicity of the antigens they express, or allow them to actively suppress antitumour immunity.²⁴ Current immunotherapy strategies therefore seek to reverse such immune avoidance mechanisms, but the ability to do so in a clinical setting was not solidified until the late 2000s.

SUCSESSES IN IMMUNOTHERAPY

Numerous cancer immunotherapies have been developed over the last two decades, of which several have demonstrated success in improving outcomes and some producing complete and lasting responses.^{25, 26}

Immune Checkpoint Inhibitors (ICI)

ICIs are monoclonal antibodies that inhibit specific receptors regulating or inhibiting T-cell activity; this allows T-cells to have a more robust response to a malignancy by bypassing their regulatory “checkpoints”.¹⁶ Since 2011, six ICIs have been approved by the FDA and Health Canada for specific indications in cancer therapy. These include: Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Avelumab and Durvalumab.^{27,28} Nivolumab (an anti-PD-1 inhibitor) in particular has shown benefit in terms of overall survival in refractory non-small cell lung cancer.²⁹ Combined anti-CTLA-4/anti-PD-1 checkpoint inhibitors show prolonged progression free survival in stage IV melanoma, which was previously regarded as an incurable and fatal diagnosis.^{30,31} Indeed ICI therapy has now emerged as the treatment of choice for melanoma.³² Data indicates similar or slightly better quality of life using ICI relative to traditional therapeutics, however investigations in this domain have been limited.^{33,34} Other approved indications for the various ICIs include renal cell carcinoma, relapsed classical Hodgkin’s lymphoma, recurrent/relapsed small cell carcinoma of the head and neck, and certain hepatocellular carcinoma patients. Trials are currently underway testing ICI indications for other cancers.²⁷

CAR T-Cell Therapies

Chimeric Antigen Receptor T-cell (CAR-T) therapy is a type of adoptive cellular therapy (ACT), in which autologous T-cells are genetically engineered to express CAR. CAR is

a synthetic receptor combining an extracellular targeting domain of an antibody with the intracellular signalling machinery of a T-cell receptor.³⁵ These constructs can be targeted to virtually any antigen present on the tumour surface.³⁵ CAR-T therapy has shown profound success in treating hematopoietic malignancies, achieving high response rates and durable remission in acute⁴ and chronic lymphocytic leukemias,³⁶ and in refractory B-cell lymphomas.³⁷ Furthermore, recent success has been achieved in the treatment of multiple myeloma with CAR-T therapy.^{38,39} Response rates vary tremendously by the type of cancer being treated. One systematic review reported a pooled complete response (CR) rate of 54.4% using CD19 targeted CAR-T in hematological malignancies but noted that CRs ranged from 77.1% in ALL to 25.5% in CLL. Similarly, overall survival (OS) ranged from 5 to 95% depending on the trial.⁴⁰ Two CAR-T therapies have been approved by Health Canada, Kymriah for pediatric relapsed or refractory ALL and Yescarta for large B-cell lymphoma.²⁸

Other Promising Therapies

Cancer vaccines, although promising for future cancer therapy, have shown limited clinical efficacy to date. The use of bacillus Calmette-Guerin (BCG) as an adjuvant in the treatment of bladder cancer demonstrates the potential of immune-activating agents in inducing an antitumour response.^{41,42} Strategies at developing *bona fide* tumour antigen-encoding cancer vaccines include autologous cell vaccines, peptide vaccines, and dendritic cell vaccines.⁴³ To date, these strategies have yielded only modest clinical benefit, but have many attractive properties such as the establishment of immunological memory.⁴³ Sipuleucel-T, a dendritic cell vaccine, has more recently been approved by FDA for prostate cancer treatment, and shows modest yet significant improvements in patient outcomes.¹⁶

Oncolytic viruses (OV) are modified viruses which target and lyse cancer cells, promoting an antitumour immune response.¹⁶ OVs are another emerging avenue of cancer immunotherapy. One OV therapy, Talimogene Laherparepvec (T-VEC), has been FDA-approved, showing efficacy in the treatment of advanced melanoma.^{44,45} Clinical trials are underway for additional OV therapies.¹⁶

Tumour infiltrating lymphocyte (TIL) therapy, another type of ACT therapy, involves the isolation and replication of autologous TILs from a patient's tumour biopsy, and reinjection of the replicated T-cells into the tumour. TIL therapy has shown efficacy in metastatic melanoma, with a 40% response rate observed, even in patients after failed ICI therapy. Advancements in TIL therapy show potential application to breast, ovarian, and colorectal cancers.⁴⁶

CURRENT BARRIERS AND RESEARCH DIRECTIONS

Though immunotherapies have shown unprecedented successes, the field is not without its limitations – namely, new toxicities, variable responses to therapy, and high costs.^{10,11} These specific barriers will be outlined below.

Broadly, immune related adverse events (irAEs) refer to the diverse immunopathological and autoimmune toxicities caused by therapeutic activation of the immune system.⁴⁷ Both acute and delayed multisystem reactions have been observed with ICI, including pneumonitis, kidney dysfunction, and neuropathy.⁴⁸ Deaths directly attributed to treatment with checkpoint inhibitors are rare with one systematic review estimating fatalities to be on the order of 0.3-1.3%.⁴⁹ In one study treating patients with metastatic melanoma with nivolumab, ipilimumab, or a combination thereof 12%, 16%, and 39% of patients had to discontinue treatment due to irAEs although these patients still showed improvement.⁵⁰ Cytokine release syndrome (CRS) following administration

of CAR T-cells is a well-recognized and potentially deadly phenomenon that results from hyper-secretion of cytokines with effects reminiscent of an influenza infection.^{51,52} While fatal events are uncommon overall in CAR T-cell therapy, they have been observed. Subsequent analysis has sometimes been able to correlate mortality and other adverse events with factors such as the antigen targeted, the CAR construct used, and the disease burden.⁵³ With continued documentation and gained experience from irAEs, the field is increasingly able to address the underlying mechanisms and provide practice recommendations for side effects.^{54,55} For example, understanding the role of IL-6 in CRS has enabled the use of IL-6 blocking antibodies to mitigate these effects.⁵² Preclinical studies have demonstrated that on-target-off-tumour toxicities can be separated from the antitumour functions of adoptively transferred cells.⁵⁶ Guidelines also exist for the management of severe toxicities associated with ICI and typically revolve around immunosuppression using modalities including corticosteroids, mycophenolate mofetil, infliximab, and immunoglobulin.⁵⁷ Thus, while toxicities remain a concern, progress continues to be made in addressing them.

Clinical utility of immunotherapeutics is hindered by their inconsistent nature. While many patients have undoubtedly benefited from immunotherapy, the same treatments show little efficacy in other individuals.⁵⁸ With ICI therapy, the tumour microenvironment⁵⁹ and number of mutations⁶⁰ have been demonstrated as contributors to response variability. Variations in the quality of patient-derived cells,⁶¹ the extent of clinical disease,⁶² and tumour adaptation⁶³ have all contributed to the disparate long-term outcomes in CAR T-cell treatment. Ongoing work in identifying biomarkers that are predictive of success in ICI and ACT are useful not only in identifying probable responders, but also in understanding why immunotherapy fails in others.⁶⁴⁻

⁶⁶ Tumours can be classified as “hot” (readily responsive to ICI) or “cold” (resistant to ICI).

Extensive research is aimed towards rendering “cold” tumours “hot.”⁶⁷ It is likely that combinations of distinct immunotherapies may be able to synergize in such instances. For example, using an OV to promote tumour infiltration could prime cold tumours for ICI.⁶⁸ Clinical combination of T-VEC and pembrolizumab resulted in a marked increase in objective response when compared to historical studies of ICI alone,⁶⁹ resulting in tremendous interest from the pharmaceutical industry.⁷⁰

One of the most significant barriers to the widespread use of immunotherapies is their cost. Studies taking the benefit of ICI as fact reach variable conclusions about the cost effectiveness of these drugs.⁷¹⁻⁷³ The need to produce patient-specific products drives up the economic burden of cellular therapies, with clinical CAR-T products costing as high as \$475,000.⁷⁴ Technical innovations, including strategies to enable the use of off-the-shelf allogenic CAR-T cells,⁷⁵ and automated production,⁷⁶ are underway to reduce the upfront costs. Practical solutions are suggested by studies showing indistinguishable outcomes with a five-fold lower dose of ICI,^{77,78} as well as proposals of innovative approaches to patents and reimbursement within the pharmaceutical industry.⁷¹ Whether these developments will be sufficient to make immunotherapy more widely available remains to be seen, but they stimulate optimism that immunotherapy price points may decrease in the future.

Immunotherapies have been marked by high costs and their distinct modes of action have resulted in new toxicities and challenges in achieving consistent, predictable responses.^{10,11} However, as “living drugs”, these agents also have advantages compared to traditional cancer therapeutics⁷⁹ and can adapt alongside a changing tumour.⁸⁰ The possibility of further tweaking these biological therapeutics provides a plethora of interventions by which immunotherapeutic approaches could overcome current limitations.^{11,81}

CONCLUSION

The past decade was unparalleled in its delivery of clinically actionable immunotherapy products.⁷⁻⁹ A search of PubMed using the key term “cancer immunotherapy” reveals 9,189 articles published in 2019, the highest of any year. 1,977 clinical trials targeting PD-1/PD-L1 and 570 CAR T-cell trials were registered on ClinicalTrials.gov in 2019.¹⁰ While significant hurdles remain, these therapies have been lifechanging and lifesaving for many patients.⁸² For some, this may be enough to say the “game has changed”. However, many other patients have yet to see significant benefit from immunotherapy for a variety of reasons.^{11,58} Thus, from a clinician’s standpoint, immunotherapy likely has a long way to go, but with the strides underway in improving and expanding its use, it is evident that this modality appears up to the challenge. Based on the unprecedented advances we have described herein we argue that, going into the 2020s, the “game” has indeed changed. While far from complete, research into immunotherapy has yielded an entirely new set of therapeutics that are mechanistically distinct from prior strategies and, by in large, has only taken off over the last decade. We emphasize that continued innovative collaboration between clinicians and basic scientists will be crucial in realizing the full potential that these paradigms have to offer.

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