Balancing the Effectiveness and Costs of Immune Checkpoint Inhibitors in Advanced Cancer

Michael McKenna

School of Medicine, Trinity College, University of Dublin, Ireland

REVIEW

Abstract

Conventional cancer therapeutics, while having transformed the survival of patients diagnosed with early stage cancer, have failed to produce similar results in patients diagnosed with more advanced cancer. It is for this reason that the arrival of immunotherapy has generated such a visceral interest in the field of oncology. Labelled 'Breakthrough of the Year' by Science in 2013, the field of immunotherapy has continued to grow exponentially, and promising preclinical results have translated into efficacious results in clinical trials, particularly in patients with end-stage disease. This has culminated in an ever-growing list of approvals for agents which have been designed to harness the power of the immune system. Immune checkpoint inhibitors in particular are regarded as potent new tools in the cancer therapeutics arsenal and have produced remarkable results in clinical trials in various cancer types. However, in the context of their increasing use in combination therapy and their remarkably high cost:benefit ratio, it must be asked whether these immune checkpoint inhibitors are a realistic solution to an ever increasing cancer burden. Is their price just a little too steep to pay?

Advanced cancer survival

Improvements in treatment modalities have transformed the survival rates of patients diagnosed with cancer. Cancer survival has more than doubled over the past 40 years (Cancer Research UK 2017a), with cancer mortality predicted to continue to decrease for the majority of cancer types over the next two decades (Smittenaar et al 2016). Unfortunately, these prominent improvements in survival have not translated across to advanced cancers, with stage IV metastatic disease continuing to show poor survival at 1 and 5 years post-diagnosis. Pancreatic cancer, which has the worst prognosis of all cancer types, has shown no improvement in survival in the past 40 years, with only 3% of patients surviving to 5 years (Cancer Research UK 2017b). 5-year survival statistics for stage IV lung cancer have been notoriously difficult to assess because such a small proportion of patients survive beyond 2 years (Cancer Research UK 2017c), while current 5-year survival statistics for Stage IV ovarian and bowel cancer are 4% and 7-8% respectively (Cancer Research UK 2017d-e). The discrepancy in outcomes on the basis of cancer stage is especially prominent when one looks at breast cancer in females, where 99% of Stage I patients will be alive at 5 years compared to 15% of Stage IV patients, and melanoma in males, where 100% of Stage I patients are alive at 5 years compared to 8% of Stage IV patients (Cancer Research UK 2017f-g).

Immunotherapy

Immunotherapy has emerged as potential lifeline for terminal cancer patients and has generated significant interest in both the academic community and the media. In contrast to previous treatment modalities which attacked tumours directly, immunotherapy indirectly targets tumours by potentiating the immune response the body generates against the cancer (Couzin-Frankel 2013). With a history dating back to Virchow's observation of immune infiltrates in tumours and Coley's use of bacteria solutions to generate inflammatory responses against cancer, immunotherapy is currently experiencing a renaissance and multiple types are in development. Promising results have been seen to date with dendritic cell therapy (Schumacher et al 2015), oncolytic virus therapy (Banchereau et al 2005), neo-antigen vaccination (Parato et al 2005) and adoptive cell transfer (Rosenburg et al 2008). However, immune checkpoint inhibitors have emerged as the leading candidates in clinical immunotherapy.

Immune checkpoint inhibitors

The immune system is capable of recognising and

destroying cancer cells, but its activity is moderated by a series of ligand-inhibitory receptor interactions known as immune checkpoints (Pardoll 2012). The purpose of these checkpoints is to maintain self-tolerance and limit collateral damage to normal tissues generated by the immune response. However they can be hijacked by tumours as a means of escaping destruction and ensuring their own survival (Topalian et al 2015). The two major immune checkpoints – cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD1) have slightly differing functions (Figure 1). CTLA4 signalling restricts T-cell activity while the immune response is initiated whereas PD1 acts later in the immune response, minimising collateral damage to adjacent tissues during chronic inflammation (Siefker-Radtke et al 2018). Therefore, blockade of these immune checkpoints could intensify the T-cell response and result in tumour eradication.

Efficacy of immune checkpoint inhibitors as monotherapies

The benefits from immune checkpoint inhibitors have been unprecedented in the history of terminal cancer treatment. Their promise was first elucidated with Ipilimumab, a CTLA-4 inhibitor, in metastatic melanoma, a cancer with a notoriously poor prognosis. Ipilimumab treatment resulted in a median overall survival of 10 months compared to a glycoprotein 100 peptide vaccine alternative, which produced a median survival of 6.4 months (Hodi et al 2010). Nivolumab, a PD-1 inhibitor, produced similar results in melanoma, with confirmed objective responses seen in 31.7% compared to 10.6% of the investigators choice-of-chemotherapy (Weber et al 2015). Nivolumab also found utility in NSCLC, with an overall survival rate of 12.2 months compared to 9.4 months in the docetaxel standard-of-care arm (Borghaei et al 2015).

Pembrolizumab, a PD-1 inhibitor similar to Nivolumab, was explored in a wide variety of trials and produced encouraging results in numerous cancer types including NSCLC (Reck et al 2016), melanoma (Robert et al 2015) and urothelial carcinoma (Balar et al 2017a). Pembrolizumab is best known as the first drug in history to receive FDA approval on the basis of a tumour characteristic, receiving approval for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) paediatric and adult solid tumours irrespective of site. Recent focus has shifted to PD-L1 inhibitors, and various agents have produced results comparable to the PD-1 inhibitors. Atezolizumab was the first of these agents to be explored. Promising response rates were seen in a phase II trial of metastatic urothelial carcinoma (Balar et al 2017b) but it ultimately failed to produce prolonged survival in a subsequent phase III trial (Powles et al 2018). However, Atezolizumab found its niche in the Phase III OAK trial, producing more favourable overall survival in NSCLC patients vs docetaxel (Rittmeyer et al 2017). However, to date, no trial has been performed to compare overall survival in NSCLC patients treated with Atezolizumab against those treated with Nivolumab. Results from next-generation PD-L1 inhibitors have been encouraging. The JAVELIN Solid Tumour trial demonstrated potent anti-tumour activity of Avelumab in platinum-refractory metastatic urothelial carcinoma (Patel et al 2018) while the ATLANTIC trial demonstrated a role for Durvalumab

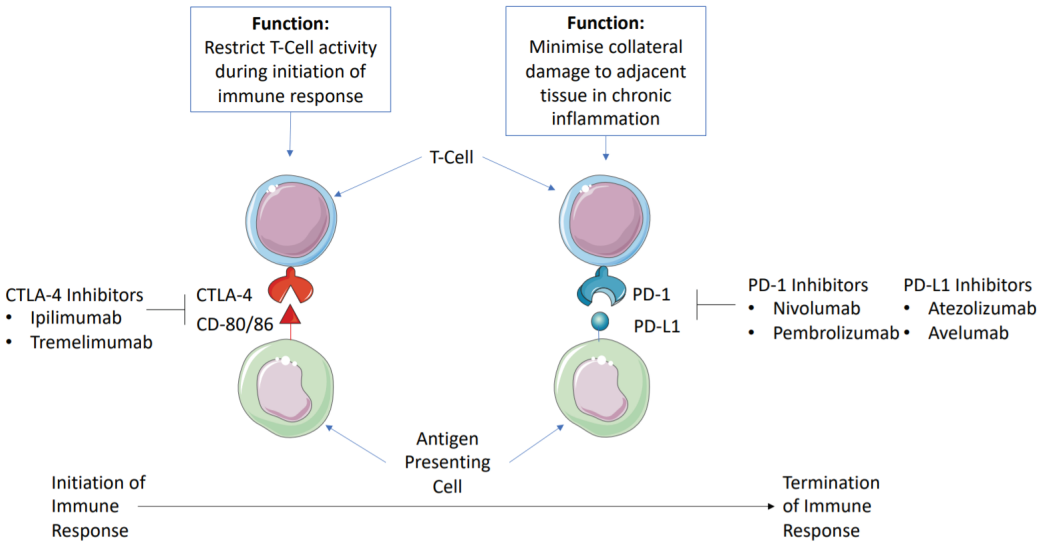

Figure 1: The major immune checkpoints, their functions and how they are targeted

as a third-line or later agent in EGFR-negative NSCLC (Garassino et al 2018).

Resistance to immune checkpoint inhibitors

The problem of resistance to immune checkpoint therapy has begun to emerge as a major limiting factor impeding their effectiveness in monotherapy. While a small proportion of patients maintain a continuous response, two significant subgroups have emerged – those failing to respond from therapy initiation (innate resistance) and those who respond initially but develop resistance over the course of therapy (acquired resistance) (Pitt et al 2016). The causes of resistance are variable and can be broadly divided into 3 main groups – impaired tumour reactive T-cell formation, impaired effector T-cell activation and impaired memory T-cells formation (Jenkins et al 2018) (Figure 2). As such, recent focus has turned towards using immunotherapies in combination therapies for terminal patients.

Combinations of different immune checkpoint inhibitors

Immune checkpoint inhibitors present an exciting avenue for combination therapy, combined either with each other or with alternative forms of therapy. The combinations of different immunotherapies continue to produce promising results, particularly combined Nivolumab-Ipilimumab which was studied first in melanoma. Initially compared against Ipilimumab monotherapy, the combination achieved a higher objective response rate (61% vs 11%) and complete response rate (22% vs 0%), as well as a significant increase in 2-year overall survival (63.8% vs 53.6%) (Postow et al 2015, Hodi et al 2016). Nivolumab-Ipilimumab was also tested against Nivolumab monotherapy, increasing median progression-free survival at initial analysis (11.5 months vs 6.9 months), accompanied by a slight increase in overall survival (58% vs 52%) at the 3-year follow-up (Larkin et al 2015, Wolchok et al 2017).

The scope of the Nivolumab-Ipilimumab combination continues to spread, showing encouraging results in trials of both non-small cell and small cell lung cancer (Hellman et al 2017, Antonia et al 2016a), metastatic renal cell carcinoma (Hammers et al 2017) and metastatic sarcoma (D'Angelo et al 2018). Combinations of newer generation anti-PD-1 and anti-CTLA-4 antibodies are also beginning to emerge such as durvalumab with tremelimumab, which displayed potent anti-tumour activity in a Phase Ib NSCLC study (Antonia et al 2016b). The potential for the combination of anti-PD-1 therapies with antibodies targeting newly discovered immune checkpoint receptors such as Tim-3 and LAG-3 has been promising to date (Sakuishi et al 2010, Woo et al 2012).

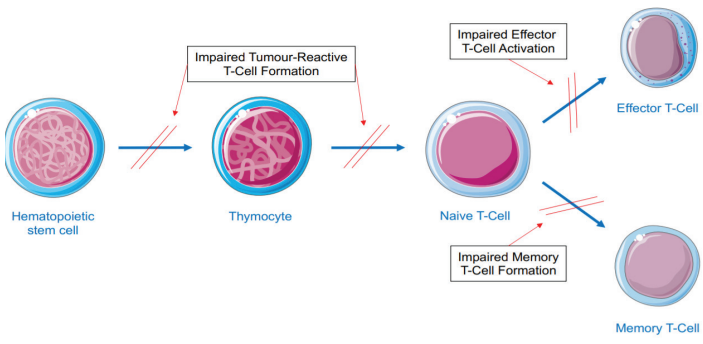

Figure 2: Mechanisms of resistance to immune checkpoint inhibitors

Combinations of immune checkpoint inhibitors with other cancer therapies

Checkpoint inhibitors have also shown promising results in combination with other forms of cancer therapy. Local control and clinical benefit was seen in one study where ipilimumab was combined with stereotactic external-beam radiation therapy (Sundahl et al 2018) while a decreased incidence of brain metastases and favourable survival outcomes were seen in a second study combining either ipilimumab, nivolumab or pembrolizumab with stereotactic radiosurgery (Chen et al 2018). Nivolumab has shown benefit when combined with various chemotherapeutic regimens in NSCLC including gemcitabine/cisplatin, pemetrexed/cisplatin and paclitaxel/carboplatin (Rizvi et al 2016, Kanda et al 2016). While still a relatively new field, checkpoint inhibitors have shown clinical efficacy in early clinical trials with various other agents including anti-angiogenic therapies (Amin et al 2014, Atkins et al 2018), MEK inhibitors (Ribas et al 2015) and BRAF inhibitors (Cooper et al 2014).

Cost-effectiveness of immune checkpoint inhibitors: These promising results have come with a steep price, with immune checkpoint inhibitors rapidly establishing themselves as some of the most expensive therapies available to modern medicine. One study from Switzerland compared the cost-effectiveness

of Nivolumab against Docetaxel for advanced non-squamous NSCLC and found that it was not a cost-effective improvement for patient care, exceeding the willingness-to-pay threshold by almost 78,000 CHF (Matter-Walstra et al 2016). A similar study conducted in Canada found that Nivolumab cost over $150,000 extra per quality-adjusted life year (QALY) compared to Docetaxel in NSCLC (Goeree et al 2016). An Australian Monte Carlo analysis found that Nivolumab was only considered cost-effective if compared against Ipilimumab for BRAF Wild-Type advanced melanoma and Nivolumab was deemed not to be cost-effective against placebo in a US study of its use in second-line metastatic renal cell carcinoma treatment (Bohensky et al 2016, Sarfaty et al 2018). While the relatively recent emergence of checkpoint inhibitor combination therapy leaves a current shortage of cost-effectiveness analysis available, one US study of the Nivolumab-Ipilimumab combination in first line metastatic melanoma found it was not cost-effective compared to Nivolumab monotherapy (Oh et al 2017).

Trends in cancer incidence and cost

The high costs of these checkpoint inhibitors cannot be ignored, especially in the context of current cancer incidence trends. Cancer incidence in Ireland is projected to grow by 84% in females and 107% in males by 2040 (National Cancer Registry Ireland 2014), mirroring trends in the United Kingdom, where incidence is projected to increase by 35% in females and 55% in males by 2030 (Mistry et al 2011). Almost a quarter of the UK population aged 65 years or older in 2040 will be cancer survivors (Maddams et al 2012). Similar statistics are seen elsewhere in the developed world – increases in age-standardised rates of cancer are seen in Australia in both males and females, while the total projected incidence of cancer in the United States is projected to rise by 45% by 2030 (Australian Institute of Health and Welfare 2012, Smith et al 2009). These trends are not restricted to the developed world; the burden of cancer continues to grow in developing countries as a result of aging populations and they will carry a significant proportion of the increases in cancer incidence, morbidity and mortality by 2030 (Thun et al 2010, Kanavos et al 2006).

This rising cancer burden is accompanied by an ever-increasing cost of cancer care. Between 2010 and 2020, the cost of healthcare will have risen by 39% in the United States, reaching an annual expenditure of $173 billion (Mariotto et al 2011). Between 1991 and 2002, the per patient cost of caring for lung, colorectal and breast cancer patients increased by over $7000, over $5000 and over $4000 respectively, and colorectal cancer expenditure alone will have increased by 89% between 2010 and 2020 (Warren et al 2008, Yabroff et al 2008). The average price of cancer drugs per patient per year rose from $5000-10,000 before 2000 to over $100,000 in 2012 and cancer drug expenditure will have risen by 50% over the 10-year period from 2010-2020 (Light et al 2013, Prasad et al 2017). Recently developed immune checkpoint inhibitors are likely to only add to this financial burden further. In NSCLC alone, Atezolizumab is estimated to cost a median of $68,960 per patient, while Pembrolizumab and Nivolumab cost $83,691 and $87,575 respectively for a total course of treatment for each patient (Ogale 2018). The Nivolumab-Ipilimumab combination costs substantially higher at $295,566 per patient and the overall cost of implementing these drugs to tackle metastatic cancer was predicted to cost as high as $174 billion per annum in America alone (Andrews 2015).

Conclusion

The spiralling cost of cancer care has extended from the healthcare provider to the patient themselves. Conservative estimates show that cancer can cost an average patient €832 per month, with 60% of patients experiencing an annual income reduction of over €16,500 (Irish Cancer Society 2015). The cost of new medications is increasingly recognised as a driving force behind the increasing financial toxicity of a cancer diagnosis and it is difficult to imagine that these new high-cost checkpoint inhibitors will do anything other than increase the burden further, on both the state and the patient. With higher cancer expenditure causing patients to delay or forgo treatment, reduce adherence to cancer treatment and increase their risk of bankruptcy, the question must be asked as to whether these expensive immune checkpoint inhibitors are the right step forward in the fight against terminal cancer.

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