NOVA

University of Newcastle Research Online

nova.newcastle.edu.au

Gedye, C.; van der Westhuizen, A.; John, T. "Checkpoint immunotherapy for cancer: superior survival, unaccustomed toxicities" Published in Internal Medicine Journal Vol. 45, Issue 7, p. 696-701

Available from: <http://dx.doi.org/10.1111/imj.12653>

This is the peer reviewed version of the following article: Gedye, C.; van der Westhuizen, A.; John, T. "Checkpoint immunotherapy for cancer: superior survival, unaccustomed toxicities" Internal Medicine Journal Vol. 45, Issue 7, p. 696-701 which has been published in final form at <http://dx.doi.org/10.1111/imj.12653>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

Accessed from: <http://hdl.handle.net/1959.13/1333246>

Checkpoint immunotherapy for cancer - superior survival, unaccustomed toxicities

Authors

Dr Craig Gedye*, University of Newcastle, School of Biomedical Sciences and Pharmacy, Hunter Medical Research Institute, New Lambton Heights, NSW 2305; and, □ Calvary Mater Newcastle, Dept. of Medical Oncology, Waratah, NSW 2298. craig.gedye@newcastle.edu.au 0432 286 616

Dr Andre van der Westhuizen, Calvary Mater Newcastle, Dept. of Medical Oncology, Waratah, NSW 2298. andre.vanderwesthuizen@calvarymater.org.au

Assoc. Prof. Tom John, Olivia Newton John Cancer and Wellness Centre, Dept of Medical Oncology, Austin Hospital, □ Heidelberg, VIC 3084. tom.john@ludwig.org.au

Abstract

Novel cancer immunotherapy antibodies are moving from clinical trials into routine practice, delivering sustained benefits and prolonged survival to patients with melanoma, lung, kidney and other cancers. These immunostimulatory antibodies non-specifically activate the patient's own immune system by inhibiting immune system checkpoint proteins. This mechanism of action is entirely different to traditional cancer treatments such as chemotherapy. Whilst there are virtually no immediate toxicities, serious life-threatening autoimmune side effects such as colitis, dermatitis, hypophysitis, pneumonitis and hepatitis can occur, sometimes starting long after the treatment has been given. Recognition, referral and prompt treatment with immunosuppressive drugs like corticosteroids can control these immune-related side effects without compromising efficacy. This exciting new class of drugs is defining a new paradigm in cancer therapy.

Keywords: immunotherapy, checkpoint proteins, cancer, melanoma, lung cancer, immune related side effects

Conflicts of Interest: Nothing to declare

Word Count: 1486

Acknowledgements and Funding: CG is supported by an NHMRC Early Career Fellowship, TJ is supported by an NHMRC Early Career Fellowship, the Cancer Council and Victorian Cancer Agency.

Checkpoint immunotherapy for cancer - superior survival, unaccustomed toxicities**Abstract**

Novel cancer immunotherapy antibodies are moving from clinical trials into routine practice, delivering sustained benefits and prolonged survival to patients with melanoma, lung, kidney and other cancers. These immunostimulatory antibodies non-specifically activate the patient's own immune system by inhibiting immune system checkpoint proteins. This mechanism of action is entirely different to traditional cancer treatments such as chemotherapy. Whilst there are virtually no immediate toxicities, serious life-threatening autoimmune side effects such as colitis, dermatitis, hypophysitis, pneumonitis and hepatitis can occur, sometimes starting long after the treatment has been given. Recognition, referral and prompt treatment with immunosuppressive drugs like corticosteroids can control these immune-related side effects without compromising efficacy. This exciting new class of drugs is defining a new paradigm in cancer therapy.

Introduction

Novel personalised cancer treatments that target mutated molecular pathways using small molecule inhibitors and monoclonal antibodies that activate the immune system are rapidly augmenting traditional treatments like chemotherapy, radiation and surgery.

The immune system is intimately involved in cancer development and control. Cancers are more common in immunosuppressed patients (e.g. HIV, transplantation) and immune therapies are useful in specific settings (1). Examples include antibodies that target the immune system to cancer cells (e.g. rituximab and trastuzumab), intravesical Bacillus Calmette–Guérin in bladder cancer and vaccines against metastatic prostate cancer (ProstVac, Provenge®). High-dose immune cytokines like interleukin-2 may cure a minority of patients (<10%) with kidney cancer and melanoma but are very toxic (2).

Antibodies that activate the immune system by inhibiting “immune checkpoint” proteins are delivering benefits in several cancers, with the risk of autoimmune side effects. Unlike chemotherapy, these toxicities are delayed and thus require ongoing vigilance for recognition, prompt treatment and referral.

Control of the Immune System: Immune Checkpoints

The immune system is divided into innate and adaptive systems. Peptides from pathogens and cancer cells are “presented” to adaptive immune cells (e.g. antibody-secreting plasma cells and cytotoxic CD8+ T-lymphocytes) by antigen-presenting cells (APC; e.g. dendritic

cells), which continuously sculpts the immune system's interpretation of "self" vs. "non-self".

Costimulatory molecules act as "checkpoints" to control the response of immune cells (Figure 1), and can be inhibitory (e.g. CTLA4, PD-L1) or pro-inflammatory (e.g. CD28, CD40). Insufficient checkpoint signalling can lead to autoimmune diseases like thyroiditis and inflammatory bowel disease. Cancers exploit immune checkpoints to evade immune destruction. These insights led to the development of antibodies inhibiting CTLA4 and PD1 immune checkpoints as cancer therapies.

Anti-Immune Checkpoint Antibodies: Anti-CTLA4

Ipilimumab (Yervoy®) was the first anti-CTLA-4 antibody to be developed, and showed encouraging 30% two-year survival (vs. ~10% historical) (3). In a phase III trial in metastatic melanoma ipilimumab (3mg/kg, three-weekly, four doses) was tested against a vaccine or a combination of vaccine and ipilimumab (4). Tumour shrinkage was modest (ipilimumab 10.9%, vaccine 1.5%, combination 5.9%) but patients receiving ipilimumab had unequivocally improved median overall survival (OS 10 months; 20% alive at two years, vs. 6.4 months and 14%, vaccine alone). Ipilimumab 10mg/kg three-weekly has also been shown to be superior to chemotherapy (5). Ipilimumab was the first therapy to show a statistically significant and clinically meaningful survival benefit in metastatic melanoma.

In some patients tumours initially appear to grow then later regress, possibly due to immune cell infiltration. To measure immune related progression free survival (irPFS) and define progression, tumours must grow on two successive scans (6).

In non-small cell lung cancer (NSCLC), ipilimumab has no effect alone, but delivers a modest improvement in irPFS (5.7 vs. 4.6 months placebo) when given concurrently with chemotherapy (7). Improved irPFS was greatest in squamous cell carcinoma patients, launching a randomized double-blinded placebo-controlled phase III study in this subgroup.

Advanced mesothelioma has a dismal prognosis, with some responses and modest survival benefits from combination chemotherapy. In 29 patients in a small phase II trial, tremelimumab, another anti-CTLA-4 antibody with similar side effects and immune responses as ipilimumab, demonstrated encouraging results; two patients achieved a durable partial response and nine experience disease stabilization (8). Again, these preliminary results are also being tested in a larger placebo controlled study.

Tremelimumab was tested in melanoma but some patients on the control arm received compassionate ipilimumab off-protocol, confounding interpretation of the trial (9).

Rarely, patients with small cell lung cancer (SCLC) develop autoimmune paraneoplastic syndromes such as Lambert Eaton Myasthenic syndrome, which is associated with improved survival. This suggests that SCLC may respond to immunotherapy and several studies testing CTLA4 antibodies in SCLC patients show early evidence of benefit (10).

Anti-Immune Checkpoint Antibodies: Anti-PD1

PD-1 and its ligand PD-L1 (Figure 1) have also been identified as targetable immune checkpoint molecules (11). Phase I trials showed that a single dose of nivolumab (BMS-936558), a fully humanized anti-PD-1 antibody, was safe and benefited heavily pre-treated patients (12). Fortnightly nivolumab yielded tumour shrinkage in 28% of melanoma patients, 18% of NSCLC patients and 27% of kidney cancer patients (13). Remarkably many of these responses were long-lasting (14). Severe (grade 3/4) immune related side effects (irSEs) including hypophysitis, hepatitis and colitis developed in 13% of patients. Three patients died on trial due to pneumonitis, though recognition may have been delayed in two patients with NSCLC. There appears to be similar efficacy between PD1 inhibition and PDL1 inhibition in NSCLC, however the incidence of pneumonitis appears higher in patients treated with PD-1 antibodies compared to PD-L1 antibodies.

Given the benefits of ipilimumab or nivolumab in melanoma, these were combined in a phase I/II trial with spectacular results (15). 40% of patients treated with the combination experienced tumour shrinkage, and 65% of patients experienced shrinkage or stable disease. Significant side effects occurred in 53% of patients but were similar in quality and severity to patients taking either drug alone.

Pembrolizumab (MK-3475) is another anti-PD-1 antibody with similar benefits. 38% of metastatic melanoma experienced partial response after fortnightly pembrolizumab (16). Common irSEs were fatigue, skin rash, pruritus, and diarrhoea, but were mostly low grade

and easily controlled. These benefits were long lasting, with 81% of patients whose cancers responded still alive and on treatment after one year.

Routine Clinical Management using Anti-Immune Checkpoint Antibodies

Nivolumab and pembrolizumab are still in clinical trials in many cancers, but recognising their dramatic benefits led to early compassionate access for melanoma patients before formal regulatory approval.

Ipilimumab is PBS reimbursed as a single agent in metastatic melanoma. Four infusions (3mg/kg) are given at three-weekly intervals. 10-15% of patients experience partial tumour shrinkage, and another 20-30% of patients will experience stable disease, resulting in benefit for 30-40% of patients. Benefits develop slowly, weeks or months after treatment, and the meaningful benefit of “stable disease” has altered treatment goals and generated new immunotherapy response assessment criteria (6). By contrast, the effect of PD-1/PD-L1 inhibition is relatively rapid with responses often seen within six weeks of treatment.

No biomarker predicts response to ipilimumab, but a rise in peripheral lymphocyte count (17), or low pre-treatment serum VEGF levels (18) are associated with improved survival. Tumour cell PD-L1 expression may predict for efficacy of anti-PD-1 antibodies (19) but responses have been reported in patients with PD-L1-negative tumours.

Immune Related Side Effects of Anti-Immune Checkpoint Antibodies

Immediate toxicity of anti-CTLA-4 and anti-PD1 antibodies is minimal; the important toxicities of these drugs are delayed irSEs (Figure 2A). Monitoring includes regular clinical assessments and liver and hormone blood tests. Unlike chemotherapy, where side effects occur within hours or days, irSEs often occur weeks, even months after treatment (Figure 2B). IrSEs also have a prolonged duration and can recur or worsen despite initial relief from corticosteroids.

Approximately 60% of ipilimumab treated patients experience an irSE, which are severe (requiring treatment or hospitalization) in approximately 15% (Figure 2). The most serious and potentially life-threatening irSE of ipilimumab is inflammatory colitis, which can present subtly with diarrhoea, bloating and abdominal discomfort, but then rapidly progress to haematochezia, bowel perforation, peritonitis and death. Initial management is with anti-diarrhoeals (Table 1) with a low threshold to escalate to oral and/or intravenous high-dose corticosteroids. Corticosteroids usually work rapidly but are weaned slowly over 4-6 weeks. Rarely patients require escalation to the anti-TNF- α antibody, infliximab (20). Medications that suppress bowel activity or secretions (e.g. codeine or octreotide) may mask symptoms and are contraindicated. Colonoscopy is recommended if there is any uncertainty about the diagnosis. Stool testing for pathogens and *C.difficile* toxin is performed to rule out infective causes.

If steroids are delayed in severe colitis, the patient risks severe morbidity or death. If colitis develops but subsides it can recur with reduced latency and higher severity after further ipilimumab. In clinical trials diarrhoea/colitis was first reported five weeks after commencing ipilimumab, but anecdotally we have observed colitis in patients before three weeks.

Rash is common, often maculopapular and pruritic (Figure 3A), responds to emollients and topical steroids, but systemic steroids can sometimes be required. Endocrinopathies (such as hypothyroidism and hypophysitis) are uncommon, but can occur long after treatment, presenting subtly with headache, fatigue, hypotension, decreased libido or visual or behavioural change, and often require ongoing hormone replacement (Figure 3B). Inflammatory hepatitis, pneumonitis and neuropathies are rare. Steroid therapy does not appear to inhibit the clinical effectiveness of ipilimumab. Detailed guidelines for management of ipilimumab irSEs are available online (<http://www.yervoy.com.au/hcp/>).

Conclusion

With the success of immune checkpoint inhibition in melanoma, trials are ongoing in many cancers including lung, breast, kidney, glioma, mesothelioma and bladder cancers. Checkpoint immunotherapeutic antibodies induce durable remissions in some patients, but have subtle, indolent and potentially life-threatening toxicities. Prompt identification and treatment can prevent consequent morbidity and mortality, and deliver the full potential of these novel cancer therapies. Immune checkpoint antibodies have already entered routine

melanoma treatment paradigms and they are likely to play an important part in the treatment of many other tumour types.

For Peer Review

Figure Legends

Figure 1. A. Lymphocytes and antigen-presenting cells (including tumour cells) recognize self vs. non-self. B. At a molecular level, this recognition occurs by interaction of the T-cell receptor (TCR) with peptides presented on histocompatibility molecules (MHC). The response of the lymphocyte to the tumour cell depends on the balance of positive and negative costimulatory molecules that act as immune checkpoints. C. If more negative co-stimulatory signals (e.g. CTLA4, PD1) are present, the lymphocyte becomes anergic and the tumour cell evades destruction. D. Blockade of these negative costimulatory signals by antibodies against CTLA-4, PD-1 or PD-L1 can alter the balance of costimulatory signals and lead to lymphocyte activation and tumour cell killing.

Figure 2. A. Immune related side effects (irSE) of anti-CTLA4 and anti-PD1 antibodies. Innocuous symptoms might be the first sign of serious life-threatening irSE. B. Four ipilimumab infusions are given at three weekly intervals, with CT reimaging to assess response one and two months after therapy is complete. irSEs (y-axis representing relative incidence) can occur during or even after ipilimumab treatment.

Figure 3. A. Ipilimumab can cause a maculopapular pruritic rash, which most often responds to emollients and topical corticosteroids. B. Hypophysitis is an uncommon complication of anti-CTLA4 immunotherapy, and in this patient presented with lethargy, headache, loss of libido and postural hypotension. High-dose corticosteroids rapidly relieved headache and averted an Addisonian crisis, but hypopituitarism persisted and required ongoing hormonal monitoring and supplementation.

Table

Stools per day	Mucus/blood in stool	Abdominal pain	Abdominal bloating	Ileus	Fever	Grade of colitis	Treatment	Minimum Follow-up and Referral
<3	-	-	-	-	-	1	Loperamide 2mg after each stool, max 8 per day	Daily review; Call Oncologist
3-6	+/-	+/-	+/-	-	-	2	Stop ipilimumab Prednisone po 1mg/kg/d	Review by Oncologist
>7	+/-	+/-	+/-	-	-	3	Methylprednisolone IV 2mg/kg/d	Oncology Inpatient
>7	+	+	+	+/-	+/-	4	Infliximab 5mg/kg IV Mycophenolate po	Oncology Inpatient

Table 1. Escalating management of inflammatory colitis associated with ipilimumab.

Colitis may present subtly and may respond to symptomatic management, but escalation to high-dose corticosteroids or complex immunosuppressants is mandated upon worsening symptoms. Prompt assessment, referral and re-assessment can safely manage these immune related side effects.

References

1. Cebon J, Gedye C, John T, Davis ID. Immunotherapy of advanced or metastatic melanoma. *Clin Adv Hematol Oncol*. 2007;5(12):994-1006.
2. Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. *The cancer journal from Scientific American*. 2000;6 Suppl 1:S11-4. Epub 2000/02/24.
3. O'Day SJ, Maio M, Chiarion-Sileni V, Gajewski TF, Pehamberger H, Bondarenko IN, et al. Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: a multicenter single-arm phase II study. *Ann Oncol*. 2010;21(8):1712-7. Epub 2010/02/12.
4. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-23. Epub 2010/06/08.
5. Robert C, Thomas L, Bondarenko I, O'Day S, M DJ, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364(26):2517-26. Epub 2011/06/07.
6. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. *Clinical Cancer Research*. 2009;15(23):7412-20.
7. Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non-Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study. *Journal of Clinical Oncology*. 2012;30(17):2046-54.

8. Calabr L, Morra A, Fonsatti E, Cutaia O, Amato G, Giannarelli D, et al. Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. *The Lancet Oncology*. 2013;14(11):1104-11.
9. Ribas A, Kefford R, Marshall MA, Punt CJA, Haanen JB, Marmol M, et al. Phase III Randomized Clinical Trial Comparing Tremelimumab With Standard-of-Care Chemotherapy in Patients With Advanced Melanoma. *Journal of Clinical Oncology*. 2013.
10. Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Annals of Oncology*. 2013;24(1):75-83.
11. Brahmer JR, Tykodi SS, Chow LQM, Hwu W-J, Topalian SL, Hwu P, et al. Safety and Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer. *New England Journal of Medicine*. 2012;366(26):2455-65.
12. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I Study of Single-Agent Anti-Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. *Journal of Clinical Oncology*. 2010;28(19):3167-75.
13. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. *New England Journal of Medicine*. 2012;366(26):2443-54.

14. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014;32(10):1020-30. Epub 2014/03/05.
15. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369(2):122-33. Epub 2013/06/04.
16. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med*. 2013;369(2):134-44. Epub 2013/06/04.
17. Ku GY, Yuan J, Page DB, Schroeder SEA, Panageas KS, Carvajal RD, et al. Single-institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting. *Cancer*. 2010;116(7):1767-75.
18. Yuan J, Zhou J, Dong Z, Tandon S, Kuk D, Panageas KS, et al. Pretreatment Serum VEGF Is Associated with Clinical Response and Overall Survival in Advanced Melanoma Patients Treated with Ipilimumab. *Cancer Immunology Research*. 2014;2(2):127-32.
19. Taube JM, Klein AP, Brahmer JR, Xu H, Pan X, Kim JH, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clin Cancer Res*. 2014. Epub 2014/04/10.
20. Minor DR, Chin K, Kashani-Sabet M. Infliximab in the treatment of anti-CTLA4 antibody (ipilimumab) induced immune-related colitis. *Cancer Biother Radiopharm*. 2009;24(3):321-5. Epub 2009/06/23.

For Peer Review

Figure 1. A. Lymphocytes and antigen-presenting cells (including tumour cells) recognize self vs. non-self. B. At a molecular level, this recognition occurs by interaction of the T-cell receptor (TCR) with peptides presented on histocompatibility molecules (MHC). The response of the lymphocyte to the tumour cell depends on the balance of positive and negative costimulatory molecules that act as immune checkpoints. C. If more negative co-stimulatory signals (e.g. CTLA4, PD1) are present, the lymphocyte becomes anergic and the tumour cell evades destruction. D. Blockade of these negative costimulatory signals by antibodies against CTLA-4, PD-1 or PD-L1 can alter the balance of costimulatory signals and lead to lymphocyte activation and tumour cell killing.

190x245mm (72 x 72 DPI)

Figure 2. A. Immune related side effects (irSE) of anti-CTLA4 and anti-PD1 antibodies. Innocuous symptoms might be the first sign of serious life-threatening irSE. B. Four ipilimumab infusions are given at three weekly intervals, with CT reimaging to assess response one and two months after therapy is complete. irSEs (y-axis representing relative incidence) can occur during or even after ipilimumab treatment.

190x73mm (72 x 72 DPI)

Figure 3. A. Ipilimumab can cause a maculopapular pruritic rash, which most often responds to emollients and topical corticosteroids. B. Hypophysitis is an uncommon complication of anti-CTLA4 immunotherapy, and in this patient presented with lethargy, headache, loss of libido and postural hypotension. High-dose corticosteroids rapidly relieved headache and averted an Addisonian crisis, but hypopituitarism persisted and required ongoing hormonal monitoring and supplementation.
190x98mm (72 x 72 DPI)