Taylor & Francis
Taylor & Francis Group

Expert Review of Anticancer Therapy

ISSN: 1473-7140 (Print) 1744-8328 (Online) Journal homepage: https://tandfonline.com/loi/iery20

Why do the majority of patients not respond at all, or only partially or transiently, to immunotherapy?

Angus G Dalgleish

To cite this article: Angus G Dalgleish (2019): Why do the majority of patients not respond at all, or only partially or transiently, to immunotherapy?, Expert Review of Anticancer Therapy, DOI: 10.1080/14737140.2019.1696676

To link to this article: https://doi.org/10.1080/14737140.2019.1696676

Accepted author version posted online: 25 Nov 2019.

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Review of Anticancer Therapy*

DOI: 10.1080/14737140.2019.1696676

Why do the majority of patients not respond at all, or only partially or transiently, to immunotherapy?

Angus G Dalgleish

Institute of Immunity and Infection, St George's University, London

Keywords: immunotherapy, oncology, cancer vaccines, checkpoint inhibitors, biomarkers

1. Introduction

The response to immunotherapy is often dramatic but relatively uncommon and until recently difficult to improve upon. The modern era of immunotherapy was arguably ushered in with the discovery of William Coley's (eponymously named) toxins. The development of cancer vaccines and cytokines, such as Interleukin-2 (IL-2), continued to induce marked clinical responses but only in a minority of patients (rarely above 20%) [1].

The advent of the checkpoint inhibitors (CPIs), such as Ipilimumab (ipi), Nivolumab (nivo), and Pembrolizumab (pembro) have led to responses of up to 40% in melanoma when used as single agents but more importantly increased survival, although at the expense of significant toxicity (a feature also shared with high dose IL-2 based regimens) especially when given in combination. The holy grail of optimising these treatments has been to find biomarkers that will predict responders to these agents [2].

Such is the depth and volume of research worldwide in this area, there is no shortage of leads. These include the direct assessment of PD-L1 expression on tumour cells as a predictor of response

to anti-PD1 antibodies. However, initial enthusiasm for this marker has waned as 10-20% of patients with negative expression will benefit from treatment. As a single biomarker it is not adequate for determining clinical response [3].

The importance of tumour infiltrating lymphocytes (TILs) has been recognised since Rosenberg and colleagues sought to improve the response rate to high dose IL-2. It is now well recognised that a dense TIL is associated with an increased response rate to the CPIs, especially if the density increases following treatment. However, it is not absolute enough to establish a level at which it is not worth treating [4].

Another marker used for patient selection is the mutational or neo-antigen burden produced by somatic mutations.

Patients with colorectal cancer with mismatch repair deficient (MMRD) whose mutational burden is 20X more than those without, are many times more likely to respond to CPIs, together with an increased overall survival [5].

Within the tumour, immune response genes (IRG's), such as gamma interferon, are likely to be over-expressed >2,5 fold in responders. A 28 gene panel associated with clinical benefits in melanoma patients treated with Pembrolizumab has been presented as a model to predict responders [6].

Combinations of these approaches are being studied to increase the specificity and sensitivity of predicting responders

2. Practical Issues

Even if these approaches can accurately predict responders then the main advantage will be financial, in that 60% of patients will not receive a very expensive treatment with significant toxicities. However, the main question should be, how can we identify patients who won't respond to treatment and what is required to tender them potential responders? Towards this end, there are many trials of combinations that either do not increase the response rate or, if they do, at greatly increased toxicity [7]. This is particularly true in melanoma when combining checkpoint inhibitors, however, combination with chemotherapy [8] and tyrosine kinase inhibitors [9] in lung cancers and renal cancer, respectively, have benefit in progression free survival and overall survival with reportedly acceptable toxicity.

3. Predicting the non-responders

My own group have struggled for years to try to understand why some patients have dramatic clinical responses, sometimes complete, whereas the majority do not. The main rationale is that responders have either been primed to the treatment signal, or that non-responders have an inhibitory environment affecting the stroma or immune response, such as high suppressive or regulatory cell activity. Initial studies focused on cytokine changes pre and post cancer vaccine treatment but were very disappointing as it was thought an increase in all cell mediated cytokines would be a logical predictor. Unfortunately, it was of no value whatsoever. However, it was not until we applied proteomic analysis and mass spectrometry to stored serum from a dendritic cell-based melanoma vaccine study that it became apparent that the pre-vaccinated status was more important than the post-vaccine induced changes. The data from this study showed that clinical non-responders had a higher signature of inflammatory markers [10]. Mathematical analysis enabled us to identify ApoE as a new entity in these patients. This finding has also been found in non-responders to Pembrolizumab in a 300 patient study by Jeff Webber and colleagues using a similar approach [11].

4. Implications

Chronic inflammatory status induces cell mediated immunosuppression and an increase in growth, angiogenic and wound healing factors. Thus, would pre-treatment with anti-inflammatory and immune modulators be a sufficient prime to increase the response to CPIs? Early studies suggest this is the case and studies have commenced using combinations to suppress inflammation and enhance the innate immune response before CPI exposure. It is important to differentiate between different classes of anti-inflammatories as steroids, which have anti-inflammatory properties may impair the clinical benefit of CPIs.

Another focus of research looking at what features determine responsiveness is the makeup of the microbiome. Several groups have reported marked differences in the biological flora and responsiveness to CPIs. Improving poor responders with faecal transplants have been reported [12]. However, it is worth noting the 'healthy' microbiomes are associated with 'healthy' diets and correlate with high fibre diets, in particular. As this is already known to correlate with a much lower colorectal cancer incidence, it has to be asked if patients with a lower inflammatory marker signature have the favourable micro biome signature as well [13].

The above helps explain the presence of the negative or inhibitory factors, but what about 'priming'?

Our own observations noted that patients who had been on a cancer vaccine or immune modulator had a higher and quicker response to CPIs. This was particularly marked in patients who had been on IMM-101, a heat killed Mycobacterium obuense preparation [14]. As well as stimulating the innate immune response, including NK cells and gamma delta T-cells (via mDl activation) it also inhibits Th-2 tumoural activity, often over expressed in cancer patients with different biomarkers. Several groups using other types of vaccines, whether antigen or non-antigen specific, are also reporting increased responses to CPIs when given before but, in some cases, not afterwards [15]. The sequence of

treatments may be more important than combination, as suggested by previous reports with vaccination prior to CPIs, and this may well apply to any treatment that activates and sheds antigens, such as radiotherapy (RT) ablations and certain chemotherapy regimens. Although RT is associated with abscopal responses in melanoma it may be more effective at priming in lung cancer [16].

5. Conclusion

From this brief review it is clear that whereas there is no single predictive biomarker to predict possible patient response to a CPI-based treatment, there is an exciting trend that a signature of several chronic inflammatory markers is associated with non-responsiveness. In addition, when priming with a vaccine or anti-inflammatory agent, it enhanced the response to a CPI especially when given before, in the case of antigen-specific vaccines, as there was no effect when given afterwards. One such study (NCT03711188) is already recruiting and about to increase the number of centres involved.

Thus, the importance is the sequence of these interventions, as opposed to combinations [17], as well as the doses where more is not always better, a situation that has not been fully explored with CPIs, given that overweight patients seem to do better with CPIs in a number of cancer types, compared to their non-overweight counterparts [18].

Funding

This article was not funded.

Declaration of interest

Angus Dalgleish serves on the advisory board of LDN Pharma, Jay Pharma, and Immodulon Therapeutics, and has received meeting expenses from Immodulon. The author has also received from ICVI, Celgene, LDN Pharma and Jay Pharma. The authors have no other relevant affiliations or

financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

A reviewer on this manuscript has received funding for clinical trials from Bristol-Myers Squibb and Merck, and received advisory board funding from Bristol-Myers Squibb. Another peer reviewer has received honoraria as a speaker at scientific events and advisory role by Bristol-Myers Squibb, Pfizer, MSD, Ipsen, Roche, Eli-Lilly, AstraZeneca and Novartis. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

*1. Barroso-Sousa, R, and Ott, PA, Transformation of Old Concepts for a New Era of Cancer Immunotherapy: Cytokine Therapy and Cancer Vaccines as Combination Partners of PD1/PD-L1 Inhibitors, Curr Oncol Rep, 2018 Nov 15;21(1):1

Review of concept of previous immunotherapy being enhanced by the new checkpoint inhibitors.

2. Rodríguez-Cerdeira, C, Gregorio, MC, López-Barcenas, A, et al., Advances in Immunotherapy for Melanoma: A Comprehensive Review, Mediators Inflamm. 2017; 2017: 3264217

3. Patel, SP, and Kurzrock, R, PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy, Mol Cancer Ther, 2015;14(4):847-56

4. Badalamenti, G, Fanale, D, Incorvaia, L, et al., Role of tumor-infiltrating lymphocytes in patients with solid tumors: Can a drop dig a stone? Cell Immunol, 2018; 1:103753

5. Oliveira, AF, Bretes, L, and Furtado, I, Review of PD-1/PD-L1 Inhibitors in Metastatic dMMR/MSI-H Colorectal Cancer, Front Oncol, 2019;9:396

6. Ayers, M, Lunceford, J, Nebozhyn, M, et al., IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade, J Clin Invest, 2017;127:2930-2940

7. Szostak, B, Machaj, F, Rosik, J, and Pawlik, A, CTLA4 antagonists in phase I and phase II clinical trials, current status and future perspectives for cancer therapy, Expert Opin Investig Drugs, 2019 Feb;28(2):149-159

8. Leonetti, A, Wever, B, Mazzaschi, G, et al., Molecular basis and rationale for combining inhibitors with chemotherapy in non-small cell lung cancer, Drug Resist Updat. 2019 Sep;46:100644

9. Rebuzzi, SE, Perrone, F, Bersanelli, M, et al., Prognostic and predictive molecular biomarkers in metastatic renal cell carcinoma patients treated with immune checkpoint inhibitors: a systematic review, Expert Rev Mol Diagn, 2019;24:1-17

*10. Leeman, H, Kaminska, E, Green, D, et al., Serum *Apolipoprotein E* and Other Inflammatory Markers Can Identify Non-Responding Patients to a Dendritic Cell Vaccine, Transl Oncol, 2019;3: 397–403

Proteomic evidence of an inflammatory marker 'signature' predicting non-responders to a DC based vaccine

* 11. Weber, JS, Sznol, M, Sullivan, RJ, et al., A Serum Protein Signature Associated with

Outcome after Anti-PD-1 Therapy in Metastatic Melanoma, Cancer Immhnol Res, 2018;6:79-86

Amazingly consistent finding re inflammatory markers and non-responders to anti-PD1 therapy

12. Elinav, E, Garrett, WS, Trinchieri, G, and Wargo, J, The cancer microbiome, Nat Rev Cancer, 2019;19:371-376

13. Chen, J, Pitmon, E, and Wang, K, Microbiome, inflammation and colorectal cancer, Semin Immunol, 2017;32:43-53

*14. Dalgleish, AG, Mudan, S, and Fusi, A, Enhanced effect of checkpoint inhibitors when given after or together with IMM-101: significant responses in four advanced melanoma patients with no additional major toxicity, J Transl Med, 2018;16: 227

Evidence of a Th-1 stimulative but also an anti-inflammatory agent priming for rapid and complete responses to CPIs

15. Verma, V, Shrimali, RK, Ahmad, S, et al., PD-1 blockade in subprimed CD8 cells induces dysfunctional PD-1^{+}CD38^{hi} cells and anti-PD-1 resistance, Nat Immunol, 2019;20:1231-1243

16. Theelen, WSME, Peulen, HMU, Lalezari,, F, et al., Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial, JAMA Oncol, 2019;5:1276-1282

*17. Dalgleish, AG, and Stern, PL, The failure of radical treatments to cure cancer: can less deliver more? There Adv Vaccines Immunother, 2018;6(5-6):69-76

A review of the history of oncology, showing that all modalities were initially used at an intensity and dose way above the eventual standard of care.

18. Cortellini, A, Bersanelli, M, Buti, S, et al., A multicenter study of body mass index in cancer patients treated with anti-PD-1/PD-L1 immune checkpoint inhibitors: when overweight becomes favourable, J Immunother Cancer, 2019;7:57