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Tailoring precision immunotherapy: coming to a clinic soon?

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ABSTRACT

Cell-based and antibody-based cancer immunotherapies have been widely tested across increasing numbers of cancers with an unprecedented number of successful practice-changing immunotherapy clinical trials, achieving significant survival outcomes and, characteristically, some very long-term survivors. Still, a sizeable proportion of patients, especially with solid tumours, do not benefit from immunotherapy. Here, we summarise key literature on immunotherapy biomarkers and resistance mechanisms and discuss potential strategies to overcome such resistance to improve patient outcomes. The ever-expanding understanding of the tumour-immune interaction and the tumour microenvironment allows a real opportunity to identify predictive biomarkers and tailor immune-based therapies, including designing rational combination drugs to enhance clinical outcomes, and to identify patients most likely to benefit from immunotherapy. Where there has never been a *precision chemotherapy* clinic in the last 70 years since its inception, even with no shortage of trying, the hope and evolution of a functional *precision immunotherapy* cancer clinic is a much more likely reality.

INTRODUCTION

There has been remarkable progress in the development of systemic cancer therapies since the birth of cytotoxic chemotherapy in the 1940s and the first hormonal therapies developed in the 1970s. In the 1990s, imatinib against chronic myeloid leukaemia heralded the era of molecular targeted therapy. In all these years, the only few validated predictors of chemotherapy efficacy include the use of Recurrence Score (Oncotype DX and MammaPrint) in early-stage hormone receptor-positive breast cancers[1–3] and the detection of the promoter methylation status of the O6-methylguanine-DNA methyltransferase gene, which predicts response to temozolomide in patients with glioblastoma multiforme.[4] Extensive research into drug efflux and multidrug resistance has yielded no therapeutic impact in overcoming chemotherapy drug resistance. Precision therapy against oncogene driver mutations has led to the development of an ever-increasing number of targeted drug agents, although the eventual number of patients who benefit remains limited. Cancer immunotherapy had its early beginnings with Coley's toxin at the turn of the 20th century,[5] Bacillus Calmette-Guerin (BCG) against superficial bladder cancer in the 1970s[6] and cytokine infusions such as interleukin (IL)-2 against renal cell carcinoma (RCC) in the 1980s.[7] However, these remained blunt tools and offer only a glimpse of the potential of cancer immunotherapy.

The hypothesis of immunoediting came about in recent decades, with three phases described: elimination, equilibrium and escape.[8 9] The host immune system discriminates 'self' from 'non-self' and eliminates non-self tumour cells through the recognition of tumour antigens; these antigens exist either as tumour-specific antigens (TSAs) which are unique to tumour cells or tumour-associated antigens (TAAs) that are also found, though less abundantly, on normal tissues (e.g. cancer/testis antigens).[10] Apart from specific viral oncoproteins, TSAs are mainly derived from 'neoantigens' that are generated from genomically unstable cancer cells and form potential targets for precision immunotherapy.[11] Tumour cells develop immune escape strategies, one of which is the subversion of the immune checkpoint pathways. The well-described immune checkpoint pathways include the inhibitory programmed death (PD)-1 and PD ligand-1 (PDL1) interaction, as well as cytotoxic T-lymphocyte associated protein-4 (CTLA4) and CD80/CD86 interaction with competitive inhibition of the costimulatory domain CD28.[12]Both of these inhibitory pathways form the scientific rationale for the development of monoclonal antibodies against PD1, PDL1 and CTLA4. Precision immunotherapy also comes in the form of adoptive cell therapy, which uses lymphocytes that are either primed or engineered to recognise and eliminate tumour cells from the body.[13] Other forms of mechanistically driven immunotherapy include oncolytic viruses, dendritic cell (DC) vaccine or small molecule inhibitors/monoclonal antibodies against specific immunomodulatory pathways.

With the rapid advances in immuno-oncology, it is timely to look towards a future where we can more consistently identify patients whose cancers best respond to such therapies. The determinants of response to immunotherapy have become increasingly explored and understood in the last few years. Yet it remains a highly complex landscape for clinicians to navigate and make informed treatment decisions. This review will focus on the precision biomarkers of immune checkpoint inhibitors (ICIs), T-cell therapies, and overcoming intrinsic and extrinsic resistance pathways, with an aim to identify the most ideal immunotherapy for each patient to achieve maximum benefit.

Biomarkers of ICIs

ICIs such as anti-CTLA4 antibody (ipilimumab) and anti-PD1/PDL1 antibodies (pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab and cemiplimab) have revolutionised the field of oncology and have been widely used in various cancers, including Merkel cell carcinoma (MCC), melanoma, hepatocellular carcinoma (HCC), urothelial cancers, triple-negative breast cancers (TNBCs), head and neck cancers, lung cancers, RCC and relapsed lymphomas. Patients are also surviving longer; for example, a combination of nivolumab and ipilimumab for the treatment of metastatic melanoma has yielded a 5-year overall survival exceeding 50%.[14] However, despite the promising efficacy in some tumour types, it remains a challenge to identify responders to ICIs reliably and consistently.

The initial biomarkers of ICIs were thought to be the presence, location and quantity of tumour-infiltrating lymphocytes (TILs), which were noted to have positive prognostic and predictive values across multiple tumour types, including breast, ovarian, endometrial, head and neck, gastrointestinal, non-small cell lung cancers (NSCLCs) and melanoma.[15–19] Recognising the importance of TIL as a biomarker, an international workgroup sought to standardise the assessment of TIL presence.[20 21]Further studies suggest that not all TILs are equal; the presence of interferon-gamma and other markers of T-cell activation was associated with better treatment response to anti-PD1 therapy.[22] A recent finding also suggests that bystander CD8+ T cells from TILs could recognise non-tumour epitopes and show distinct phenotypes compared with tumour-specific CD8+ TILs with CD39 expression.[23] Multiple studies have also looked into various T-cell subtypes, their ratio and correlation with ICI response but report varying results.[24 25] These observations were not consistent and may be partly due to factors in the tumour microenvironment (TME) and tumour heterogeneity. Through improved technology in high-throughput next-generation sequencing (NGS), T-cell receptor (TCR) repertoires of TILs have been explored in a few cancers, including metastatic melanoma with mixed results, with one study showing an expanded TCR repertoire leading to response to combination PD1/CTLA4 therapy but another showing poorer overall survival.[26]

Subsequently, correlation analyses of pooled genomic data from multiple clinical trials have revealed that mutational burden of cancers are closely associated with ICI treatment responses across multiple cancer types.[27–30] This clinical observation translated into tumour mutational burden being used as a surrogate marker for 'neoantigen' burden, and therefore 'immunogenicity' and response to ICIs. In the same vein, microsatellite instability high (MSI-H) or deficient mismatch repair (dMMR) tumours are associated with a higher mutational burden due to its genomic instability. Indeed, this was prospectively validated in a phase II study, leading to MSI-H status being approved as a tumour agnostic biomarker for pembrolizumab.[31] Also, neoantigen heterogeneity may influence immune surveillance and increasingly, clonal neoantigens have been shown to predict sensitivity to PD1 and CTLA4 blockade in melanoma and NSCLC.[32]

The most widely used companion predictive biomarker of anti-PD1 therapy is the immunohistochemistry (IHC) assay scoring of PDL1 on tumour and/or immune cells, that is, tumour proportion score (TPS) and combined positive score (CPS). Multiple studies in head and neck cancers, urothelial cancers, NSCLC, RCC and TNBC[33–37] have shown both PDL1 TPS and CPS to stratify response to ICIs. PDL1 expression is heterogenous and may not always be predictive of response to anti-PD1 or anti-PDL1 therapy. In fact, PD1 expression is regulated in a complex manner, being influenced by factors including cytokines, genomic aberrations, transcriptional control mechanisms, oncogenic signalling and mRNA/protein stability.[38] On top of this, structural variations (SVs) disrupting the 3′-untranslated region (UTR) of PDL1 gene also are implicated in multiple cancers, especially in T-cell leukaemia/lymphoma and diffuse large B-cell lymphoma (DLBCL).[39 40] Our own institution also reported a novel PDL1 3′-UTR SV in natural killer (NK) T-cell lymphoma that predicts response to anti-PD1 therapy,[41] which is also now being developed as a blood-based circulating-tumour DNA (ctDNA) predictive test. Furthermore, the varying assay platforms (eg, PDL1 clones 22C3, 28–8, SP263 and SP142) and cut-off of PDL1 expression have made comparison across trials challenging. We note the efforts to validate, standardise and combine these assays using multiplex immunofluorescence and digital imaging platforms.[42] The limitations of IHC-based methods should also be recognised, despite its cost effectiveness, and future studies may move toward genomic and transcriptomic studies looking at the various immune-permissive gene signatures for higher level of precision.[43 44] However, single-sample analysis and finding the optimal cut-off for different analyses would remain challenging.

Blood-based predictive biomarkers have been being increasingly reported but require further validation. These include serum markers such as raised lactate dehydrogenase[45] and peripheral blood markers, including increased absolute lymphocytes and circulating CD4+ and CD8+ T cells, lower baseline ratio of absolute

neutrophil count to absolute lymphocyte count, ratio of myeloid to lymphoid and higher frequency of Vδ2+ cells, and increased eosinophil count.[46–49] With improved NGS techniques, high mutational load may be picked up by ctDNA in peripheral blood to correlate with treatment responses.[50] Peripheral blood biomarkers may also potentially allow longitudinal observations and predictions during the patient's treatment journey. Liquid biopsy analyses of ctDNA, exosomes and autoantibodies are also being explored as potential predictive biomarkers for ICI treatment.[50–53] Recently, two separate groups have shown that tumour-secreting exosomal PDL1 influences immunosuppression and systemic immunity, which affects the responses of anti-PD1 antibody treatment.[51 52] In addition, by metabolomic analytic tools, increased serum kynurenine to tryptophan ratio is an acquired resistance mechanism to ICI treatment and correlates to worse clinical outcome, suggesting another new potential strategy to stratify patients for ICI treatment.[54]

The aetiology of cancer, including viral-driven cancers, may form a basis for predicting immunotherapy benefit, with their presence of surface viral proteins and influence on the TME. ICI has shown striking clinical efficacy in polyomavirus-associated MCC[55–57] and, to a less extent, human papillomavirus-associated cancers (eg, squamous cell carcinoma of cervix, head and neck, and anus) and Epstein-Barr virus (EBV)-associated cancers (eg, nasopharyngeal carcinoma (NPC), lymphoepithelioma-like carcinoma (LELC), post-transplant lymphoproliferative disorder (PTLD), Burkitt's lymphoma, NK T-cell lymphoma and other B-cell malignancies).[58–61] MCC has shown remarkable clinical response to anti-PD1 and anti-PDL1 therapy, ranging from 50% to 70% in some studies.[55–57] A Korean group characterised the genomic characteristics of 61 patients with gastric cancer to seek biomarkers and reported an overall response rate (ORR) of 50% in PDL1-positive gastric cancer, 85.7% in MSI-H gastric cancer and 100% in EBV-associated gastric cancer to anti-PD1 therapy,[60] although with a small sample size. However, the ORR in advanced NPC is comparably low, with 20.5% response to nivolumab and 25.9% response to pembrolizumab in the second-line setting.[58 59]

The gut microbiota and its correlation with response to ICI has been reported in pre-clinical studies.[62–66] The studies also showed that by oral administration of specific bacteria into preclinical mouse models, the efficacy of ICIs could be improved. Through a diet/supplement survey on a completed ICI clinical trial with stool sample collection,[62 67] high-fibre diet, defined as *full of vegetables, fruits and whole grains*, is highly correlative with several specific types of microbiota and better response to anti-PD1 antibody treatment—heralding the possibility of designing specific diets to improve ICI benefit—a first for any kind of cancer treatment.

Biomarkers of adoptive T-cell therapy

Harnessing tumour-specific T cells, either with TILs or genetically modified (GM) T cells for antitumour effect, has been pursued actively in clinical research, again a demonstration of precision immuno-oncology. Chimeric antigen receptor (CAR) T-cell therapy is manufactured through genetic modification to express antigen-specific CARs and costimulatory domains on a T cell, followed by ex vivo cell expansion and reinfusion back to the patient.[68] They can expand exponentially in vivo, especially when preceded by cytoreductive preconditioning, to eliminate cancer cells in a targeted, human leucocyte antigen (HLA)-unrestricted manner. To date, CD19-directed CAR T-cell therapy has established itself in the treatment of relapsed haematological malignancies, including DLBCL,[69] B-acute lymphoblastic leukaemia (B-ALL),[70] chronic lymphoblastic leukaemia (CLL)[71] as well as multiple myeloma,[72] with complete response rates ranging between 30% and 90%.

Despite CAR-T therapy's efficacy in haematological malignancies, this dramatic success has yet to be reproduced in solid cancers. Adoptive transfer of TILs, TCR-redirected and GM-TCR T cells have a longer track record in solid tumours but with mixed outcomes. These forms of cell therapies are capable of recognising somatically mutated neoantigens presented by HLA molecules as opposed to CAR T-cells which bind surface TAAs. Autologous TIL and GM-TCR therapy rely on reactivity of infused T cells, an intact antigen-presenting machinery (APM) in cancer cells and a permissive host immune state. Through small-scale clinical studies since the 1980s, adoptive transfer of ex vivo expanded TILs has consistently demonstrated their potential in tumour control, especially in metastatic melanoma.[73] However, for GM-TCR therapies, specificity for a variety of TAAs such as NY-ESO-1 and MAGE-A3[74–76] has been engineered into T cells for more precise tumour targeting.

Being a 'living therapy', the efficacy of adoptive cellular therapy depends on its interaction with the host milieu, and hence biomarkers may either be host related or cell therapy related. In a CAR-T study in CLL, raised levels of specific plasma markers (Interleukin 12 (IL12), DC-LAMP, TRAIL and Fas ligand) before treatment were associated with longer overall survival.[77] Conversely, higher IL-6 and soluble PDL1/2 were found to correlate with worse survival outcomes. Responding patients also had low peripheral monocytic myeloid-derived suppressor cells (MDSCs), which are immunosuppressive.[77] These host immune characteristics, detected by serum biochemical assays and flow cytometry analyses, could be employed as biomarkers to improve outcomes in future cell therapy studies. One phase II study suggests that the serum level of IL-9 may predict response to TIL therapy in advanced melanoma.[78] This study was not able to identify other significant clinical host characteristics that may separate the responders from non-responders, except that patients who had previous anti-CTLA4 therapy appeared to have a shorter duration of response to TIL.[78]

In terms of cell product-related biomarkers, one group recently reported the phenotypical, functional and genomic characteristics of CD19 CAR-T in 41 patients

with relapsed CLL,[79 80] and identified memory T cells (CD27+CD45RO−CD8+) and memory-related IL-6/STAT3 gene signature, which correlated with high clinical response. Also, higher exhaustion marker expression (eg, TIM3 and LAG3) and higher glycolytic activity in the CAR-T products correlated with worse clinical outcomes. In another clinical trial investigating CD19 CAR-T in relapsed DLBCL, in vivo persistence of CAR-T was observed in patients with better and more sustained responses.[81] These are also described in some TIL studies where persistent response correlated with the detection of the TIL product in vivo after infusion, though this observation is not always consistent in other studies.[82]

Adoptive transfer of in vitro activated and expanded autologous T cells that target virus antigens has also demonstrated its potential. Infusions of HPV-specific cytotoxic T cells (CTLs) have resulted to tumour response in cervical and other HPV-associated cancers.[83] EBV-specific CTLs have also demonstrated promising clinical benefits for EBV-positive cancers, including patients with PTLD and advanced NPC.[84 85] In our phase II clinical trial of EBV-specific CTL infusion following first-line combination chemotherapy in patients with advanced NPC, manufactured and expanded T cells that contained EBV LMP2A specificity were found to correlate with better survival, whereas a higher percentage of MDSCs found in peripheral blood before EBV-specific CTL infusion after chemotherapy predicted poorer survival outcomes.[85] These studies suggest that fine tuning, sorting and selection for a fitter, better T-cell product as cell therapy, guided by a constellation of biomarkers, may produce more precise immunotherapy. This can be enhanced by strategies with T-cell constructs and/or combined drugs which can circumvent the immunosuppressive TME.

Resistance mechanisms and the TME

One of the biggest challenges of immuno-oncology is the complex multifactorial resistance mechanism landscape, whether primary or acquired, intrinsic or extrinsic to tumour cells.[86 87] Examples of intrinsic resistance pathways against ICIs include loss of HLA loci and neoantigen expression, genetic or epigenetic subversion of APM, upregulation of alternative pathways such as TGFβ and JAK/STAT signalling pathways, or other oncogenic alterations, including activation of Wnt/β-catenin, loss of *PTEN* and amplification of MYC oncogenic pathways.[87–91] These resistance mechanisms are fuelled by the genomic instability of tumour cells, coupled with the 'immunoediting' process, where the selection pressure exerted by the host immunity, or immunotherapy agents, drive further resistance.[92]

The TME of solid tumours is a major barrier for therapeutic efficacy of both ICI and adoptively transferred T cells by limiting T-cell infiltration[93] and T-cell activation,[94] and counteracting T-cell cytotoxicity via regulation of immunosuppressive mechanisms.[95] The presence of stroma, cancer-associated fibroblasts, immunosuppressive immune cells (regulatory T cells, MDSCs and tumour-associated macrophages (TAMs)) and immunosuppressive cytokines in the TME can significantly contribute to the suppression of TIL effector functions and compromised antitumour immunity.[96] Upregulation of angiogenesis factors (VEGF family proteins) in the TME is one of the classical responses to hypoxia, which then promotes T-cell dysfunction and upregulation of coinhibitory receptors, contributing to T-cell exhaustion.[97 98] The hypoxic microenvironment of the TME also drives the production and accumulation of metabolites such as adenosine, which promote tumour growth, migration and also immunosuppression within the microenvironment via its binding to adenosine receptors.[99–101] High tumour-secreted lactic acid accumulation due to hypoxia could also suppress CTL function.[102–104] Increased tryptophan catabolism can also result in immunosuppression via indoleamine 2,3-dioxygenase (IDO1) upregulation.[105] Some of these pathways serve as potential therapeutic biomarkers in designing rational combinations of ICI with other potentially synergistic drugs, where a multitude of clinical trials are ongoing.

The TME has also the ability to induce post-translational modifications to chemokines. Production of reactive nitrogen species by MDSCs within the TME induces nitration of CCL2, resulting in trapping of T cells in the stroma surrounding tumour cells of human colon and prostate cancers.[106] In multiple solid tumours, FasL expression was associated with reduced CD8+ T-cell infiltration and increased FoxP3+ regulatory T-cell infiltration.[107] Tumour endothelial cells can express FasL and endothelin B receptor[107 108] or functional abnormalities causing impaired infiltration of effector CD8+ T cells.[109] Apart from MDSCs, TAMs can be recruited by factors within the TME, inhibiting the antitumour immune response and aiding tumourigenesis by invasion of nearby tissues, stroma remodelling and promotion of tumour angiogenesis and cell proliferation.[110] Recruitment of TAMs to TME is primarily determined by the CCL2-CCR2 axis. Early-phase trials of monoclonal antibody against CCL2 showed initial but modest effects in patients with metastatic castration-resistant prostate cancer,[111 112] reflecting the multiple potential targeting pathways and combinatory strategies.

Multiomics analysis of more than 10 000 samples from 33 cancer types further revealed six pan-cancer immune TME subtypes, which could define immune response patterns.[113] Most of the tumours could be classified into immune-inflamed, non-inflamed, excluded or immunosuppressed based on their oncogenic, immune and metabolic genetic signatures.[96 114]Other forms of 'immunoscores' or 'immunograms' exist,[115 116] but no unifying scoring system has been commonly agreed on currently by the wider scientific community. It is with an ever-expanding understanding of the TME that we can best validate biomarkers to predict response to ICI, as well as apply novel, multipronged approaches to counter resistance mechanisms.[96 117]

Fine tuning highly personalised immunotherapy

In light of the suppressive TME being a major barrier to response to immunotherapy, extensive efforts are ongoing to turn 'cold' tumours into 'hot' tumours. Strategies to reprogramme the immunoexcluded or immune suppressive landscape with 'activating' combinatory therapies to overcome intrinsic or extrinsic resistance are ongoing in the preclinical and early clinical phases. Interestingly, radiation also may contribute to improving TIL infiltration and response to ICIs, even in off-target (non-irradiated) sites, also known as the 'abscopal effect'.[118] Such strategies interrogating and using the new knowledge of both 'seed and soil' move beyond conventional principles of combining non-cross-resistant cytotoxic chemotherapy to overcome resistance.

Preclinical studies have demonstrated that targeting the VEGF/VEGFR pathway, in combination with cell vaccines[119 120] and adoptive T-cell therapy, leads to higher intratumoural CD8+ T-cell infiltration.[121] Recent successful clinical examples include the positive landmark phase III studies of atezolizumab with bevacizumab in the treatment of advanced HCC,[122] and axitinib with pembrolizumab in the treatment of metastatic RCC.[35] However, a recent negative phase III trial of IDO1 inhibitor with anti-PD1 therapy is a sobering reminder that despite a rationally designed drug combination, overcoming resistance to ICI remains challenging.[123] Neoadjuvant studies have also begun to reveal crucial translational readouts especially about primary resistance and the TME, potentially revealing further biomarkers of response.[124]

With advances in NGS technology and neoantigen prediction capabilities, efforts are ongoing to improve the specificity and efficacy of autologous TIL therapy by preselecting neoantigen-reactive TILs. As a clinical proof of principle, Rosenberg's group succeeded in achieving objective tumour regression and persistent remission for selected patients with chemorefractory metastatic cholangiocarcinoma and colorectal and breast cancers by using neoantigen prediction algorithms to produce somatic-mutation antigen-specific TILs.[125–127] This remains a highly tailored, time-intensive and labour-intensive personalised form of cell therapy.

Similarly, efforts to improve the efficacy and specificity of pre-existing CAR-T therapy are ongoing, and novel, new-generation CARs are being explored through new therapeutic targets, for instance, CD19/22 bispecific CAR-Ts developed to overcome the issue of CD19 antigenic loss in B-ALLs.[128 129] Armoured CAR-T is also been developing to improve efficacy and to overcome immunosuppressive TME.[130] Efforts to overcome defective APM and HLA loci loss also include the exploration of the innate immunity, including the development of adoptive NK cell therapy, with promising early signals.[131]

Promising new interdisciplinary technologies will augment precision immunotherapy. A recent deep-learning approach successfully predicts the microsatellite instability status in gastrointestinal cancers,[132] and radiomics can now monitor TIL distribution and assess response to ICI.[133 134] Systems and computational biology, artificial intelligence, deep learning and digital medicine will all play an increasing role in precision immunotherapy, including improving the power of prediction, patient enrichment, diagnostics, therapeutic design and decision making, monitoring, evaluation of outcomes and survivorship.[135]

CONCLUSIONS

The aspirational goal of precision immunotherapy is to be able to identify the right patient for the right treatment and to accurately predict a patient's best response to highly tuned, personalised immunotherapies guided by biomarkers, including phenotypic, genotypic, proteomic, cellular or metabolic ones. In the treatment journey, we envision a comprehensive 'immunoscore' for each patient, with the aid of machine learning and algorithms assigning weightage to respective biomarkers.

With improved technology and reduced cost of NGS and other deep analytics, further composite analyses can be made of the TME, host immune profile, and the tumour omics in therapeutic decision making. A patient entering the future precision immunotherapy clinic, instead of receiving only his tumour PDL1 expression by IHC, may receive comprehensive reports of PDL1 expression by multiplex immunofluorescence imaging, mRNA sequencing and/or exosome analyses. If the patient is identified to harbour known resistance pathways, rational strategies with combinatorial treatment approaches and sequencing can be designed for better outcomes. Lifestyle and biology modifying strategies may include prescribing an oral microbiome pill, avoiding prolonged antibiotics and consuming more high-fibre diet to optimise ICI response. Highly customised, fitter, stronger, more persistent, 'better armed' T cells can be used as a new generation of engineered CAR-T or other adoptive cell therapies. In addition, third-party tumour-specific donor T cells sourced from a donor cell bank, requiring either only a partial HLA match or gene-editing to avoid detection by host immunity.

We look forward to a future where such cutting-edge technologies will become more cost-effective to enable rapid and accurate clinical decision making, patient management and long-term follow-up. While still a work in progress, tailoring 'bespoke' precision immunotherapy for each cancer patient could become a routine reality and not just a quixotic quest.

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