PROJECT NOTES

By Pawel Rosikiewicz,
www.SimpleAI.ch

dictionary:

- **Neoantigens** :
  - Tumor-specific mutations form novel immunogenic peptides called neoantigens. Neoantigens can be used as a biomarker predicting patient response to cancer immunotherapy. Although a predicted binding affinity (IC_{50}) between peptide and major histocompatibility complex class I is currently used for neoantigen prediction, large number of false-positives exist. https://www.annalsofoncology.org/article/S0923-7534(19)45468-9/fulltext

- **ICPIs**
  - **T**reatment with immune checkpoint inhibitors (ICPIs)

- **Tumor immunotherapy**
  - aims to control tumor development by activating the immune system to attack tumor cells.
  - By selecting appropriate antigens, notably neoantigens produced by tumor-specific mutations, an effective tumor-specific immune response can be mounted, and immune tolerance can be minimized. Non-synonymous somatic mutations will produce altered peptides, among which, some are processed and presented by the major histocompatibility complex (MHC) in order to generate neoantigens. These molecules are the key factors required for successful immunotherapy, including immune checkpoint inhibitors (ICIs), personalized tumor vaccines and adoptive T cell transfer immunotherapy (2–4). These strategies have shown promise in the treatment of solid tumors
  - A higher number of DNA mutations are associated with higher number of candidate peptides, and results in an increased probability of successfully presented neoantigens (8). The response to immunotherapy correlates with tumor mutation burden (TMB) and mainly with the number of mutations in the coding region of the genome (exome) of the tumor cells.

- **PFS - progression-free survival**
  - The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to see how well a new treatment works.

- **PD1, PD-L1 - immune regulatory genes**
  - **https://en.wikipedia.org/wiki/PD-L1**
  - Programmed death-ligand 1 (PD-L1) is a 40kDa type 1 transmembrane protein that has been speculated to play a major role in suppressing the adaptive arm of immune systems during particular events such as pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis.
  - PD-L1 and immunotherapy :
    - https://www.abcam.com/cancer/cancer-immunotherapy-and-the-pd1pdl1-pathway
    -

    SEE MY NOTES BELOW – more info there,

ECOG Performance Status Scale

- describes a patient's level of functioning in terms of their ability to care for them self, daily activity, and physical ability (walking, working, etc.).
- scale 0-5,
- alternatives: **KARNOFSKY PERFORMANCE STATUS**
- https://ecog-acrin.org/resources/ecog-performance-status/

ECOG Performance Status Scale

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982 Dec;5(6):649-655. PMID: 7165009.

FMO ne mutation burden per MB

⇒ **'FMOne mutation burden per MB'** - Tumor Mutational Burden (TMB) measured with Foundation Medicine panel; https://www.foundationmedicine.com/test/foundationone-cdx

⇒ **Tumor mutational burden (TMB)—**the number of somatic mutations per DNA megabase (Mb), used as neoantigen burden that is an independent biomarker associated with ICPI outcomes

- TMB can be reliably estimated using validated algorithms from next-generation sequencing assays that interrogate a sufficiently large subset of the exome as an alternative to whole-exome sequencing.
- elevated TMB can result from :
  - exposure to cigarette smoke
  - ultraviolet radiation
  - deleterious mutations in mismatch repair leading to microsatellite instability,
  - or from mutations in the DNA repair machinery.
- patients with higher TMB experience longer survival and greater response rates following treatment with ICPIs compared with those who have lower TMB levels
  - example : TMB threshold of ≥10 mutations per Mb to be predictive of longer progression-free survival in patients with non-small cell lung cancer
- CAUTION: Methods for the calculation of TMB are not standardized between laboratories, with significant variables being the gene content of the panels sequenced and the inclusion or exclusion of synonymous variants in the calculations.

Articles and online materials

- **Comparison of commonly used solid tumor targeted gene sequencing panels for estimating tumor mutation burden shows analytical and prognostic concordance within the cancer genome atlas cohort** https://jitc.bmj.com/content/8/1/e000613
  - Caution; they used somatic sniper, from David E. Larson, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3268238/
  - Its early version had problems with fixed number of case-control samples, and min-max used for estimating most probable combination of variants at a given position, then tested with multinomial distrib.
  - It could lead to several artifacts, by lowering the number of observed/accepted variants, even if supported by empirical data
- **Tumor Mutational Burden as a Predictive Biomarker for Response to Immune Checkpoint Inhibitors:** A Review of Current Evidence Published online 2019 Oct 2. doi: 10.1634/theoncologist.2019-0244
- **Comparison of commonly used solid tumor targeted gene sequencing panels for estimating tumor mutation burden shows analytical and prognostic concordance within the cancer genome atlas cohort https://jitc.bmj.com/content/jitc/8/1/e000613.full.pdf**

Neoantigen burden per MB

⇒ **tumor neoantigen burden (TNB)** is defined by the number of neoantigens per megabase in the genome region (13, 14). Notably, TMB has become a biomarker for immunotherapy, assuming that higher TMB will increase the probability of tumor neoantigens and specific T-cell responses (15).

- CHALLENGES:
  - not all mutations produce neoantigens. Only a limited number of mutations can be properly processed, presented on the surface of the MHC complex and recognized by T cells (19)
  - The TMB noted in **pediatric tumors is considerably low** (20). However, in certain tumors, such as pediatric medulloblastoma or acute lymphoblastic leukemia, which exhibit minimal mutational burden, a strong anti-tumor immune response can be induced by **high-quality neoantigens** (21, 22).
- TNB vs TMB
  - A positive correlation has been noted between TMB and TNB.
  - However, TNB is directly used for neoantigen evaluation and may be considered an improved biomarker for immunotherapy compared with TMB (23–25).
  - High TNB was associated with durable progression-free survival (PFS) in patients with non-small cell lung cancer (NSCLC) treated with programmed death 1 (PD-1) inhibitors (26). In addition, TNB correlated with clinical benefit in patients with metastatic melanoma treated with cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibitors (27). Similarly, a phase I/II trial performed in patients with stage IV melanoma demonstrated that their clinical benefit was associated with a proposed immune activation signatures score. Among the score items, high TMB and predicted TNB were significantly associated with improved PFS and overall survival (28). The present review investigated the application of TNB as a biomarker in immunotherapy and other therapies and provided an in-depth discussion of the mechanisms, clinical application and challenges of this biomarker.

Articles and online materials

- **Beyond Tumor Mutation Burden: Tumor Neoantigen Burden as a Biomarker for Immunotherapy and Other Types of Therapy Front. Oncol., 29 April 2021 | https://doi.org/10.3389/fonc.2021.672677**
  - **the potential application of TNB as a biomarker was evaluated.**
  - **The methods of neoantigen prediction were summarized and the mechanisms involved in TNB were investigated.**
  - **The impact of high TNB and increased number of infiltrating immune cells on the efficacy of immunotherapy was also addressed.**
  -

Cancer immunotherapy and the PD-1/PD-L1 checkpoint pathway

Read about the PD-1/PD-L1 pathway, its function in cancer, and how it is being used in immunotherapy.

RELATED

PD-L1/ PD-1 products

PD-L1 [28-8] RabMAb® antibody

PD1 monoclonal antibody

PD-L1 trial panel

Compare PD-L1 clones

Identify T cells with FOXP3 antibody

T cell cytokine ELISA kits and reagents

Immuno-oncology resources

Immune checkpoint pathway

Immune cell markers

Effector T cell markers

Hallmarks of cancer

Protocols

Flow cytometry immunophenotyping

PD-L1 [28-8] RabMAb® protocols for automated IHC

Overview

Immune checkpoint inhibitors

The immune system plays an important role in protecting us from disease and clearing the body's own unhealthy and ailing cells. The T cells of the immune system have a capacity to selectively recognize and kill pathogens or unhealthy cells, including cancer cells, by orchestrating a coordinated immune response including innate and adaptive responses.

Many checkpoints ensure the immune system cells do not mistakenly destroy healthy cells during an immune response (known as an autoimmune reaction). Cancer cells can exploit these immune checkpoints as a way to evade immune detection and elimination.

By blocking immune checkpoint proteins, including PD-1, PD-L1 and CTLA-4, with monoclonal antibodies, the immune system can overcome cancer's ability to resist the immune responses and stimulate the body's own mechanisms to remain effective in its defenses against cancer.

What is the PD-1/PD-L1 pathway?

The PD-1 (programmed cell death-1) receptor is expressed on the surface of activated T cells. Its ligands, PD-L1 and PD-L2, are expressed on the surface of dendritic cells or macrophages. PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors that can halt or limit the development of the T cell response. The PD-1/PD-L1 interaction ensures that the immune system is activated only at the appropriate time in order to minimize the possibility of chronic autoimmune inflammation.

The role of PD-1/PD-L1 in cancer

Under normal conditions, the immune system performs a series of steps which lead to an anticancer immune response and cancer cell death, known as the cancer immunity cycle[1]:

1. Tumor cells produce mutated antigens that are captured by dendritic cells
2. The dendritic cells prime T cell with tumor antigen and stimulate the activation of cytotoxic T cells
3. Activated T cells then travel to the tumor and infiltrate the tumor environment
4. The activated T cells recognize and bind to the cancer cells
5. The bound effector T cells release cytotoxins, which induce apoptosis in their target cancer cells

The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism exerted by tumor cells in response to endogenous immune anti-tumor activity. PD-L1 is overexpressed on tumor cells or on non-transformed cells in the tumor microenvironment[2]. PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T cells, which leads to the inhibition of the cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment.

Using PD-1/PD-L1 and immunotherapy

Monoclonal antibody therapies against PD-1 and PD-L1 are being routinely used including:

- Nivolumab, an anti-PD-1 drug developed by Bristol-Myers Squibb, which is approved for previously treated metastatic melanoma and squamous non-small cell lung cancer.
- Pembrolizumab, developed by Merck is approved for previously treated metastatic melanoma.

There are several other immunotherapy options being used or in development.

Combination immunotherapy

The efficiency of the immune checkpoint blockade with monoclonal antibodies in cancer treatment is remarkable, but not all patients respond to a single therapy. To enhance and broaden the anti-tumor activity of immune checkpoint inhibition the next step is combining agents with synergistic mechanisms of action. An example of this is the success of the combination of PD-1/PD-L1 inhibition blockage with complementary checkpoint inhibitor CTLA-4 in melanoma and non-small cell lung cancer[3].

Adoptive T cell therapy

Adoptive T cell therapy involves first isolating tumor-specific T cells from patients and then expanding these *ex vivo*. The tumor-specific T cells can then be infused into patients to give their immune system the ability to overwhelm remaining tumor cells.

T cells can be harvested either from the patient's tumor (tumor-infiltrating lymphocytes, TILs) or peripheral blood (peripheral blood lymphocytes, PBLs). Tumor specificity must be induced in PBLs either through antigen-specific expansion or genetic engineering[4]. After expansion in culture, tumor-specific T cells can be reinfused into the cancer patient.

Another type of adoptive cell therapy is CAR T cell therapy, where T cells are engineered to express chimeric antigen receptors (CARs) that recognize cancer-specific antigens. This means researchers can prime the cells to recognize and kill tumor cells that would otherwise escape immune detection[5].

CAR-T cells and T cells with engineered tumor-specific TCRs show anti-tumor activity in some solid tumors and hematological malignances[1].

References

1. Chen, D. and Mellman, I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* **39**, 1–10 (2013).

2. Pardoll, D.M. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*, **12**, 252–264 (2012).

3. Ott, P.A., et al. (2017). Combination immunotherapy: a road map. *J Immunother Cancer*, **5**:16 (2017).

4. Perica, K., et al. Adoptive T cell immunotherapy for cancer. *Rambam Maimonides Med J*, **6**: e0004 (2015).

5. Grupp, S., et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med*, **368**, 1509-1518 (2013).

Review Article | Published: 30 October 2020

The rediscovery of platinum-based cancer therapy

Sven Rottenberg, Carmen Disler & Paola Perego

Nature Reviews Cancer **21**, 37–50 (2021) | Cite this article

10k Accesses | **130** Citations | **39** Altmetric | Metrics

Abstract

Platinum (Pt) compounds entered the clinic as anticancer agents when cisplatin was approved in 1978. More than 40 years later, even in the era of precision medicine and immunotherapy, Pt drugs remain among the most widely used anticancer drugs. As Pt drugs mainly target DNA, it is not surprising that recent insights into alterations of DNA repair mechanisms provide a useful explanation for their success. Many cancers have defective DNA repair, a feature that also sheds new light on the mechanisms of secondary drug resistance, such as the restoration of DNA repair pathways. In addition, genome-wide functional screening approaches have revealed interesting insights into Pt drug uptake. About half of cisplatin and carboplatin but not oxaliplatin may enter cells through the widely expressed volume-regulated anion channel (VRAC). The analysis of this heteromeric channel in tumour biopsies may therefore be a useful biomarker to stratify patients for initial Pt treatments. Moreover, Pt-based approaches may be improved in the future by the optimization of combinations with immunotherapy, management of side effects and use of nanodelivery devices. Hence, Pt drugs may still be part of the standard of care for several cancers in the coming years.

Platinum-based antineoplastic

From Wikipedia, the free encyclopedia

Platinum-based antineoplastic drugs (informally called **platins**) are chemotherapeutic agents used to treat cancer. They are coordination complexes of platinum. These drugs are used to treat almost half of people receiving chemotherapy for cancer. In this form of chemotherapy, commonly used drugs include cisplatin, oxaliplatin, and carboplatin, but several have been proposed or are under development.[1] Addition of platinum-based chemotherapy drugs to chemoradiation in women with early cervical cancer seems to improve survival and reduce risk of recurrence.[2]

In total, these drugs can cause a combination of more than 40 specific side effects which include neurotoxicity, which is manifested by peripheral neuropathies including polyneuropathy.[3]

Mechanism of action [edit]

As studied mainly on cisplatin, but presumably for other members as well, platinum-based antineoplastic agents cause crosslinking of DNA as monoadduct, interstrand crosslinks, intrastrand crosslinks or DNA protein crosslinks. Mostly they act on the adjacent N-7 position of guanine, forming a 1, 2 intrastrand crosslink.[4][5] The resultant crosslinking inhibits DNA repair and/or DNA synthesis.

Platinum-based antineoplastic agents are sometimes described as "alkylating-like" due to similar effects as alkylating antineoplastic agents, although they do not have an alkyl group.[6]

Examples [edit]

Strategies for improving platinum-based anticancer drugs usually involve changes in the neutral spectator ligands, changes in the nature of the anions (halides vs various carboxylates), or changes in the oxidation state of the metal (Pt(II) vs Pt(IV)). Nanotechnology has been explored to deliver platinum more efficiently in the case of lipoplatin, which is introduced into the tumor sites thereby reducing the chance of toxicity.[7]

Cisplatin was the first to be developed.[8] Cisplatin is particularly effective against testicular cancer; the cure rate was improved from 10% to 85%.[9] Similarly, the addition of cisplatin to adjuvant chemotherapy led to a marked increase in disease-free survival rates for patients with medulloblastoma - again, up to around 85%. [10] This application of cisplatin was developed by pediatric oncologist Roger Packer in the early 1980s. [11]