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AGNOSTIC THERAPY IN CANCER TREATMENT

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Abstract: Introduction: Advances in tumor biology and immunology continue to refine our understanding of cancer. In recent years, genetic alterations responsible for oncogenesis in a wide variety of cancers have been discovered, along with the discovery that some markers that can be targeted by drugs, regardless of the site of origin. Targeted therapies have transformed cancer treatment, allowing cancer treatments to evolve from chemotherapy to targeted therapy. Recent clinical trials based on biomarkers represent a significant change in cancer treatment. With the growth of studies, we have so far seen a large increase in biomarker-based agnostic treatment indications. The complex and heterogeneous biology of the various types of cancer represents a challenge. **Objective**: In this literature review, we present a brief history of the development of agnostic therapies and the medications approved to date by the US health agency as agnostic therapies. We also recognize the challenges to improving agnostic therapies. **Method**: Bibliographic review, using PubMed, The Lancet, New England and Nature as databases. Articles published between 2016 and 2022 were selected. **Results:** Still new on the oncology scene, it is clear that the evidence is still scarce, but very impactful, and the potential for growth and the milestone that this type of treatment has is remarkable. **Conclusion**: Tumor-agnostic treatment represents a new way of thinking about cancer therapies, different from traditional chemotherapy regimens, with a long way to go but with enormous potential for growth.
Keywords: Agnostic therapy; biomarkers; cancer; neoplasia; FDA;

INTRODUCTION

Historically, since chemotherapy began to be used in the 1940s, the treatment of tumors has been divided according to their tissue of origin. Cancer therapies were then developed to treat a tumor originating in a specific organ. With technological developments and greater knowledge of human DNA and its mutations, the identification of molecular markers and their relationship with oncogenesis has allowed us to stratify the various types of cancer according to a molecular pattern[1]. In this way, it was noticed that tumors of different origins shared, in some cases, the same molecular basis and, consequently, could be sensitive to the same treatments[2].

The word agnostic comes from ancient Greek and means, "without" (a) "knowledge" (gnõsis). The concept of agnostic therapy in cancer treatment is based on the fact that the treatment of tumors is defined by their molecular profile, regardless of their anatomical site of origin or their histology. Tumor-agnostic treatment is a new way of treating cancer, regardless of the organ or tissue in which the cancer originates, as long as it contains among its molecular characteristics the presence of a common target

The concept that tumor biology can better define subpopulations of patients with identifiable changes in various histological types ushered in a new era of drug development defined by the search for agnostic therapies[3].

In this review, we present the advances in histologic-agnostic therapies and their rapid development in recent years, as well as pointing out challenges for the progression of studies in this area of oncology, which has excelled in clinical oncology.

METHODOLOGY

A literature review was carried out using PubMed, The Lancet, New England and Nature as databases. Articles published between 2016 and 2022 were selected.

RESULT

Although the results are promising and have a major impact, care must be taken when extrapolating treatment to tumor types not included in the studies, so that histological agnostic therapies are not susceptible to over--application. Continuous evaluation is also needed, as tumors have a high mutagenic load and are susceptible to developing resistance. The incorporation of longitudinal genomic sequencing of tumors throughout clinical trials has been used for this assessment of primary and secondary resistance[1]. The availability of genetic tests and their cost must also be taken into account. Although there is already evidence of the usefulness of these tests and even cost savings, there is still little availability and willingness of payers to cover such tests, which reduces the volume of patients receiving these tests, thus reducing the group of patients with genomic results available to identify opportunities for targeted therapy. [3,4]

After reviewing the current literature on the subject, which is still new to the oncology scene, it is clear that the evidence in this area is still scarce, but very impactful, and the potential for growth and the milestone that this type of treatment has is remarkable.

DISCUSSION

In recent years, a lot has been learned about the specific changes in genes and proteins in cells that cause them to grow uncontrollably and become cancer cells (these genetic and protein changes are also called biomarkers). Finding these specific changes in a person's cancer cells can sometimes affect their treatment. With technological developments, the use of biomarkers has been used to classify and define therapeutic targets within a given histological type of cancer. For example, breast cancer is classified into disease subclasses according to the state of expression of hormone receptors or HER2, as is non-small cell lung cancer according to specific mutations. With the benefit of selecting patients who may be more likely to have a response to a specific therapy[1,5]. For example, in people with lung cancer, cancer cells are now tested for genetic or protein alterations to see if certain targeted therapy drugs might be useful for them. Moving forward, new drugs are now approved based mainly on whether the cancer cells have specific genetic or protein alterations, regardless of where the cancer started.

Drugs approved for use in this way are called tumor-agnostic drugs or tissue-agnostic drugs. The development of agnostic drugs originated from the identification of high microsatellite instability (MSI-H) status, also called deficiency of repair enzymes (dMMR). MSI-H tumors share common histopathological features, including lymphocytic infiltration, somatic hypermutation and increased neoantigen formation. These neoantigens can serve as targets for the immune system, making a tumor susceptible to immunotherapy[6]. In addition, MSI--H tumors can positively regulate immune checkpoints, such as PD-1 or programmed death ligand 1 (PD- L1), in lymphocyte infiltration[7,8]. These findings led to the hypothesis that MSI--H/dMMR is a biomarker for high neoantigen load and sensitivity to immune checkpoint inhibitors (new class of immunotherapy), leading to the design of a series of studies investigating the efficacy of the anti-PD1 monoclonal antibody, pembrolizumab, in patients with MSI-H tumors, regardless of the organ of origin[1]. After evaluation of the studies, the overall response rate (ORR), defined by the reduction in tumor size, was 36 to 46% in 15 different histological types, with durability of responses (78% of responses continued after 6 months from the start of treatment)[9,5]. These results led the US regulatory agency FDA (Food and Drug Administration) to approve pembrolizumab as the first medication for agnostic treatment of cancer[10].

Following this approval, there was an acceleration in the approval of other drugs for the same purpose. In this sense, other targets were identified.

NTRK MERGER

The tropomyosin-related kinase (TRK) proteins TRKA, TRKB and TRKC are membrane receptors with an important role in the physiology of the nervous system. These glycoproteins are encoded by NTRK1, NTRK2 and NTRK3 and are involved in cell proliferation, differentiation[11]. Larotrectinib is a potent TRK inhibitor and has been evaluated for the treatment of patients with metastatic or unresectable solid tumors, the original publication included data from 55 patients with one of 17 different types of solid tumors driven by NTRK fusion, with an overall response rate of 80%[12]. In 2018 it was approved by the FDA.

Also evaluated and approved for use was entrectinib, a tyrosine kinase inhibitor, based on studies that showed an overall response rate of 57%, with 7.4% of patients showing complete disappearance of the tumor. The most common cancer sites were lung, colorectal, salivary gland, breast and thyroid.[13]

dMMR

As previously mentioned, microsatellite instability or repair enzyme deficiency (dMMR), the new drug Dostarlimab was tested and approved, based on a study of 209 patients with advanced or recurrent solid tumors with dMMR who progressed after systemic therapy and had no alternative treatment with an overall response rate (ORR) and duration of response of 41.6% and 34.7 months respectively[14].

BRAF V600E MUTATION

The BRAFv600 mutation has been found in various solid tumors such as colon cancer, melanoma, lung cancer and in hematological neoplasms such as hairy cell leukemia. The identification of the reactivation of the mitogen-activated protein kinase (MAPK) pathway as an escape mechanism led to the approval of a combination therapy of BRAF and mitogen-activated extracellular signal-related kinase (MEK) inhibitors for melanoma patients with BRAF mutation[3,15]. Recently, in 2022, the combination of dabrafenib, a selective BRAF inhibitor, in association with trametinib, a MEK1/2 inhibitor, was also approved for patients with solid tumors that have progressed after previous treatment and with no other satisfactory alternative. It was also observed that 41% had an objective response. The studies included patients with 24 tumor types. Among the most representative tumor types, the overall response rate was 46% (95% CI: 31, 61) for biliary tract cancer, 33% (95% CI: 20, 48) for high-grade glioma (combined) and 50% for low-grade glioma[16,17].

RET MERGER

Although only a small subset of cancers have this mutation, those that do, such as lung cancer, affect a large number of patients. Based on this, selpercatinib, an oral RET kinase inhibitor, was evaluated as a treatment. Efficacy was demonstrated in a multicenter, open-label, multi-cohort study that evaluated 41 patients with RET fusion-positive tumors (except non-small cell lung cancer and thyroid cancer) with disease progression after previous systemic treatment or who had no satisfactory alternative treatment options. The overall response rates (ORR) and duration of response among evaluable patients were 44% and 24.5 months, respectively. Tumor types with responses included pancreatic adenocarcinoma, colorectal, salivary, unknown pri-

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mary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small bowel and cholangiocarcinoma[18]. Also leading to FDA approval of this medication.

APPROVED THERAPIES

We currently have six therapies approved by the FDA as agnostic therapies in cancer treatment: pembrolizumab, larotrectinib, entrecitinib, dorstalimab, dabrafenib/trametinib and selpercatinib, mentioned earlier in the article.

Medicines	Biomarker	**Year of** FDA **approval**
Pembrolizumab	MSI-H/dMMR	2017
Larotrectinib	NTRK merger	2018
Entrectinib	NTRK merger	2019
Dorstalimab	dMMR	2022
Dabrafenib + Trametinib	BRAF V600E mutation	2022
Selpercatinib	RET merger	2022

Table 1. Drugs approved by the FDA as agnostic therapy

MSI-H, high microsatellite instability; dMMR, deficiency of repair enzymes;

In Brazil, the only cancer drug with a site-agnostic indication is larotrectinib.

Although treatments are targeted to tumor alterations identified through genetic sequencing, even when drugs are a good match for a specific mutation, they don't always work, showing that there are still limitations in the development of agnostic drugs. Results presented at ASCO 2018 showed that in a mixed histology cohort (n = 65 patients; 45 tumor types) based on the presence of activating mutations in PIK3CA, treatment with the PI3K inhibitor taselisib did not lead to any objective response, suggesting that the mutational status of PIK3CA, independent of tumor histology, is an insufficient predictor of taselisib activity. [19]

CONCLUSION

The approvals of agnostic therapies represented an important milestone in the history of oncology. Cancer treatment can now be approved based on common genomic alterations rather than the primary site, leading to an integration of genomic therapy with clinical practice. Future improvements in genetic and immunological knowledge and their interaction will make it possible to understand how oncogenesis works and new therapies can be tested.

Tumor-agnostic treatment represents a new way of thinking about cancer therapies, different from traditional chemotherapy regimens, and is a form of personalized, precision therapy with great growth potential. However, it faces major challenges, such as patient selection and statistical analysis involving multiple, potentially heterogeneous histologies.

AUTHORS' CONTRIBUTION

Conception, research design and writing of the Manuscript: Bruno Alexandre de Sene Ferregutti Gomes Critical review of the manuscript intellectual content: Gregório pinheiro Soares

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