Biological Cancer Therapies

Subjects: Oncology

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Biological cancer therapy involves treatment with natural molecules made by the body or made in a laboratory. These therapies either help the immune system fight the cancer or attack the cancer directly. These include treatment with monoclonal antibodies, adoptive cell transfer, gene therapy, treatment with cytokines, cancer vaccines, oncolytic viruses, immunoconjugates and the use of targeted therapy.

Keywords: biological therapy ; cancer ; oncolytic viruses ; CAR T cells ; immunotherapy ; cancer microenvironment

1. Introduction

Cancer is one of the leading causes of death in the world, generates enormous costs and is a major burden on humanity. According to the GLOBOCAN online database report from 2020, it is forecast that the annual number of cancer cases in the world will increase from 19.3 million in 2020 to 28.4 million in 2025 (an increase of 47% compared to 2020) [1]. Oncologists emphasize that classical chemotherapy is already reaching the limits of its effectiveness, therefore, other methods are needed that would enable progress in the treatment of many types of cancer [2]. This problem particularly affects older patients, who most often suffer from these diseases and, at the same time, due to their age and other loads, tolerate chemotherapy much less well than young patients. The hope is in biological therapies that can reduce side effects by acting more selectively on cancer cells.

Biological cancer therapy involves treatment with natural molecules made by the body or made in a laboratory. These therapies either help the immune system fight the cancer or attack the cancer directly. These include treatment with monoclonal antibodies, adoptive cell transfer, gene therapy, treatment with cytokines, cancer vaccines, oncolytic viruses, immunoconjugates and the use of targeted therapy. Biological therapies used in cancer treatment are currently booming and are targeted therapies that fit perfectly into the emerging trend of precision oncology, which uses the results obtained by next-generation sequencing (NGS) methods to detect new, rare mutations in cancer cells in order to tailor treatment to a specific patient [3]. In the biological therapy of cancer, molecules that target genetic aberrations in oncogenes and tumor suppressor genes leading to tumor development are essential. Classic examples of such molecules are: imatinib, a BCR-ABL tyrosine kinase inhibitor used in chronic myeloid leukemia; vemurafenib, a BRAF seronine/threonine kinase inhibitor for the treatment of melanoma; or osimertinib, approved by the FDA and the EC in 2017 for the treatment of non-small cell lung cancer in the presence of the EGFR T790M mutation [4][5][6][7].

Monoclonal antibodies play a huge role in cancer therapy. The first data on the effectiveness of the use of murine monoclonal antibodies against antigens overexpressed in neoplastic cells came from studies in laboratory animals [8]. The problem with the use of these antibodies was that they were multi-species and thus not very effective because they did not work well with the components of the human immune system, and in addition, they were immunogenic and were neutralized by the human immune system [9]. Only the development of the methods of obtaining recombinant antibodies opened the way to therapy, which has already contributed to success in oncology many times, see review [10]. These recombinant antibodies were created by combining the variable part of the murine antibody with the constant part of the human [11]. Chimeric antibodies with reduced immunogenicity were obtained, which, thanks to the human Fc fragment, could cooperate with cells of the human immune system and with complement components. Then, by further reducing the proportion of the murine variable part, humanized antibodies were obtained that are 85–90% human [9][12].

It is important to look at cancer in a multidirectional way, in the development of which the microenvironment also participates, with numerous modulating factors affecting the adhesion, migration, proliferation and drug resistance of cancer cells. The combination of strategies targeting tumor cells and normal tumor-associated cells may have greater therapeutic effects.

2. Research on Improving the Effectiveness of Biological Therapies

One of the major problems in the fight against cancer is that cancer stem cells can survive treatment by slowly dividing, being resistant to cytostatic drugs and escaping the immune system. Until we deal with cancer stem cells, we will not be able to effectively treat this disease.

Finding the therapeutic targets of key importance for managing the behavior of cancer stem cells among a multitude of different pathways could effectively block the development of the disease. The example of CML stem cells shows that in these cells, unlike in CML progenitor cells, there is cooperation between BCR-ABL and many growth factors, tumor suppressors, as well as factors that govern the quiescence and maintenance of CML stem cells [13]. The co-operations of various factors with BCR-ABL modulate the signaling of this fusion protein and lead to resistance to TK inhibitors. Epigenetic modifiers and metabolic reprogramming of stem cells and the role of microRNAs in their survival should also be taken into account [14]. Another approach is to identify tumor-specific surface markers for individual cancer stem cells and to develop monoclonal antibodies for them [15]. The listed exemplary concepts of new therapeutic strategies represent a rather distant perspective in cancer therapy.

One should take into account that therapies targeting cancer stem cells can also affect normal stem cells due to the many similarities between transformed and normal cells. The design of therapies against cancer stem cells should target cancer stem cells as precisely as possible and should also overcome the conditions of a specific tumor microenvironment with poor vascularization and low oxygen levels not conducive to drug penetration [16].

In the case of leukemias or lymphomas, the method of elimination of cancer stem cells may be their mobilization into the peripheral blood, followed by isolation by modified leukapheresis combined with the capture of these cells with an antibody specific for their markers. The search for such markers is still ongoing.

3. Directed Enzyme Prodrug Therapy in Treatment of Cancer

An interesting strategy is the antibody-directed enzyme prodrug therapy (ADEPT) therapy being developed. The idea of ADEPT technology is related to the use of monoclonal antibodies that can be used as carriers of unique enzymes and binding specifically to tumors, where they can transform many prodrug molecules into potent cytotoxic agents within tumors [17]. This enables attaining higher drug concentrations than in the case of direct administration. Drug is thus produced extracellularly, and being a small molecule, it can diffuse through the mass of the tumor and also kill cells through transitive effect [18]. ADEPT is a less toxic chemotherapy for normal tissue and thus it can be combined with other methods, including immune therapy, in order to obtain better clinical benefits [19].

ADEPT using G2 (CPG2) carboxypeptidase, a bacterial enzyme isolated from Pseudomonas sp. [20], has been applied clinically, and it has no human analogue, catalyzing the degradation of reduced and non-reduced folates. Preclinical studies of CPG2 conjugated to non-internalizing antibodies targeting secreted tumor-associated antigens, such as human chorionic gonadotropin (hCG) and carcinoembryonic antigen (CEA), were performed in a mouse model with human choriocarcinoma xenografts-CMDA prodrug. They demonstrated complete or partial regression of tumor in the mouse [21] [22].

The clinical trial uses CPG2 chemically conjugated to the F(ab)SD fragments of the murine anti-CEA A5B7 monoclonal antibody. In addition, another murine monoclonal antibody (SB43) targeting CPG2 has been developed. SB43 inactivates CPG2 and, to avoid the inactivation of CPG2 in tumors, it has been chemically galactosylated (SB43gal), thus it is quickly cleared from the circulation via carbohydrate receptors in the liver [23].

4. Applications and Potential of Biological Therapies

Of the different biological therapies, recombinant antibodies have so far played the most important role in the treatment of cancer, some of which have proven to be breakthrough therapies such as checkpoint inhibitors. That is why such therapies are still intensively developed. The FDA has recently approved not only blinatumomab but also some other antibodies. The anti-EGFR/cMET antibody, amivantamab, approved by FDA in 2021 through an accelerated procedure, is intended for NSCLC patients with an EGFR exon 20 mutation in disease progression following platinum therapy [24]. The EGFR inhibitors available so far have not brought positive therapeutic results in patients with an exon 20 mutation, while, following amivantamab, the ORR was 40% and the mean duration of response (DOR) was 11.1 months. Treatment was discontinued in 11% of patients due to adverse reactions. The most common adverse effects included rash, dyspnea, fatigue, muscle and skeletal pain or edema [25]. Another humanized BsAb approved by the FDA in 2021 along the fast-track is zenocutuzumab (MCLA-128). The target of this BsAb is HER2 on another epitope than trastuzumab and HER3.

This drug appears promising in the monotherapy in patients with gastric cancer, with progression following an earlier treatment [26]. It is furthermore characterized by good tolerance. This drug is also subject to testing in terms of combined therapy with hormonal therapy with trastuzumab and vinorelbine [27].

Almost all CAR T cell therapies used in the clinic are dedicated mainly to B-cell leukemia and target the CD19 antigen. Several therapies have been developed for this leukemia: tisagenlecleucel has been approved for the treatment of pediatric patients with refractory B-ALL [28], then for patients up to 25 years of age with relapsed B-ALL and for adults with diffuse large B-cell lymphoma [29]. Axicabtagene ciloleucel [30] has also been approved for adults with refractory diffuse large B cell lymphoma. In 2020, the FDA approved brexucabtagene autoleucel for patients with mantle cell lymphoma [31] [32] while, in 2021, it approved B-cell maturation antigen (BCMA)-directed autologous CAR T cells (idecabtagene vicleucel) for patients with multiple myeloma [33]. Characteristic of this type of therapy are the high response rates, and, despite the fact that it may even cause serious side effects, as mentioned in chapter 4, it is of great interest among clinicians due to its high therapeutic potential.

The situation is different in the case of solid tumors, for which this therapy is ineffective. One problem is that CAR T cells can only recognize extracellular antigens. Improving the effects of therapy in solid tumors may be achieved after the development of CAR T cells targeting multiple therapeutic targets or by finding suitable neoantigens. Another obstacle in using this therapy on a large scale is its high cost, which makes the therapies unattainable for poorer societies.

Of the oncolytic viruses studied so far, one of the aforementioned T-VECs (IMLYGIC ® , Amgen Inc., Southend Oaks, CA, USA) has been used, which has proved to be relatively effective in the treatment of melanoma as an alternative to other therapies. Clinical studies show that the use of oncolytic viruses together with other therapies may improve the prognosis of patients [34]. The activity of viruses consisting in causing the lysis of tumor-specific cells together with the stimulation of the immune system acts as a potential in situ anti-cancer vaccine. In the case of therapy with oncolytic viruses, the risks associated with the use of potential pathogenic particles should be taken into account, and despite the “devirulence” of oncolytic viruses, care should be taken when using them. Moreover, one type of oncolytic virus is not sufficient to destroy all cancer cells due to the heterogeneity of cancerous tissues and the complexity of cancer cells. Selected cancer cells and non-transformed support cells may be resistant to certain oncolytic viruses, indicating that one type of virotherapeutic agent may not be effective for all types of cancer. Limited identification of the virus and methods of its delivery to an individual patient vary [35].

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