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(REVIEW ARTICLE)



A review of biologic anti-cancer medicines

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Abstract

Biologic medicines prepared using living organisms by the process of biotechnology have demonstrated improved bioavailability, specificity and effectiveness in the treatment of various diseases especially cancer. Cancer is caused due to malfunctioning of the immune system, and biologic therapy can repair, stimulate, or enhance the immune response. Biologic antibodies prepared in laboratory can bind to the surface of cancer cells and target them in a specific way. They can also work synergistically with chemotherapy to improve the outcome. Since biologics utilize the immune system, it may be advantageous to use them before the immune system is compromised. In spite of these advantages, high cost of these products may limit their use. The first biologic approved for therapeutic use was biosynthetic “human” insulin made by recombinant DNA technology in 1982. Since then, biologics have had a profound effect on rheumatology, dermatology, gastroenterology, oncology, and other medical disciplines. Conventional treatments like surgery and radiotherapy are effective in case of localized tumors, but may not be effective for disseminated disease or tumors located in non-invasive areas that are difficult or dangerous to reach. Despite the potency of cytotoxic chemotherapy and the specificity of immunotherapy, neither method alone has been sufficient to eradicate the disease. There is evidence that standard chemotherapy may work in synergy with active immunization for more effective antitumor immunity, and there is great potential for the combination of these treatment modalities. This review aims to enumerate the various biologic anti-cancer preparations available in market along with their mechanism of action and intended medical use.

Keywords: Biologic anticancer; Monoclonal antibodies; Cytokines; Interferon; Epidermal growth factor, FDA.

1. Introduction

The scientific basis of cancer metastasis has been studied in animal tumor models. Over the last 60 years, discoveries have been made in molecular biology, immunology and virology, and novel types of cancer treatment have been developed. These include targeted therapies via small molecule inhibitors (SMIs) or monoclonal antibodies (MABs). In recent years, two novel types of immunotherapy have had a marked impact on oncology: Checkpoint inhibitory MABs and chimeric antigen-specific receptor (CAR)-transfected T-cells (CAR-T cells). Cancer immunotherapy has been demonstrated to be capable of producing sustainable responses in numerous types of cancer. Antigen-specific immune responses can be markedly effective, even in late stage disease. In addition, two other types of biological therapy, antitumor vaccines and oncolytic viruses (OVs), have been developed in recent decades. These types of therapy are physiological and well tolerated. The present review is aimed to focus on the side effects of treatment in general. The World Health Organization (WHO) has defined side effects as grades 0-4 (6). The present review noted that not only cytostatic drugs, but also several of the novel drugs of the last decade, can generate severe adverse events (AEs). Since it is important to understand the difference between therapies with grade 3 and 4 side effects and those with grade 0-2 side effects, this review detailed the functioning of the immune system. The immune system has been optimized by evolution, including mechanisms of immunological tolerance towards self-antigens, mechanisms of memory function and the antiviral type I interferon (IFN) response system. This review also provided overviews regarding the various

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types of cancer therapy, the mechanisms of self-tolerance in T and B lymphocytes, and the important parameters that differentiate chemotherapy, immunotherapy and OV therapy.

2. Classification of different biologic agents

2.1. Cytokines



- Interferon
- Interleukins
- Monoclonal antibodies
- Colony-stimulating factors



2.2. Growth factors





- Hematopoietic growth factors
- Granulocyte colony-stimulating factor

2.3. Vaccines

Table 1 A Review of USFDA Approved Biologic Anticancer Medicines

S.No	Name of the product	Manufactured by	Mechanism of action	Approved indications
1.	Avastin (Bevacizumab) 	Genentech	Bevacizumab is a recombinant humanized antibody that blocks angiogenesis by inhibiting vascular endothelial Growth factor A [1].	Metastatic Colorectal cancer Non-Small Cell Lung cancer Metastatic Breast cancer Renal cancers Brain cancers Ovarian cancer
2.	Zevalin (Ibritumomab tiuxetan) 3.2mg per 2 ml 	IDEC Pharmaceuticals	The antibody binds to the CD20 antigen found on the surface of normal and malignant B cells (but not B cell precursors), allowing radiation from attached isotope (mostly beta emission) to kill it and some nearby cells. In addition antibody may itself trigger cell death via antibody-dependent cell mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis. Together these actions eliminate B cells from the body, allowing a new population of healthy B cells to develop from lymphoid stem cells[2].	Non-Hodgkin's follicular lymphoma

<p>3.</p>	<p>Herceptin (Trastuzumab) 150 mg Powder for concentrate for solution for infusion.</p> 	<p>Genentech, Inc.</p>	<p>The most well-known effect of Trastuzumab is the inhibition of the MAPK and PI3K/Akt pathways, which leads to an increase in cell cycle arrest, and the suppression of cell growth and proliferation. By interfering with the dimerization of HER2</p> <p>Trastuzumab inhibits HER2 activation and suppresses Akt phosphorylation. Other groups critically showed that trastuzumab, by binding to HER2 can block tyrosine kinase Src signaling and thus, increase PTEN level and activity. This also results in the suppression of PI3K/Akt signaling and reduction in cell growth and survival. In general by binding to extracellular domain of HER2 can potently suppress cancer cells growth, proliferation and survival in both direct and indirect manners [3].</p>	<p>Metastatic Gastric cancer Metastatic Breast cancer</p>
<p>4.</p>	<p>Bexxar (Tositumomab)</p>  <p>DARYA OSMAN HUSSEIN</p>	<p>GlaxoSmithKline</p>	<p>Induction of apoptosis, complement dependent cytotoxicity (CDC), and antibody dependent cellular cytotoxicity (ADCC) mediated by the antibody. Additionally, cell death is associated with ionizing radiation from the radioisotope[4].</p>	<p>Indicated for the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy. BEXXAR is not indicated for the initial treatment of patients with CD20 positive non-Hodgkin's Lymphoma.</p>
<p>5.</p>	<p>Rituxan (Rituximab) 100mg/10ml</p>	<p>Genentech, Inc.</p>	<p>The antibody binds to the cell surface protein CD20. CD20 is widely expressed on B cells from early pre-B cells to later in differentiation, but it is absent on terminally differentiated plasma cells</p> <p>Although the function of CD20 is unknown, it may play a role in Ca influx across the plasma membrane maintaining intracellular Ca</p>	<p>Non-Hodgkin's Lymphoma Chronic Lymphocytic Leukemia</p>

			<p>concentration and allowing activation of B cells.</p> <p>Rituximab tends to primarily affect the malignant B cells with the highest levels of CD20.</p> <p>It caps CD20 to one side of B cells and drawing proteins over to that side. The presence of the cap changes the effectiveness of natural killer (NK) cells. When an NK cell is latched onto the cap, it has an 80% success rate in killing the cell[5].</p>	
6.	<p>Mylotarg (Gemtuzumab ozogamicin) 5mg/vial</p> 	Wyeth Pharmaceuticals Inc.	<p>Gemtuzumab is a monoclonal antibody to CD33 linked to a cytotoxic agent from the class of Calicheamicins. CD33 is expressed in most leukemic blast cells and also in normal hematopoietic cells, the intensity diminishing with maturation of stem cells [6].</p>	<p>Treatment of newly-diagnosed CD33-positive acute myeloid leukemia.</p> <p>Treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and in pediatric patients 2 years and older.</p>
7.	<p>Campath (Alemtuzumab)</p> 	GENZYME	<p>It is a monoclonal antibody that binds to CD52, a protein present on the surface of mature lymphocytes but not on stem cells from which these lymphocytes are derived. After treatment with Alemtuzumab, these CD52-bearing lymphocytes are targeted for destruction [7].</p>	<p>Chronic lymphocytic leukemia</p> <p>Multiple sclerosis</p>
8.	<p>Vectibix (Panitumumab)</p> 	Amgen	<p>EGFR is a transmembrane protein. Panitumumab works by binding to the extracellular domain of the EGFR preventing its activation. This results in halting of the cascade of intracellular signals dependent on this receptor[8].</p>	<p>Used in the treatment of EGFR expressing metastatic colorectal cancer with disease progression despite prior treatment.</p>








9.	<p>Arzerra (Ofatumumab)</p> 	GlaxoSmithKline	Ofatumumab binds specifically to both small and large extracellular loops of CD20 molecule and mediates immune effector functions to result in B cell lysis.[9].	chronic lymphocytic leukemia
10.	<p>Erbitux (Cetuximab)</p> 	Eli Lilly	<p>It is an epidermal growth factor inhibitor. It is a chimeric (mouse/human) monoclonal antibody given by intravenous infusion that binds to and inhibit EGFR. Approximately 75% of patients with metastatic colorectal cancer have an EGFR-expressing tumor and are therefore considered eligible for treatment with Cetuximab or Panitumumab, according to FDA guidelines[10].</p>	Metastatic colorectal cancer, metastatic non-small cell lung cancer and head and neck cancer.

Table 2 Few Recently Approved Biologic Drugs 2020

S. No	Name of the drug	Manufactured by	Mechanism of action	Approved indications
11	<p>Neratinib(nerlynx) 120/160/200/240mg</p> 	Puma Biotechnology, Inc	Neratinib is a kinase inhibitor that irreversibly binds to Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), and HER4. In vitro, neratinib reduces EGFR and HER2 autophosphorylation, downstream MAPK and AKT signaling pathways, and showed antitumor activity in EGFR and/or HER2 expressing carcinoma cell lines [11].	HER2-overexpressed/amplified breast cancer,
12	Tazemetostat (tazverik)	Epizyme, Inc	<p>Tazemetostat is a cancer drug that acts as a potent selective EZH2 inhibitor.</p> <p>Tazemetostat blocks activity of the EZH2 methyltransferase, which may help keep the cancer</p>	Treatment of metastatic cancer

			cells from growing. Most cases of epithelioid sarcoma begin in the soft tissues[12].	
13	Avapritinib (ayvakit) 	Blue print medicines	Avapritinib is a kinase inhibitor specifically intended for adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) that harbor a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation inhibitor[13].	treatment of tumors due to one specific rare mutation
14	Pembrolizumab (Keytruda) 	Merck & Co Inc.	Pembrolizumab is a therapeutic antibody that binds to and blocks PD-1 located on lymphocytes. This receptor is generally responsible for preventing the immune system from attacking the body's own tissues; it is a so-called immune checkpoint[14].	Melanoma Non-Small cell Lung cancer Head and Neck squamous cell cancer Classical Hodgkin lymphoma
15	Isatuximab(sarclisa) 100mg/5ml 	Sanofi-Aventis	Isatuximab is an anti-CD38 mAb intended to treat relapsed or refractory multiple myeloma. As of 2015, it is in phase II trials for multiple myeloma and T-cell leukemia[15].	Multiple myeloma

3. Conclusion

Primary tumors usually can be treated with a combination of standard therapies; however, preventing metastasis through disseminated tumor cells is not always possible. The goals of cancer immunotherapy are to prevent the disease from spreading and to improve the patient's quality of life. Recent studies have suggested that there may be synergy between immunotherapy and standard chemotherapy; therefore, it may be beneficial to start biologic therapy earlier in the cancer treatment, before the immune system is compromised. Although the side-effect profile of biologic agents is relatively mild compared with traditional chemotherapy, biologics often cost much more. Pharmacists should be aware of special storage, preparation, and handling instructions. Moreover, pharmacists should counsel patients about possible side effects, storage issues, and administration techniques for medications that are self-administered. With regards to future developments, it has been suggested to combine vaccines, and immune checkpoint inhibitors to facilitate effective tumor immunotherapy. The main conclusions of this review are: i) It may be beneficial for immunotherapy to be included in standard care. Rules of evidence based medicine should be adjusted to the needs of individualized immunotherapy studies, as well as to multimodal therapy studies in general. ii) Recommendations for the use of cytostatic drugs that produce severe side effects and low efficacy should be reviewed by societies of internal medicine.

Compliance with ethical standards

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Disclosure of conflict of interest

All author(s) declare(s) that there is no conflict of interest. If there are potential conflicts of interest, we highly encourage each author to identify and declare clearly to avoid any future investigations by the publisher.

References

- [1] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125085s225lbl.pdf, Last accessed on 07/07/2020].
- [2] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125019s0156.pdf, Last accessed on 07/07/2020].
- [3] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf, Last accessed on 07/07/2020].
- [4] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125011s0126lbl.pdf, Last accessed on 07/07/2020].
- [5] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf, Last accessed on 07/07/2020].
- [6] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf, Last accessed on 07/07/2020].
- [7] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103948s5070lbl.pdf, Last accessed on 07/07/2020].
- [8] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125147s080lbl.pdf, Last accessed on 07/07/2020].
- [9] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125326lbl.pdf, Last accessed on 07/07/2020].
- [10] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125084s0228lbl.pdf, Last accessed on 07/07/2020].
- [11] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208051s000lbl.pdf, Last accessed on 07/07/2020].
- [12] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211723s000lbl.pdf, Last accessed on 07/07/2020].
- [13] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212608s000lbl.pdf, Last accessed on 07/07/2020].

- [14] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125514Orig1s054lbl.pdf, Last accessed on 07/07/2020].
- [15] Highlights of prescribing information [Drugs at FDA Access data portal, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761113s000lbl.pdf, Last accessed on 07/07/2020].

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