

The Present and Future Trend of Monoclonal Antibody

Muyan Qian

Aquinas International Academy, Beijing, China

zhangailin@ldy.edu.rs

Abstract. Over the past three decades, the realm of monoclonal antibodies has witnessed a remarkable metamorphosis. Initially conceptualized and utilized as mere scientific instruments, these antibodies have now evolved into potent therapeutic agents, revolutionizing the landscape of modern medicine. The United States and Europe, being at the forefront of medical advancements, have embraced this transformation, with nearly 30 therapeutic monoclonal antibodies currently available in their markets. These antibodies, tailored to target specific antigens, offer a precision in treatment that was previously unattainable. This review delves into the intricate journey of monoclonal antibodies, tracing their origins, their initial applications in research, and their eventual rise as therapeutic giants. Furthermore, the paper sheds light on the challenges faced in their development, the breakthroughs that propelled their success, and the potential future innovations that could further harness their capabilities. As standing on the cusp of medical breakthroughs, understanding the past and potential future trajectories of monoclonal antibodies becomes paramount.

Keywords: Monoclonal antibody, cancer therapy, Pertuzumab, Trastuzumab.

1. Introduction

The treatment of several illnesses has been transformed by monoclonal antibody targeting technology. Orthoclone OKT3, also known as Muromonab-CD3, targeted the CD3 antigen on T cells and was the first clinical success. It showed notable success in treating autoimmune disorders and organ transplant rejection. The FDA gave the medication its approval in 1986, establishing the groundwork for further monoclonal antibody treatments.

Significant improvements in the treatment of HER2-positive-breast-cancer have been made thanks to Herceptin-targeted therapy. Trastuzumab, a monoclonal antibody, has been used successfully for over 25 years, and a lot of research has been done on more recent, targeted HER2 therapies. This includes HER2-targeting tyrosine kinase inhibitors, monoclonal antibodies, along with antibody-drug conjugates. Thanks to these medications, patients who have HER2-positive-breast-cancer are now living longer [1, 2].

Currently, the usual course of care for restricted HER2- breast cancer consists of chemotherapy plus a year of trastuzumab-adjuvant therapy. However, illness relapses may still occur, motivating efforts to research intensified therapeutic strategies. These strategies include extending the duration of HER2-targeted therapy or combining it with other HER2-targeted drugs. Clinical trials have been approved for a variety of treatments, including adjuvant therapy with T-DM1, adjuvant therapy with multiple HER2-targeted drugs, and extended-duration anti-HER2 therapy [1, 2].

New research, however, suggests that not all patients gain enough from these additional treatments. As a result, precision medicine has to be customized for each patient and the unique genetics, biology, and clinical traits of each tumor. It is crucial to discover biomarkers which can identify the patients who will profit most from therapy that is escalated or de-escalated. The future of HER2-targeted therapy will need a variety of therapeutic options customized to each patient given the variability of HER2-positive individuals in terms of tumor biology and clinical features.

Overall, the use of monoclonal antibodies to target illness has revolutionized medical care, with particular success in HER2-targeted therapy for breast cancer. As a result of continuous research, more effective and individualized medicines will be developed by tailoring treatment plans to the unique patient features.

2. Mechanism of monoclonal antibody

As our knowledge of HER2's biology has increased, so too have the medications that target it. HER receptors are composed of a transmembrane domain, an intracellular tyrosine kinase domain, and an extracellular ligand-binding domain. Following homodimerization or heterodimerization caused by ligand binding to HER proteins, signaling pathways that encourage cell proliferation and growth while inhibiting apoptosis are activated. Although other HER proteins, particularly HER3, prefer it as a dimerization partner, HER2 does not have a known ligand. Through ligand-dependent heterodimerization, ligand-independent dimerization, and aberrant signaling, HER2 overexpression or amplification enhances signaling. The highest response to HER2-targeted therapy has been shown in "HER2-positive" tumors.

2.1. Pertuzumab

The monoclonal antibody pertuzumab targets the extracellular domain of the HER2 receptor, which is overexpressed in many cancer types including breast cancer and gastric cancer. Pertuzumab binds to a particular region of the HER2 receptor, in contrast to other drugs that target the receptor, such as trastuzumab (Herceptin). By attaching to a specific epitope and preventing HER2 from dimerizing with other EGFR family members including HER1, HER3, and HER4, pertuzumab may disrupt the downstream signaling pathways that promote the development and survival of cancer cells. Due to their complementary modes of action, pertuzumab and trastuzumab have been discovered to effectively treat patients with HER2-positive-breast-cancer.

2.2. Trastuzumab

The HER2 receptor is yet another target of the monoclonal antibody trastuzumab, which is overexpressed in several types of gastric and breast cancer. By binding to the extracellular domain of the HER2 receptor, trastuzumab prevents HER2 activation and subsequent signaling cascades that are implicated in the growth of cancer cells and patient survival. The immune system may target cancer cells for complement-mediated cytotoxicity, phagocytosis, and antibody-dependent cell-mediated cytotoxicity due to trastuzumab's affinity for the HER2 receptor. Trastuzumab has been discovered to have a synergistic effect with chemotherapy when taken in concert with other drugs, improving outcomes for patients with HER2-positive-breast-cancer.

Although both medications primarily target the same receptor, HER2, there is a tiny differential between them.

3. Targeted Specific Cancers

Monoclonal antibody therapy is a crucial approach for treating various cancers. Several specific cancers can be targeted through monoclonal antibody therapies. For instance, breast cancer can be treated with monoclonal antibodies like trastuzumab and pertuzumab, which target the HER2 protein on the cancer cells. Lung cancer can be targeted by monoclonal antibodies such as nivolumab and pembrolizumab, which target the PD-1 and PD-L1 proteins on the cancer cells. Colorectal cancer can be treated with the monoclonal antibody bevacizumab, which targets the VEGF protein responsible for cancer cells' blood supply. Additionally, monoclonal antibodies like rituximab, alemtuzumab, and ofatumumab target specific proteins on blood cancer cells, like CD20 and CD19. These targeted therapies have been proven effective in treating cancer, improving the patients' longevity and their quality of life.

4. Improving Ways

Although this technology is extremely popular and has significant benefits for patient survival rates and tumor suppression, there are still several issues that can be improved upon.

When used in conjunction with anthracyclines for the treatment of early and metastatic breast cancer (MBC), trastuzumab-related cardiotoxicity is a significant adverse effect. Ongoing monitoring in the adjuvant situation with dual HER2-targeted treatment consisting of trastuzumab and pertuzumab in HER2+ MBC, however, has not demonstrated an aggravation of cardiotoxicity or an increase in cardiac events [1, 3-6].

Due to the fact that tyrosine kinase inhibitors (TKIs) target the epidermal growth factor receptor (EGFR), typical side effects include gastrointestinal toxicity and skin rash [1, 7-9].

Increased levels of liver enzymes are frequently observed in patients receiving ado-trastuzumab emtansine (T-DM1) and tucatinib [1].

Thrombocytopenia has been reported in connection with T-DM1, and it is believed to be caused by the impairment of megakaryocyte differentiation induced by DM1 [1, 10].

Trastuzumab deruxtecan (T-DXd) has been linked to interstitial lung disease (ILD), as initially identified in 13.6% of the subjects in the DESTINY-Breast01 study. Four of these patients' deaths were reportedly connected to ILD, and one of them experienced a grade 3 ILD event [1, 11].

5. Conclusion

There are several routes that might result in resistance to these therapies, some of which seem to be shared by a number of anti-HER2 drugs. ADCs with potent payloads that are active even in the context of low HER2 expression or dual HER2-targeted therapy may address this problem. Trastuzumab treatment failure typically stems from inadequate HER family receptor inhibition. Potentially preventing the efficient inhibition of HER2 may be the introduction of HER2-activating mutations. Other resistance methods include HER2 truncations, such as p95HER2, which lack the ECD and are identified by anti-HER2 antibodies, and splice variants, such as 16HER2, which stabilize homodimers and constitutively activate downstream signaling.

This technology has been around for a long time since its inception, and the current techniques are relatively mature with several drugs already on the market. Although it has advanced significantly in comparison to cancer vaccines, there is still room for improvement, such as reducing toxicity and improving patient survival rates. Due to its high level of technological maturity, breakthrough progress may not be expected.

But since the field is advancing, ongoing research and advancements in technology may lead to further improvements and refinements in the coming years. Recent studies had come up with some interesting, advanced strategies. Researchers are constantly exploring ways to enhance the effectiveness and safety of monoclonal antibodies.

One potential area of future development is the exploration of novel antibody formats or antibody-drug conjugates. These approaches involve modifying the structure of antibodies or attaching drugs to them, which can increase their specificity and potency against cancer cells while reducing off-target effects. This could potentially lead to improved treatment outcomes and reduced toxicity for patients.

Additionally, researchers are striving to better understand the mechanisms of resistance that some cancer cells develop towards monoclonal antibody therapy. By identifying and targeting these resistance mechanisms, it may be possible to overcome treatment resistance and improve patient outcomes. Moreover, advances in genetic and molecular profiling techniques may allow for more personalized and targeted monoclonal antibody treatments. This approach could involve identifying unique genetic and molecular characteristics of individual patients' tumors to select the most appropriate monoclonal antibody treatment for them. This personalized medicine approach has the potential to further improve patient response rates and survival outcomes.

So, to sum up, while monoclonal antibody therapies like trastuzumab and pertuzumab have reached a level of maturity, the field is still evolving and holds promise for further advancements in the next 5-10 years. Continued research and development efforts may lead to the discovery of new treatment strategies, improved therapeutic outcomes, and ultimately better patient care.

References

- [1] Sandra MS, Mythili S, Erika H. Targeting HER2-positive-breast-cancer: advances and future directions. *Nat Rev Drug Discov*, 2022, 22 (2): 101–126.
- [2] Buss NA, Henderson SJ, McFarlane M, et al. Monoclonal antibody therapeutics: history and future. *Curr Opin Pharmacol*, 2012, 12 (5): 615-622.
- [3] Slamon DJ. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*, 2001, 344: 783–792.
- [4] Slamon DJ, Eiermann W, Robert NJ, et al. Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer. *Cancer Res*, 2016, 76: S5–04.
- [5] Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*, 2020, 21 (4): 519-530.
- [6] Piccart M, Procter M, Fumagalli D, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-positive-breast-cancer in the APHINITY Trial: 6 Years' Follow-Up. *J Clin Oncol*, 2021, 39 (13): 1448-1457.
- [7] Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med*, 2020, 382 (7): 597-609.
- [8] Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*, 2017, 18 (6): 732-742.
- [9] Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol*, 2017, 18 (6): 743-754.
- [10] Uppal H, Doudement E, Mahapatra K, et al. Potential mechanisms for thrombocytopenia development with trastuzumab emtansine (T-DM1). *Clin Cancer Res*, 2015, 21 (1): 123-133.
- [11] Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-positive-breast-cancer. *N Engl J Med*, 2020, 382 (7): 610-621.