A Brief Review: Current Developments in Immunotherapy for Cancer Prevention

Isha P. Bhadke[1], Khushi D. Shinde[2], Nikita V. Mahalle[3], Harigopal S. Sawarkar[4], Neha L. Zod[5]

[1, 2]Student, [3, 5]Associate Professor, [4]Principal
Dr. Rajendra Gode College of Pharmacy, Amravati, Maharashtra

Abstract

The depth exploration of advancements in immunotherapy for cancer prevention, with a particular emphasis on monoclonal antibody (mAb)-based therapies. Monoclonal antibodies, known for their specificity and adaptability, have become pivotal in targeted cancer therapy. The development of hybridoma technology in the 1970s revolutionized therapeutic approaches by allowing for the production of antigen-specific antibodies. Through significant advancements in mAb technology, therapeutic approaches have expanded to include rodent mAb technology, phage display, and the successful integration of mAbs with chemotherapy and immunotherapy agents. Rituximab, a chimeric mAb, exemplifies these advancements, showing efficacy in treating CD20+ malignancies, especially in non-Hodgkin's lymphoma. This review highlights the mechanisms of action of these mAbs, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and apoptosis induction, while examining combination approaches with immune modulators and chemotherapeutic agents. By addressing the challenges and future directions, this review contributes to understanding the role of immunotherapy in advancing cancer prevention and treatment.

Keywords: Cancer, Immunotherapy, Monoclonal Antibodies,Rituximab, etc.

Introduction:

The public's interest in various types of research has increased as a result of the significant scientific advancements and discoveries that have occurred in the 21st century. Modern science aims to improve people's lives by extending human lifespans on average as well as eliminating disease. Unfortunately, new issues come up as people live longer. A person's risk of developing complications, such as degenerative diseases like cancer, increases with age. . A variety of illnesses are included under cancer, and millions of new instances are reported each year, with the number predicted to rise. The purpose of this topic is to give a summary of the most recent advancements in cancer treatment. Globally, the incidence and mortality of cancer are rising as a result of the serious side effects and medication resistance of the current cancer treatmentsAccording to cancer biology, tumours are complex tissues made up of stroma associated with the tumour and heterogeneous neoplastic cells. Tumours caused by unchecked cell development that develops improperly and spreads from organ to organ or other important systems are known as cancer .Opportunities for focused therapeutic intervention are presented by the characterisation of proteins linked to tumours. We refer to this strategy as "targeted therapy." However, due to the heterogeneity of tumours, a combination of targeted therapies must be used to achieve successful clinical treatment. Monoclonal antibodies are currently the most specific targeted therapies availableOne of the main causes of death globally, cancer is characterised as a disease that starts when cells proliferate out of control and push out healthy cells. Anywhere in the body, including the liver, breasts, or lungs, cancer can arise. Many patients' survival has been successfully increased by traditional cancer treatments such surgery, chemotherapy, and radiation. Low patient response rates overshadow the clinical achievements of immunotherapies, despite the fact that they constitute a breakthrough in the treatment of advanced malignancies. It has long been the goal to develop tumor-targeted drug delivery systems that can precisely reach subcellular areas of action, recognize and enter tumor cells, and accumulate in tumor tissues. Few anticancer nanomedicines have received regulatory agency approval, despite the fact that thousands of them have shown remarkable efficacy in preclinical cancer models.

By 2030, the World Health Organisation projected that the number of new cases of cancer would reach 23.6 million per year (World Health Organisation 2014).Additionally, although monoclonal antibody monotherapy has greatly benefited the treatment of cancer, specifically non-Hodgkin's lymphoma, the combination of monoclonal antibodies and chemotherapy has increased their effectiveness even more As of right now, nanotechnology has advanced quickly to create some of the most significant cancer treatment approaches.

The most widely used nanoparticle types for treating breast cancer are liposomes, solid lipid nanoparticles, polymeric nanoparticles, and micelles Products based on monoclonal antibodies (mAbs) are very specific for a given antigen. Because of this property, the molecules are perfect for a variety of uses, such as the diagnosis and treatment of cancer.Developments in mAb-based targeted therapy for human cancers.

Numerous fields of biological and medical research were revolutionised by Kohler and Milstein's invention of hybridoma technology in 1975, for which they were granted the Nobel Prize in Medicine in 1984. Known by another name, immunoglobulins (Ig), antibodies are essential for immunity or internal defences against a wide range of invasive microbes and other pathogens. They are a significant class of glycoproteins found in vertebrate blood and other bodily fluids that contribute to the neutralising immune response. IgG, IgE, IgA, IgM, and IgD are the five common isotypes of these antibodies.

Monoclonal Antibodies

It took another ten years before the potential of this novel class of biologic products started to be recognised, despite the first therapeutic monoclonal antibody (MAb) product hitting the market in 1986. Since the mid-1990s, nearly 30 therapeutic monoclonal antibodies (MAbs) and a number of antibody-related products (such as Fc-fusion proteins) have been approved globally, making MAbs and related products a significant part of the biopharmaceutical market with multibillion-dollar sales. A murine antibody was the first MAb to be approved. A number of chimeric MAbs containing a combination of murine and human regions came next.

Monoclonal antibodies (mAbs) are a prime example of personalized therapeutics enabled by advances in our knowledge of immunology, molecular biology, and biochemistry.

The concept of mAbs as therapeutic options is modeled after the immune system, particularly the humoral immunity (i.e., antibodies) generated by the immune system in response to foreign antigen exposure.

Chimeric clones were the next developments, whereby human crystallizable fragment (Fc) regions were attached in place of murine ones. Examples of chimeric mAbs include infliximab and rituximab.

The five antibody classes (as classified by heavy chain sequence) are IgM, IgD, IgG, IgE, and IgA. Each antibody class performs a unique function in human biology. The most abundant IgG is then further divided into four subclasses based on their properties (namely, the location and quantity of disulfide bonds). For mAb therapeutics, IgG is presently the only class of antibodies utilized

Rituximab is a chimeric murine/human IgG1 monoclonal antibody that has been genetically modified to target the CD20 antigen, which is only expressed by pre-B and mature B cells. Therapy for Tumours Twelve patients with refractory or recurrent PCNSL participated in a pilot study of weekly rituximab administered by CNS Consortium.

Chemistry of Monoclonal Antibody

Through their interactions with complementary and Fc domains, the mAbs demonstrate biological effector functionality. The total molecular weight of an average IgG is around 150 kDa. It is a globular molecule with a symmetrical Y shape made up of two identical heavy chains, each weighing about 50 kDa, and two identical light chains, each weighing around 25 kDa. One variable domain and three constant domains make up the heavy chains,whereas one variable and one constant domain make up the light chains. Additionally, the variable domain is made up of three little peptide segments known as complementarity-determining regions (CDRs). The specific antibody binding is determined by the hypervariable regions known as CDRs.

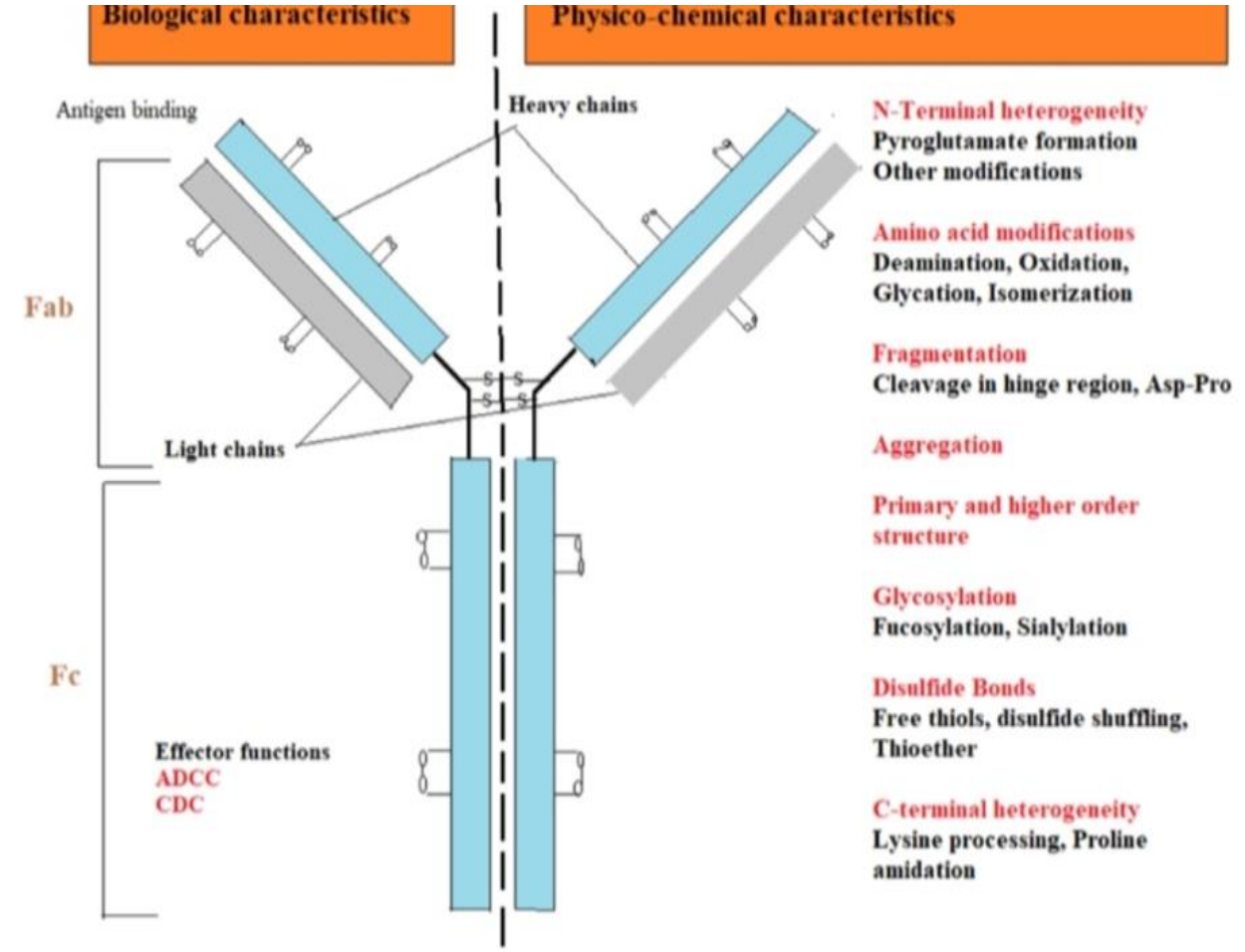

Figure 1: Structure of Monoclonal Antibodies

Advances in mAbs Production Technologies:

The rodent mAb technology has been quickly and effectively used to develop new and improved diagnostics and therapeutics to advance our understanding of human biology since 1977, when immortalised hybridoma technology was first developed and used to recognise mAb.

Hybridoma Technology:

For therapeutic purposes, mouse hybridoma technology was used to create the mAbs. This method effectively produces immortal hybridoma cells that secrete mAbs specific for the target antigen by utilising the inherent functionality of B-lymphocytes, myeloma, or immortalised malignant cells. Myeloma cells and B-cells fuse when polyethylene glycol (PEG) is present as a fusing agent. This method yields antibodies that are specific to the target antigen and have a variety of therapeutic uses. Mice, on the other hand, frequently have poor immune responses, which leads to low affinity and/or non-specific mAbs. Because of the difficulties in creating immortalised antibody-producing cell lines by hybridoma, animals other than rats have not typically been employed to create mAb.

The WHO should have held a symposium (at the National University of Singapore, October 1981) to bring together those who developed and perfected the technology and those who are using or plan to use it for the study of organisms responsible for some of the major diseases affecting mankind because monoclonal antibodies are useful for the analysis of parasite antigen.

These monoclonal antibodies have led to the development of amazing new methods for illness prevention, diagnosis, and treatment. For example, monoclonal antibodies are employed to identify different B and T cell subsets. In addition to being useful for fundamental research, this information helps doctors distinguish

between various leukaemia and lymphoma kinds and adjust treatment plans accordingly. The amount of B cells and helper T cells is crucial to measure in immunological diseases like AIDS.

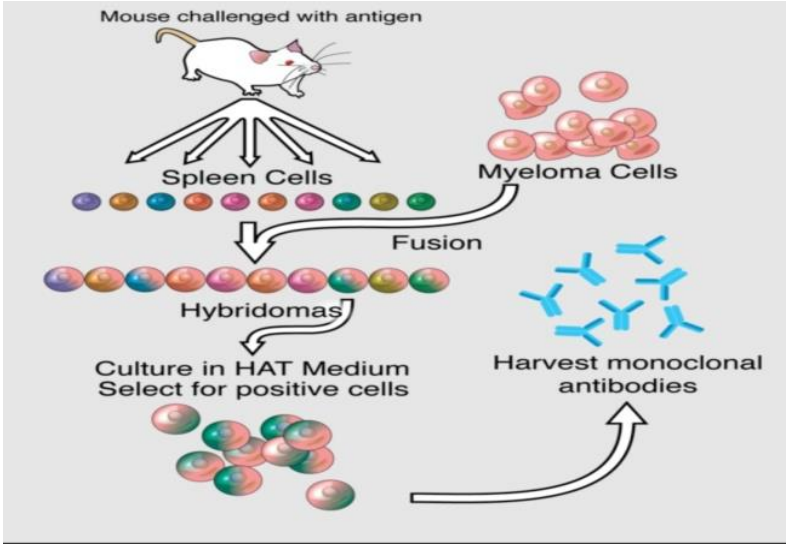

Figure 2: Production of Hybridoma Technology

Phage Display:

In 1985, G. Smith created phage display technology to show the peptides on the surface of lysogenic filamentous bacteriophages. Since then, this technology has emerged as a key technique for creating a vast array of peptides, proteins, and antibodies based on the physical connection between the genotype and phenotype of the phage (phage coat fusion protein).

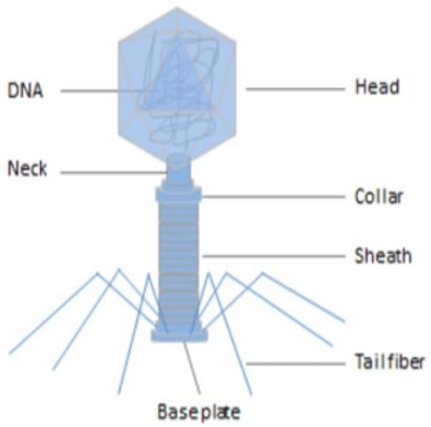

Figure 3: Bacteriophage

Rituximab

Through a variety of mechanisms, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and activation of apoptosis, the anti-CD20 chimeric monoclonal antibody rituximab kills B cells. Also capable of sensitizing cells to the effects of chemotherapy is rituximab. Numerous clinical trials have demonstrated the effectiveness of rituximab against CD20+ malignancies, making it the first monoclonal antibody licensed for use in cancer treatment.

In follicular lymphoma patients who have already received treatment, rituximab as a single medication has demonstrated a strong clinical response in multiple trials.

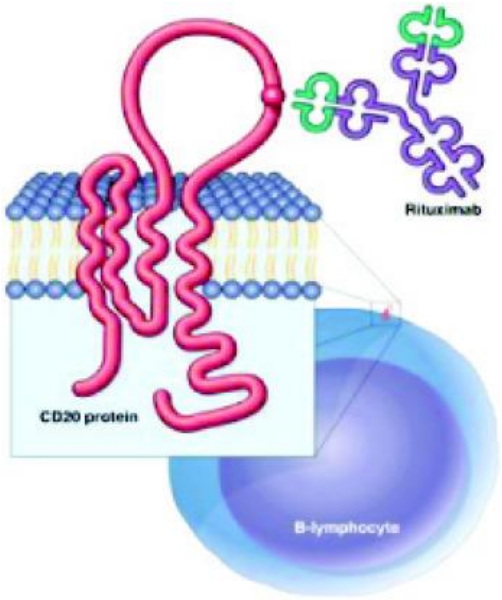

Figure 4: CD20 protein with binding site

Therapy

Rituximab (Mabthera; Produits Roche, Neuilly, France) was given intravenously at an initial rate of 50 mg/h; if no toxicity was observed during the first hour, the infusion rate was increased to 50 mg/h every 30 minutes, to a maximum rate of 300 mg/h. The infusion was interrupted if the patient experienced hypotension, edema, fever, rigors, dyspnea, or any other serious adverse effect; if that happened, the infusion was resumed at half the previous rate after the event was resolved.

Rituximab combine with Immunotherapy

Rituximab has been combined with immune system modulators such as interferon-alpha (IFN-α), interleukin-2 (IL-2), IL-12, and G-CSF in a deliberate manner. The mechanisms through which immune modulators enhance rituximab's effectiveness include the amplification of CD20 expression, the augmentation of Fc receptor density on effector cells, and the increase in effector cell numbers. In a study involving 38 patients with relapsed or refractory indolent NHL, rituximab plus IFN-α did not result in any unforeseen outcomes.

Rituximab combine with Chemotherapy

Rituximab has been paired with various chemotherapeutic drugs, taking into account the distinct mechanisms of action of rituximab and chemotherapy, as well as the synergistic activity demonstrated in laboratory studies and the minimal overlapping toxicities. When used in combination with standard-dose CHOP as the initial treatment for a small group of 40 patients with indolent NHL, rituximab achieved response rates close to 100%, with a median time to disease progression of nearly seven years. Incidents of infusion-related reactions (IRRs) occurred in 19% of cases.

Mechanism of Action

Rituximab is a chimeric monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class, comprising a murine variable region (Fab region) and a human constant region (Fc region). The Fab region has variable sections that define a specific target antigen so the antibody can attract and secure an exclusive antigen, specifically the binding of rituximab (IgG1) to CD20 on pre-B and mature B lymphocytes. The Fc region is the tail end of the antibody that interacts with cell surface receptors to activate the immune system, in this case a cascade of events leading to the ultimate depletion of circulating B lymphocytes via complement-dependent cell lysis, antibody-dependent cellular cytotoxicity, and apoptosis. Rituximab increases cell lysis by targeting CD20, preserving hematopoietic and plasma cells that do not have this surface antigen. It has been proposed that complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) are two of the cell lysis mechanisms that rituximab causes.

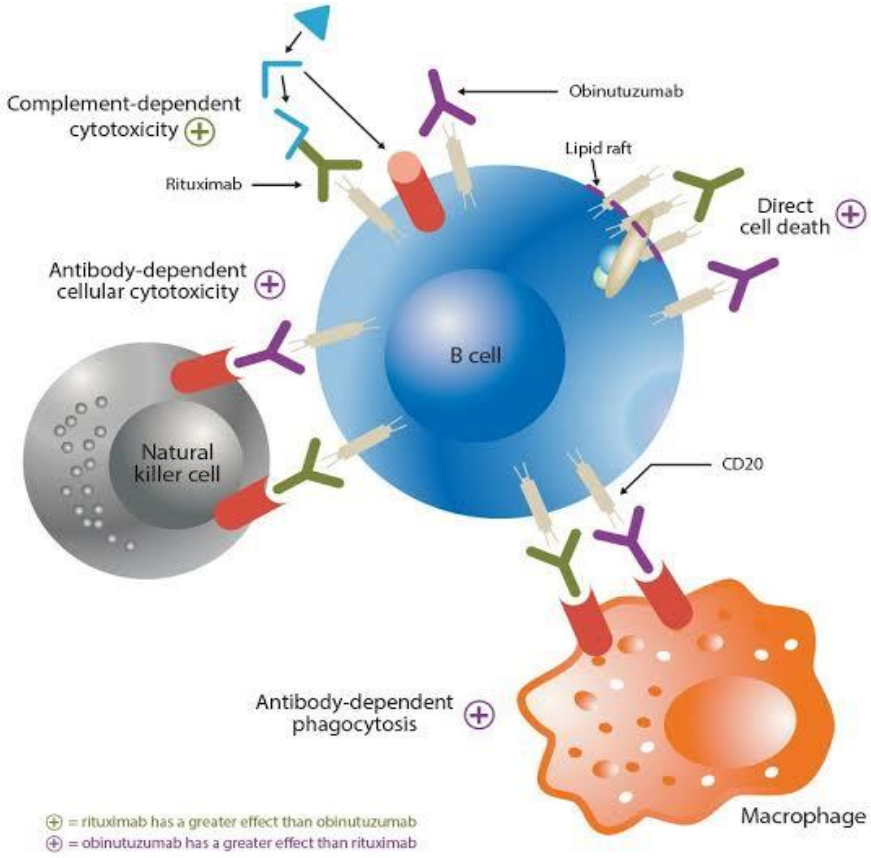

Fig. 5: Mechanism of Rituximab

Dose and Administration

When treating lymphoma, 375 mg/m2 of rituximab should be administered weekly for 4–8 weeks, or every 2-4 weeks in conjunction with the chemotherapy cycle. Vials containing 100 and 500 mg are available. To achieve a final rituximab concentration of 1-4 mg/mL, the drug dose is diluted in either 0.9% saline or 5% dextrose. Acetaminophen, a corticosteroid, and an antihistaminic such as diphenyramine are given as premedication 30 minutes before the infusion. For 30 minutes, the infusion is started very slowly at 50 mg per hour. After that, it is increased by 50 mg every 30 minutes.

Fig. 6: Rituximab Marketed Preparation

Adverse Effects

There are three types of rituximab side effects: acute, delayed, and immediate.

Infusion reactions are instantaneous reactions. They can be mild to moderate and are linked to fever, chills, nausea, pruritus, angioedema, headache, hypotension, bronchospasm, urticaria, rash, myalgia, and hypertension. Their incidence is approximately 25%.

Rarely, severe reactions like anaphylaxis that results in death, pulmonary infiltrates, acute respiratory distress syndrome, or cardiogenic shock can happen. Following rituximab treatment, patients with hematolymphoid malignancies run the risk of developing tumour lysis syndrome.

Rituximab depletes B cells, which lowers serum immunoglobulin levels and causes lymphopenia. Less than 5% of patients have neutropenia, anaemia, and thrombocytopenia. Reactivation of viral infections and bacterial infections are examples of infectious complications. Hepatic failure and fulminant hepatitis can result from hepatitis B reactivation. There have been reports of progressive multifocal leucoencephalopathy brought on by JC virus reactivation.

Due to severe cardiovascular side effects following initial treatment, kidney failure, tumour lysis syndrome, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy, the US FDA issued a black box warning on rituximab in February 2007.

Conclusion

The evolution of monoclonal antibody-based therapies marks a transformative phase in cancer immunotherapy. The development of hybridoma technology and phage display techniques has enabled the precise targeting of cancer cells, offering hope for more effective and less invasive treatments. Rituximab's success as a therapeutic agent, especially when combined with chemotherapy or immune modulators, illustrates the potential of these treatments to significantly improve patient outcomes in specific malignancies like non-Hodgkin's lymphoma. Despite these advancements, challenges such as overcoming immune resistance and managing adverse effects remain. Future research is essential to refine these therapies, expand their applications, and achieve sustained remission in diverse cancer types. This review underscores the promise of mAb-based therapies as a cornerstoneof cancer treatment, bringing us closer to improved prevention and more personalized, effective therapeutic strategies.

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