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Review Article

Monoclonal antibody: a cell specific immunotherapy to treat cancer

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ABSTRACT

Fundamentally, the therapy technique which is utilized in malignancy immunotherapy, monoclonal antibodies (mAb), is one of them, and it is used extensively as a treatment for the disease. To achieve more successful treatment, novel combination treatments and treatment procedures must be created. The purpose of this study is the improvement of mAb treatment and detail late advance and new limits, particularly in cancer therapy. With various keywords, we searched Google Scholar, PubMed, and Scopus for monoclonal antibody therapy as an alternate form of chemotherapy. The number of patients who received each therapy regimen, and the recovery rate are all displayed in this study, also a comparative study between monotherapy and chemotherapy. The result showed that rituximab had a greater overall response rate than other drugs, at 68%. In the combination treatment group (monotherapy+chemotherapy), 100% of patients had adverse events, compared to 84.2 percent in the monotherapy group. The pharmaceutical industry's fastest-growing medications, monoclonal antibodies are increasingly being examined in Clinical trials as stand-alone treatments or in conjunction with other therapies. It has a promising future since it will provide better tailored therapy and combination therapy for the treatment of cancer.

Keywords: Monoclonal antibody, Combined chemotherapy, Antibody-drug conjugates, Immunotherapy, Cancer

INTRODUCTION

The term “antibody” was coined by Paul Ehrlich in 19th century and he suggested the concept of antibodies as “magic bullet” that can be applied in any target cells without damaging other normal tissues; at the same time Emil Adolf von Behring came up with an idea on applying antibodies like immuno-therapeutics as he illustrates about immunity of diphtheria as well as tetanus might be delivered through transferring of the small amount of the serum via one animal to other.[1,2] That is why the concept of using monoclonal antibody (mAb) against cancer is being attractive day by day as it allow the major goal of cancer immunotherapy, which is to establish an unique treatment procedure that has the ability to kill specifically cancer cells by sparing other normal tissues.[3] It is developed against only a specific epitope rather than the whole epitope region of an antigen.[4] Monoclonal antibody is being more attractive as the alternative of the chemotherapy, because chemotherapy targets on the rapidly growing tissues of the body as cancer cell are comparatively rapidly growing, thus it leads to the unwanted incidence of damaging rapidly growing normal tissues (e.g., blood cells, cells lining GI tract).[5]

Muromonab is the 1st approved mAb by Food and Drug Administration (FDA) that is indicated for use in the prevention of kidney transplant rejection.[6] Muromonab is a murine origin mAb that was discovered by George Kohler and Cesar Milstein in 1975 by Hybridoma technology and they won Nobel Prize in 1984 for their contribution in immune system and production of monoclonal antibodies.[4]

But throughout clinical trial, it was observed that upon repeated administration of murine based mAbs in human, half-life is reduced & turns to be increasingly ineffective

with every individual administration. This complication arises because of human anti mouse antibody (HAMA) response in human which has been resolved by advanced rDNA technology and mouse origin mAbs are replaced by other types of mAbs such as chimeric, humanized or human antibodies.[4] There are 4 types of mAb available in which Murine mAbs are fully originated from the mouse, chimeric mAbs are produced by combination of constant region (65%) of human source and murine source whereas humanized mAbs are derived from mostly (90%) human source with a small part of the murine source, and the human mAbs are derived from fully human source engineered from transgenic mice. Among all the types of mAbs, Human mAbs have higher affinity to human antigens and has lower hypersensitivity response (Figure 1).[7] There are a lot of mAbs using in the immunotherapy for the treatment of cancer that targets and attach to a specific antigen of the surface of cancerous cells, thus preventing cell growth and disrupting certain downstream signaling cascades. First FDA approved monoclonal antibody against cancer is rituximab which is a chimeric mAb that is used in the 1st line treatment against Non-Hodgkin lymphoma, having the specificity of binding to CD20.[4] For nearly a decade, it was the best-selling oncology medicine, with $8.58 billion in sales in 2016.[8] The market of the monoclonal antibody drug is rapidly growing, and the market is being dominated by completely human.[9] Trastuzumab is humanized mAb widely used as 1st line treatment of metastatic breast cancer that works by targeting HER2. Pembrolizumab is also a humanized mAb that is used as 1st line treatment against metastatic NSCLC and melanoma through inhibiting PD-1 checkpoint molecule. Cetuximab is an example of chimeric mAb that inhibits the EGFR and used in metastatic colorectal cancer, NSCLC and metastatic SCCHN, as 2nd line treatment. Melanoma, NSCLC, renal cell carcinoma and Hodgkin's lymphoma can be treated by nivolumab that inhibits PD-1 molecule of immune checkpoint, it's a specific antigen-independent co-receptor containing fully human sequences and plays a key role in modifying immunological responses.[4]

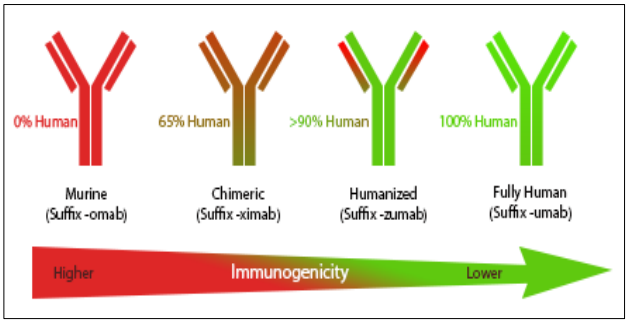

Figure 1: Schematic representation of different kind of monoclonal antibodies based on the origin of antibodies. Red area indicates murine origin and green areas indicates human origin antibody by chimerisation or humanization. Immunogenicity of is higher in murine origin antibodies compared to human origin antibody.

MONOCLONAL ANTIBODY PRODUCTION

The hybridoma method is a special laboratory method that was used to create mAb for the first time, this technique has long been a fundamental and remarkable invention to produce highly efficient mAbs.[1,10] This inevitable invention in 1975 by Georges Kohler and Cesar Milstein has revolutionized the immunotherapy concept, and enables researcher in the production of large quantities of monospecific antibody against any specific antigen.[11] In this technique, spleen cell inoculated with a particular antigen is fused with a myeloma cell line to make the survival antibodies immortal.[4] First step involves immunizing rats or mice with a particular antigen and then antibodies are raised against the antigen by stimulating through injection over a period, spleen is then removed in aseptic condition to isolate the immunized B-cells. Isolated B-cells are fused with HAT sensitive myeloma cell line in the presence of polyethylene glycol (PEG).[12] Fusion of primary B-lymphocyte with myeloma cells that is then cultivated in vitro within a selection medium result only to survive 'hybridoma' cells.[1]

Initially, the culture consists of a mixture of hybridoma cells created from several primary B-lymphocyte cells in which each of its secrete a unique antibody of its own.[1] These hybrid cells are then transferred to the ELISA plates by limiting dilution method where every single hybridoma cells in the wells generate a specific antibody against single epitope that is termed as "monoclonal antibody", screening is then performed to find out the desired antibody against the target antigen. Discovered hybridoma that produce desired antibodies are then taken into the culture vessel, cell lines can be cultured by both method-in vitro or in vivo.[12] The immortality of the hybridoma's myeloma component permits culture to become prolonged forever along with the specificity and therefore can be preserved for the generation of mAbs.[1]

Many other methods have developed in order to improve the efficiency of the fusion, selection process other than original technique and the extent of target epitopes against which the antibody can be made or the affinity of the antibody might be produced. Among these advanced methods, antibody phage display technology is nowadays a widely employed and powerful method for the generation of mAbs in which antibodies are exhibited on the outer layer of the phage by melding the coding arrangements of the immunizer variable areas to phage coat protein, antibody screening is also faster and cheaper in this techniques.[1,11] Since antibodies are cloned simultaneously as selection, they might be additionally modified to possibly improve their proclivity, modulate their explicitness, as well as to operate as an effector.[1] First mAbs produced by phage display technique is adalimumab, this is also first human antibody approved for the therapy.[11] The production of monoclonal antibody through hybridoma technology has been illustrated on the following Figure 2.

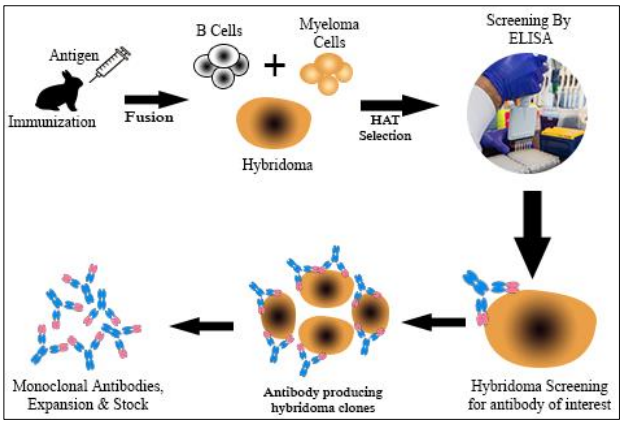

Figure 2: Illustration of monoclonal antibody production by hybridoma method. mAbs are produced through immunizing laboratory animals with a specific antigen. Extracted B cells and myeloma cells are fused and then selected in HAT medium. Thus, hybridoma producing antibodies are screened.

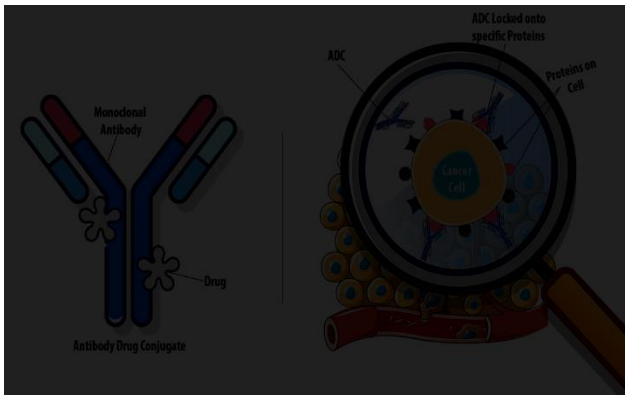

Figure 3: Illustration of mechanism of mAb-drug conjugate locking onto the target epitope of a malignant cell.

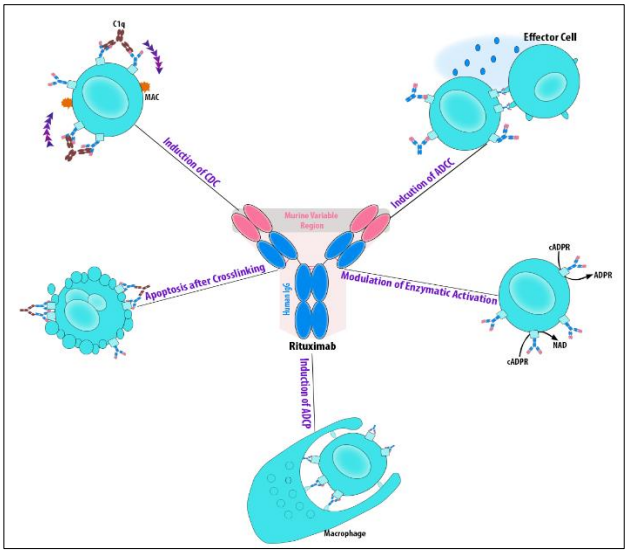

Figure 4: Illustration of different immune mechanism of the mAb drug "rituximab".

MECHANISM OF ACTION OF MABS IN CANCER THERAPY

Usually, the systems empowering remedial antibodies to hinder the development of or kill malignant growth cells can be partitioned into two classes. The components that have been proposed as assuming significant parts on the counter growth impact of mAb can be extensively isolated into those that work autonomously of invulnerable effector components and those that require safe effector co-operation. mAb mechanisms of activity that don't straightforwardly include resistant effectors incorporate enlistment of a demise signal intervened by cross connecting a surface receptor on the objective malignant growth cell or obstructing an enactment signal that is important for pro proceeding disease cell development. Antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and the ability of mAb to change the cytokine milieu or improve the advancement of a functioning enemy of cancer invulnerable reaction are all mechanisms that are vulnerable to the invulnerable framework.[13]

Antibody-dependent cellular cytotoxicity (ADCC)

ADCC, the immunizer needs to tie a particular antigen communicated on the surface of a malignancy cell. This occasion prompts the enrollment of invulnerable effector cells, like natural killer (NK) cell macrophages or neutrophils.[14] The immunizer's FC location connects with an FC receptor over an effector cell in this way. Enlistment of connector proteins and enactment of the effector cell is triggered by the commitment of an enacting FC receptor by a counteracting substance, resulting in the arrival of lytic chemicals such as perforin and granzymes, as well as the production of interferon-gamma. The latter may have a variety of effects, including inhibiting target cell proliferation, up-guiding MHC surface articulation, obstructing angiogenesis, and maybe powering an auxiliary T cell interceded resistant reaction. NK cells can also initiate the transduction of death signals to cancer cells by flagging death receptors (e.g. Fas/FasL). Remedial adequacy will be accomplished if the joined impacts of these components bring about resistant interceded annihilation of the adjoining growth cell. Right on time in vitro work and Murine models recommended ADCC as the critical effector component liable for the helpful impact of mAb focusing on growth antigens.[1]

Complement dependent cytotoxicity (CDC)

As a general rule, human antibodies including IgM, IgG1, and IgG3 are successful at initiating CMC.[13] A progression of supplement proteins present in serum interrupts the supplement course, which can be triggered by the limiting of the supplement protein C1q to the Fc location of an immune reaction tied to an objective growth cell. How much CDC is triggered by immune response restricting is reliant upon various elements including the level of antigen articulation and immune response restricting, the

supplement course can be disrupted by the limiting of the supplement protein C1q to the Fc location of an immune reaction tied to an objective growth cell surface and adversely direct supplement actuation.[1] The job of CMC has been most widely considered with the counter CD20 mAb rituximab that has a human IgG1 consistent area. In vitro studies have shown rituximab to be viable at inciting CMC. Some Murine models propose supplements as the focal instrument of activity for rituximab. Clinically, the supplements can be actuated briefly by rituximab imbuement. There is clashing proof concerning whether levels of supplement administrative proteins CD55 and CD59 assume a part in clinical reaction to hostile to malignancy mAbs including rituximab. In vitro studies exhibit a relationship between low CD55 and CD59 and more noteworthy CMC incited lysis of target cells. Still, no relationship has been found between the articulation of these proteins by threatening B cells and reaction to rituximab treatment. Subsequently, the significance of CMC in intervening the clinical enemy of lymphoma action of rituximab is indistinct. It is expected that supplement plays little part in the reaction of strong cancers to mAb, although this has not been tried broadly.[13]

Antibody-dependent cellular phagocytosis (ADCP)

Though the vast majority of the cell cytotoxic movement initiated by mAbs has been ascribed to ADCC, ADCP is likewise a significant instrument for the expulsion of malignant growth cells during mAb treatment. To summarize, ADCP is initiated by FcR-bearing effector cells, such as monocytes, macrophages, and neutrophils, recognizing the Fc space of an immunizer opsonizing an objective cell.[14] As a result, phagocytes suck up the opsonized cells or cell fragments, causing their final debasement. There is currently solid pre-clinical proof to help that this is a significant remedial system for antibodies like trastuzumab (hostile to HER2). What's more, rituximab (hostile to CD20) and expanding proof of the clinical significance of this instrument. The course of neutralizer works with antigen take-up and display by antigen-presenting cells, particularly dendritic cells and macrophages, similar to ADCP, which can cause direct cancer cell death. The antigen-introducing cell's Fc receptors detect a neutralizer that is restricted to apoptotic cells or their film sections, boosting antigen take-up, display, and acceptance of flexible resistance. Even though TAMs are possibly powerful invulnerable effector cells, they can similarly effectively advance cancer development, improvement, and invulnerable avoidance. They show heterogeneity of articulation of FcγR and cytokine discharge, with unmistakable proinflammatory (M1) and supportive of growth (M2), aggregates perceived. All things considered, the aggregate of inhabitant TAMs will impact the adequacy of ADCP and that helpful mAbs might be more viable in growths where there is a prevalence of M1 TAMs. Polarization of TAM towards an M2 aggregate may subsequently advance cancer development, yet additionally limit the efficacy of monoclonal immunizer treatments.[1]

Signaling modulation

By nature, malignancy cells have dysfunction of development markers that control cell expansion and tolerance. On the off chance that such flagging particles are communicated on the cell surface, then, at that point, focusing on monoclonal immune response might repress multiplication and promote cell passing.[1] Rituximab is a well-known example. It is linked to CD20's extracellular circle. CD20's physiological role is underappreciated, even though it has been identified as a calcium channel, among other things. Limiting rituximab to CD20 induces death in malignant B cells and is linked to CD20 re-localization to the layer microdomain, according to the researchers. Because malignant B-lymphoid cells newly dissociated from rituximab-treated patients showed features of apoptosis, this direct proapoptotic effect of rituximab can also happen in patients. In contrast to rituximab, which does not cause CD20 to relocalize to pontoons, CD20 antibodies that target unexpected epitopes are far more effective in initiating apoptotic cell death. The concentrating of the EGFR with cetuximab, a monoclonal antibody (mAb) that inhibits EGF restricting to EGFR and hence repeals pro-survival mutagenic motioning by this receptor, is a second prominent model. Cetuximab therapy inhibits the development of EGFR-bearing cancer cells in vitro. The contribution of the EGFR bar to the overall remedial impact in comparison to other impacts, such as ADCC and ADCP, is still unclear in patients treated with cetuximab. The third paradigm involves antibodies that target agonistic TNF-related apoptosis-initiating ligand receptors. The outer root of apoptosis is triggered when these mAbs are restricted to their aim, which may be aided by the Fc gap of the restorative protein. Additional cross-connection of the TRAIL receptor on the cell surface achieves this effect.[14]

Immune cells targeting

T-cells regulatory

One strategy to manage risk immunotherapy is to concentrate on the effector cells that contribute to the safe suppressive better microenvironment. CD4+, CD25+ T cells, also referred to as authoritative T cells, send inhibitory signals to susceptible cells.

CD40

CD40, which is a TNF family receptor that when activated releases IL-12, which enhances MHC articulation and antigen display by APCs. CD40 can affect B cell malignancies, melanomas, and other potent cancers.

Targeting the microenvironment of the tumor

TGF-β

As previously stated, medicines that inhibit the anti-cancer immune response and promote cancer cell proliferation

improve the cancer environment. Increased TGF levels, which are produced by Tregs and a few hazardous development cells.

Pick out solid tumors

EGFR

EGFR is found in cancers of the colon, ovary, neck and head, lung, and dangerous gliomas, among others. Through activation of the MAPK and AKT pathways, EGFR flagging causes cell proliferation, migration, and assault.

HER2

Quality-enhanced HER2 is seen in roughly 30% of breast cancers, as well as some adenocarcinomas of the gastrointestinal tract, prostate, ovary, and lung.

IGF

The insulin-like development generator receptor (IGF-1R) is thought to play a crucial role in change and cell development, and it has been found in a wide range of malignancies.

RESULT AND DISCUSSION

Atezolizumab is a humanized Fc-engineered monoclonal antibody. It creates bond with programmed death ligand-1 (PD-L1). Atezolizumab also prevents from interacting with the PD1, programmed cell death protein-1 and B7.1 receptors or CD80. This unblocks the immune response inhibition mediated by PDL1/PD1, allowing the antitumor immune response to reactivate. In single-arm trials, atezolizumab treatment resulted in verified objective antitumor responses in 15–25 percent of patients. The safety profile suggests that most patients tolerated atezolizumab well, with fatigue, nausea, reduced appetite, constipation, pyrexia, and urinary tract infection being the most prevalent side effects (20%).[16] Monoclonal antibody avelumab attach with the PD-L1 in humans that blocks the connection between PD-L1 and PD-1. As a result, T-cell reactivation, and effector cell actions against tumor cells. The objective response rate was 46.7 percent among 240 evaluable patients (complete response in 22.9 percent, including 3 of 16 possibly immunocompromised individuals), and illness control was 71.2 percent. There were no new safety signals discovered.[17] Combination treatment with bevacizumab outperformed monotherapy in terms of ORR and OS. In combination medication, however, greater grade 3/4 consumption-related adverse reactions were reported than in using single monotherapy treatment. Combination treatment had considerably better ORR, OS, and PFS than monotherapy.[18] 4.5% keratitis, 27.3% stomatitis, 40.9% hypomagnesemia, 77.3% skin responses, and 13.6% paronychia were the most common adverse effects associated with cetuximab after cetuximab-containing chemotherapy following immunotherapy. On cetuximab-containing chemotherapy following immunotherapy, 40.9 percent of patients had a partial response, 45.5 percent had stable illness, and 13.6 percent had progressing disease, providing an ORR and DCR of 40.9 percent and 86.4 percent, respectively.[20] The FDA authorized the first formulation of daratumumab, which has been used in most clinical trials. The formulation for use under the skin was recently authorized as well. Infusion responses, which include nasal congestion, headache, throat irritation, vomiting, cough, fevers, chills, and nausea were the most prevalent adverse effects of daratumumab when used alone or in combination with any backbone medication. Human monoclonal antibody, daratumumab is directed against a specific epitope through the receptor of CD38 glycoprotein. It kills cells by activating immune effectors that rely on antibody-dependent cellular cytotoxicity pathway, Fc. Complement-dependent cytotoxicity pathway, crosslinking-mediated apoptosis pathway, and antibody-dependent cellular phagocytosis.[42]

Human immunoglobulin G1 monoclonal antibody, durbalumab decreases the binding of PD-L1 to PD-1 and CD80. The inhibition allows T lymphocytes to detect and destroy tumor cells. 63.9 percent of patients experienced a treatment-related AE of any severity. Fatigue, diarrhea, and a loss of appetite were the most reported symptoms.[23] Elotuzumab had an ORR of 1.4 percent when used alone. Pyrexia and weariness were reported as adverse events in 17.6% and 8.8% of participants, respectively. Humanized monoclonal antibody, elotuzumab (elo) has been shown to be effective as a single agent as well as combination form for the treatment of patients having multiple myeloma with RRMM and newly diagnosed multiple myeloma (NDMM).[24] Dinutuximub binds to surface GD2 and causes tumor regression through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Patients having high-risk Neuroblastoma get aggressive chemotherapy and stem cell transplantation, leaving them immunocompromised.[22]

The immunoglobulin (Ig) G1 isotype, Ipilimumab enhances antitumor response by binding to anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) selectively. AEs affect 69.5 percent of people. The most common ADRs were diarrhea (12.4 percent), liver problem (9.9%), and colitis (8.0 percent). Serious ADR occurred in 40.8 percent of cases.[25]

A new anti-CD38 immunoglobulin G1 kappa mAb, isatuximab allow to create bond with a particular epitope on CD38. Mainly isatuximab targets the tumor cells via a variety of path, including antibody-dependent cellular phagocytosis, antibody-dependent cellular cytotoxicity, immune cell depletion/inhibition of immunosuppressive cells, and complement-dependent cellular cytotoxicity, according to preclinical studies. Isatuximab, on the other hand, appears to be unusual surrounded by anti-CD38 mAbs in that it can elicit direct apoptosis without the need for cross-linking. 23% cough, 37% Fatigue, 24% upper

respiratory tract infection, and 32% nausea were the most prevalent TEAEs (>10%), omitting hematological TEAEs and IRRs. Isatuximab-related TEAEs of grade 3/4 were seen in 17% of individuals. In 43 percent of patients, serious TEAEs were noted.[26]

With mogamulizumab, the overall response rate (ORR) was 28 percent against 4.8 percent with vorinostat. In individuals with stage III illness, mogamulizumab enhanced ORR by 22.7 percent compared 0. The ORR was 30.1 percent among patients who switched from vorinostat to mogamulizumab. Infusion-related events (33.2 percent vs 0.5 percent) and skin eruptions attributable to medication were among the TEAEs that occurred in more than 20% of patients with mogamulizumab versus vorinostat (23.9 percent versus 0.5 percent). Diarrhea (61.8 percent versus 23.4 percent), nausea (42.5 percent versus 15.2 percent), thrombocytopenia (30.6 percent versus 11.4 percent), dysgeusia (29.0 percent versus 3.3 percent), and elevated blood creatinine were all more prevalent with vorinostat than with mogamulizumab (28.0 percent versus 3.3 percent).[27]

Necitumumab is a monoclonal antibody made from recombinant human immunoglobulin G1 that binds to EGFR with high affinity and blocks the receptor from being activated by other ligands. This inhibits downstream signaling, disrupting cell cycle progression and mitosis, blocking apoptosis suppression, and reducing angiogenesis via effects on angiogenic factor synthesis.[43] Completely humanized monoclonal antibody, Pembrolizumab stops the interactivity of PD-1 with its PD-L1, ligands, and PD-L2. Patients with earlier treated PD-L1–positive advanced cervical carcinoma, monotherapy exhibited good anticancer efficacy and tolerable safety. Hypothyroidism (10.2 percent), reduced appetite (9.2 percent), tiredness (9.2 percent), and diarrhea (8.2%) were the most prevalent treatment-related AEs.[44]

The ORR for obinutuzumab (44.6%) was greater than rituximab (33.3%) when they used on patients with follicular lymphoma. Cough and infusion-related responses, which were greater in the obinutuzumab arm. But there were no new safety signals for obinutuzumab. A chimeric type I anti-CD20 mAb, rituximab has improved outcomes in patients with aggressive and indolent B-cell chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL). Obinutuzumab outperformed rituximab in terms of ADCC (antibody–dependent cell-mediated cytotoxicity), B-cell depletion, direct cell death induction in nonhuman monkey lymphoid tissues and whole human blood, and anticancer efficacy examined in human xenograft models.[32] Pertuzumab attach to HER2's extracellular domain II. It works in tandem with trastuzumab, blocking ligand-dependent HER2–HER3 dimerization and sending signal via intracellular pathways such as phosphatidylinositol 3-kinase (PI3K/Akt). Pertuzumab has been demonstrated to have anticancer efficacy in both neoadjuvant situations and metastatic. This Mab is presently being evaluated in adjuvant situation.[37] Human monoclonal antibody, ofatumumab wants to create bond with a specific epitope on the CD20 protein that consists of both tiny and big loops. In vitro, ofatumumab activates antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity (CDC) to kill primary tumor cells and a panel of tumor B-cell lines. Cells with low CD20 expression levels, such as complement-resistant B-cell lines and freshly separated CLL cells, ofatumumab shows greater C1q binding and more robust CDC than rituximab.[45] The adverse event rate for ofatumumab treatment in severely pre-treated patients having poor-prognosis chronic lymphocytic leukemia was found to be 29 percent. Neutropenia (ten percent), thrombocytopenia (five percent), anemia (three percent), pneumonia (17 percent), and fever (3%) were among the grade 3–4 side effects (3 percent). The overall response rate was 22%.[33]

In terms of safety, diarrhea (thirty four percent versus twenty three percent), nausea (seventy three percent versus fifty two percent), mucositis (fifty three percent versus thirty five percent), fatigue (sixty nine percent versus sixty nine percent), vomiting (forty five percent versus nineteen percent), and musculoskeletal pain (sixty four percent versus twenty five percent) were the most commonly reported all-grade adverse events (AEs) in the olaratumab group versus chemotherapy, respectively (20 percent versus 9 percent). Lympopenia (77 percent versus 73 percent), neutropenia (65 percent versus 63 percent), thrombocytopenia (63 percent versus 44 percent), and hyperglycemia (52 percent versus 28 percent) were the most prevalent all-grade hematologic AEs (Gina Columbus, 2019). Completely human monoclonal antibody, Panitumumab attacks epidermal growth factor receptor (EGFR). It had been used for patients with wild-type Kirsten rat sarcoma viral oncogene homologue (KRAS) cancers who have progressed despite receiving conventional chemotherapy.[35]

Rituximab as combination with chemotherapy used in induction treatment for CD20+ B-NHL (CD20 positive B-cell non-Hodgkin lymphomas). On the other hand, In CD20+ B-NHL induction treatment, obinutuzumab significantly improved PFS but has a greater incidence of AEs than rituximab. 90Y-ibritumomab tiuxetan enhanced ORR and Ofatumumab lowered ORR.[46] Trastuzumab in addition to chemotherapy showed the higher ORR that is 60 percent. When coupled with trastuzumab a taxane-based regimen provided a higher PFS in HER2-positive patients. But it didn't show same effect of an OS advantage when compared to nontaxane-based regimens.[41]

Comparisons with monoclonal antibody as single monotherapy and combination monoclonal antibody and chemotherapy monotherapy serve to provide the unambiguous observation after their safety and effectiveness data (Figure 6).

The nivolumab group had a 19.3 percent ORR compared to 21.5 percent in the chemotherapy arm, recurring

metastatic esophageal squamous cell carcinoma (ESCC). Rashes, diarrhea, reduced appetite, constipation, upper respiratory tract infection, musculoskeletal discomfort, cough, pneumonia, pyrexia, anemia, pruritus, lethargy, hypothyroidism and nausea were the most prevalent side effects in 10% of patients who received nivolumab.[31]

In the necitumumab arm, the ORR was 31%, compared to 29% in the chemotherapy-only arm. The group of necitumumab had a disease control rate that is eighty-two percent (ORR plus stable illness), while the chemotherapy group had seventy-seven percent disease control rate. In contrast to 62 percent of patients treated with chemotherapy alone, 72 percent of patients treated with necitumumab had adverse effects. Hypomagnesemia (9 percent versus 1%), skin rash (4 percent versus 1%), and venous thromboembolic events were all substantially more common in the necitumumab/chemotherapy arm (5 percent versus 3 percent). In the necitumumab/chemotherapy group, adverse events led to treatment discontinuation at a rate of 31%, while in the chemotherapy alone arm, it was 25%. Adverse events with a mortality consequence were reported in 12% and 11% of the cases, respectively.[28] PD-L1 tumors patients were seen in both the combination treatment and monotherapy pembrolizumab groups. The objective response rate (ORR) and median overall survival (OS) were not statistically different between the monotherapy groups and the combination treatment (47.4 percent versus 54.5 percent). In the combination treatment group, 100% of patients had adverse events (AEs), while in the monotherapy group had 84.2 percent AEs (adverse event), while in the combination treatment group showed 100% AEs. Treatment discontinuations proceed when patient owing to AEs was more common in the monotherapy group and in combination treatment group (21.1% versus 45.2%) at one year.[47]

Table 1: Name of monoclonal antibody, antigen, indication and their safety and efficacy data.

Name	Antigen name	Indication	Efficacy (%) (the overall response rate)	Safety study	Ref.
Atezolizumab (humanized IgG1)	PD-L1	Urothelial carcinoma, non-small cell lung cancer (NSCLC), (2016) TNBC-triple-negative breast cancer (2019) ES-SCLC (extensive-stage small cell lung cancer) (2019, March 18)	14.8	Common AEs ≥20% 11% diarrhea, 19% fatigue 11% nausea, 3% pyrexia, 10% pruritus, 3% dyspnea and 2% pneumonitis, and 4% pneumonia	16
Avelumab (humanized IgG1)	PD-L1	Merkel cell carcinoma (MCC) (2017, March 23)	46.7	Diarrhea, fatigue, nausea, musculoskeletal pain, infusion-related reaction, rash, peripheral edema, and reduced appetite (88%); serious AEs: anemia, acute kidney injury, abdominal pain, asthenia, cellulitis and ileus (1%)	17
		Urothelial carcinoma (2017, May 9)		Death 6%; adverse effect 41%; serious adverse effect: urinary tract infection, musculoskeletal pain, creatinine increased, dehydration, hematuria, intestinal obstruction, and pyrexia 2%; common AEs-20% infusion-related reaction, fatigue, musculoskeletal pain, decreased appetite, urinary tract infection and nausea	
Bevacizumab (human IgG1)	VEGF	Colorectal (2004), non-small cell lung (2006), renal (2009), glioblastoma	Disease control 31	Common AEs 20% hypertension, fatigue, neutropenia/fever, hand-and-foot syndrome, diarrhea, nausea/vomiting, and sensory neuropathy	18

Continued.

Name	Antigen name	Indication	Efficacy (%) (the overall response rate)	Safety study	Ref.
		(2009), and ovarian (2018) cancers, breast cancer in 2008			
Cemiplimab (human IgG4)	PD-1	Locally advanced CSCC or CSCC (cutaneous squamous cell carcinoma) (2018, Sept 28)	58	Serious AEs: pneumonitis, hypo- and hyperthyroidism, infusion reactions, hepatitis, adrenal insufficiency, colitis, nephritis, and diabetes mellitus; common AEs: diarrhea, rash and fatigue	19
		Advanced NSCLC-non-small cell lung cancer (2021, Feb 22)	37		
		Locally advanced basal cell carcinoma (laBCC)	29		
Cetuximub (chimeric IgG1)	EGFR	HNSCC (head and neck squamous cell carcinoma), (2006). colorectal cancer (2004)	40.9 10 to 13	Acne-like rash, fatigue, vomiting, nausea, fever/chills, infusion-related reactions, and diarrhea	20
Daratumumab (human IgG1)	CD38	Multiple myeloma (2015)	31.1	Common AEs ≥20%, upper respiratory tract infection, fatigue, neutropenia, nausea, cough, back pain, anemia and thrombocytopenia	21
Dinutuximub (chimeric IgG1)	GD2	Neuroblastoma (2015)	40 - 50	Infections, infusion-related responses, low blood pressure, and discomfort	22
Durbalumab (human IgG1)	PD-L1	Urothelial bladder cancer (2017)	31.0	Adverse effect: 63.9 percent of the population. Fatigue 13.1%, nausea 6.6 percent, pyrexia 6.6 percent, diarrhea 9.8%, appetite loss 8.2%, arthralgia 6.6 percent, asthenia 6.6 percent	23
Elotuzumab (humanized IgG1)	SLAMF7	Multiple myeloma (2015)	1.4	17.6% and 8.8%, respectively, had pyrexia and tiredness	24
Ipilimumab (human IgG1)	CTLA-4	Melanoma (2011) and renal cell carcinoma (2018)	10	69.5% common: diarrhea (12.4 percent), liver problem (9.9), and colitis (8.0 percent). Serious: 40.8 percent of cases, liver disease (6.9%), colitis (6.2%), and diarrhea (5.1%)	25
Isatuximab (chimeric IgG1)	CD38	Multiple myeloma (2020)	16.7	29.8%, upper respiratory infection, infusion-related responses, tiredness, hypertension, diarrhea, pneumonia, dyspnea, sleeplessness, bronchitis, cough, and back discomfort	26
Mogamulizumab (humanized IgG1)	CCR4	Cutaneous T cell lymphoma (2018)	28	54.9%; 20 percent: infusion-related events (33.2 percent), and drug-induced skin eruptions (23.9 percent); common : diarrhea (23.4%), nausea (15.2%), thrombocytopenia (11.4%), dysgeusia (3.3%), and elevated blood creatinine levels (3.3 percent)	27
Necitumumab (human IgG1)	EGFR	Squamous non-small cell lung cancer (2015)	31	72%, hypomagnesemia (9%), skin rash (4%), and venous thromboembolic events (5%); serious 48%	28

Continued.

Name	Antigen name	Indication	Efficacy (%) (the overall response rate)	Safety study	Ref.
Nivolimab (human IgG4)	PD-1	Melanoma (2014)	32	9% rash, itching, upper respiratory tract infections, and edema	29
		Lung (2015)	19	Hypothyroidism 20%, rash 17%, pneumonitis 10%, diarrhea 7%, hyperthyroidism 4%, hypersensitivity 3%, hHepatitis 1%, nephritis 1%, limbic encephalitis 1%, polymyalgia rheumatica 1%	30
		Renal cell carcinoma (2015)	21.5	79% nausea (14%), pruritus (14%), fatigue (33%)	28
		Esophageal squamous cell carcinoma (2020)	19.3	10%	31
Obinutuzumab (Humanized IgG2)	CD20	Chronic lymphocytic leukemia (2013)	44.6	15 percent in total; 64 percent of infusion-related reactions, 23 percent of people are tired; cough accounted for 21%, upper respiratory tract infection accounted for 9%, and pyrexia accounted for 6%. additional AEs include headache 8%, nausea 8%, diarrhea 7%, arthralgia 4%, decreased appetite 8%, asthenia 6%, neutropenia 3%, dizziness 4%, back pain 7%, bronchitis 7% etc.	32
Ofatumumab (human IgG1)	CD20	Chronic lymphocytic leukemia (2014)	22	A total of 29% of patients were thought to be directly linked to an adverse event caused by ofatumumab. 17% fever, 10% Neutropenia, 3% anemia, 5% thrombocytopenia, and 17% pneumonia were among the grade 3–4 side effects	33
Olaratumab (human IgG1)	PDGFRα	Sarcoma (2016)	18.2	Nausea (73%), tiredness (69%), musculoskeletal discomfort (64%), mucositis (53%), vomiting (45%), diarrhea (34%), and headache (20%). Common: lymphocytic leukopenia (77%), neutropenia (65%), thrombocytopenia (63%), and hyperglycemia (52%) and febrile neutropenia (13 percent)	34
Panitumumab (human IgG2)	EGFR	Colorectal cancer (2006)	33	Common: 94%, rashes (47 percent), acneiform dermatitis (39 percent), pruritus (36 percent), erythema (33 percent), dry skin (21 percent), and paronychia (20 percent); very common: ≥20%	35
Pembrolizumab (humanized IgG4)	PD-1	Melanoma (2014), various (2015)	39.6	Loss of appetite, tiredness, rash, pruritus, pyrexia, diarrhea, cough, musculoskeletal discomfort, dyspnea, nausea and constipation were only few of the symptoms; immune-mediated AEs: nephritis, pneumonitis, endocrinopathies, hepatitis, and colitis	36
Pertuzumab (humanized IgG1)	HER2	Breast cancer (2012)	3.4	93%, fatigue 17 percent, asthenia 17 percent, back pain 17 percent, diarrhea 48.3 percent, nausea 34.5 percent,	37

Continued.

Name	Antigen name	Indication	Efficacy (%) (the overall response rate)	Safety study	Ref.
				vomiting 24 percent, diarrhea 48.3 percent, nausea 34.5 percent, vomiting 24 percent, diarrhea 48.3 percent, nausea 34.5 percent, vomiting 24 percent, fatigue 17 percent, asthenia 17 percent. 3 percent of people get pain in their extremities. 7 percent of people have oropharyngeal discomfort.	
Ramucirumab (human IgG1)	VEGFR2	Gastric cancer (2014)	20.2	The rate of grade 3-4 toxicity was 9.6 percent, neutropenia was 5.4 percent, therapy was stopped in 3% of patients owing to toxicity	38
		Hepatocellular carcinoma (2019)	7	6% progression of malignant neoplasm, 2% elevated bilirubin level, 1% hyperbilirubinemia, 5% elevated aspartate aminotransferase level, 5% Ascites, 12% hypertension, 5% asthma, 5% thrombocytopenia and 5% asthma	39
Rituximab (chimeric IgG1)	CD20	B-cell lymphoma (1997)	68	Thrombocytopenia (31%), neutropenia (13%), and leukopenia (31%). (4 percent), hemoglobin levels dropped (2 percent), savage (10 percent), pruritus (ten percent), fever (eight percent), urticaria (eight percent), diarrhea (six percent)	40
Trastuzumab (humanized IgG1)	HER2	Breast cancer (1998)	49.4	44.1%	41

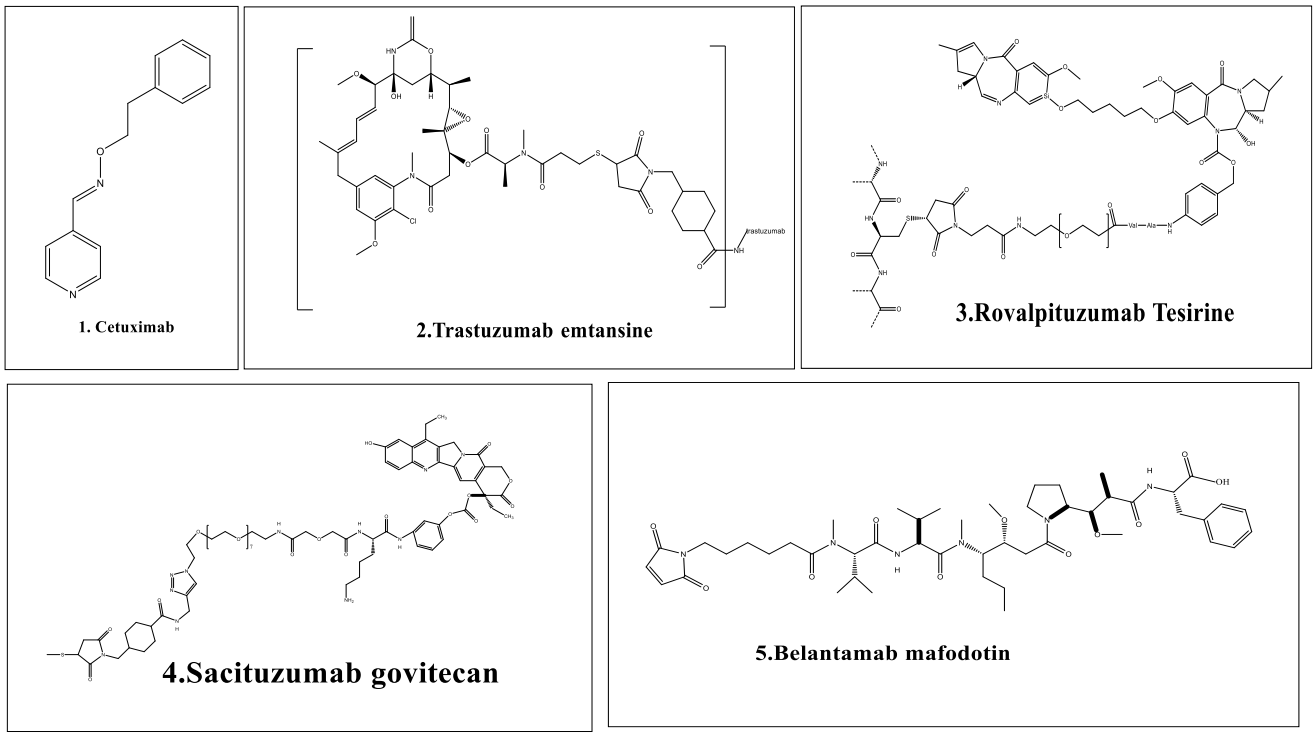

Figure 5: Chemical structure of different mAb drugs.

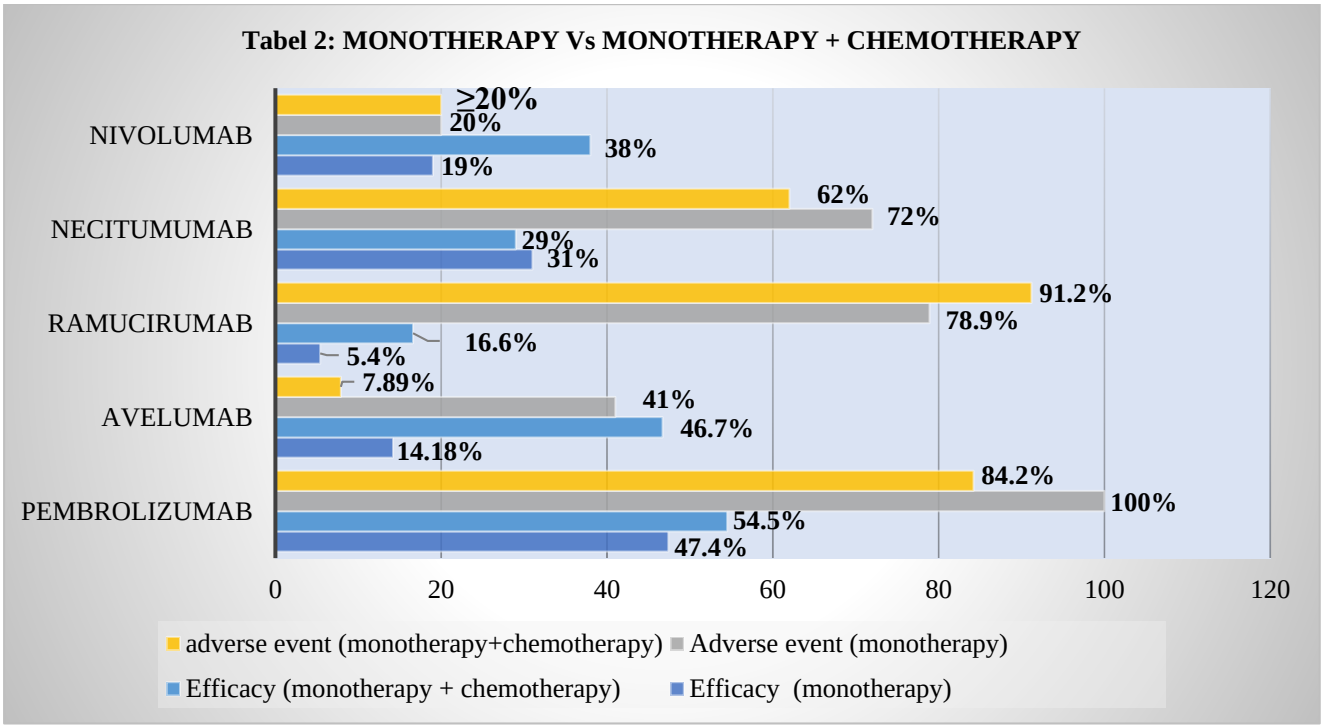

Figure 6: AEs and efficacy rate different mAb drugs upon administration of monotherapy and monotherapy+chemotherapy.

CONCLUSION

As compared to traditional chemotherapy, the side effects of unconjugated CmAbs are typically modest, but conjugated CmAbs cause significant side effects. There is no doubt that the development of CmAbs marked a significant step forward in cancer therapeutics, and with a higher success rate in bringing these drugs to market than small molecular drugs, pharmaceutical companies are expected to continue working toward more specific, less toxic, and cost-effective CmAbs.

The development of biomarkers, the discovery of appropriate tumor antigens, and the recognition of toxicity concerns are all key components of cancer immunotherapy's success. More efficacious treatments will be generated as the molecular and cellular elements of the malignant cells interacting become better understood. The current medical technique ensures that various carcinogenic mechanisms can produce one of the most effective interventions.

In a summary, monoclonal antibodies, the fastest-growing medicines in the pharmaceutical sector, are increasingly being tested in clinical trials as single agents or combinations with other treatments (e.g., other antibodies, vaccinations, and biologic medications, as well as standard cytotoxic chemotherapy, radiotherapy.). As a result, antibody medicines have a bright future ahead of them, offering improved customized therapy and combination therapy for cancer treatment.

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