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Monoclonal antibodies used for management of hematological disorders

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ABSTRACT

Objectives: Monoclonal antibodies (MAs) are increasingly becoming part of therapeutic armamentarium for hematologists and hemato-oncologists. There is paucity of review on majority of these antibodies in one place. The objective of this review is an attempt to fill the gap in paucity of review on majority of these monoclonal antibodies (MAs) in one place.

Material and Methods: 'Pubmed' and 'Scopus' database was explored focusing on monoclonal antibodies (MAs) in clinical hematological practice. Emphasis was given to the more recently published review articles on different monoclonal antibodies (MAs).

Results: In the present review, a total of 23 different monoclonal antibodies (MAs) were discussed; some are very frequently used and some rarely. Monoclonal antibodies (MAs) are used for treatment of diverse hematological conditions, i.e. malignant and benign disorders and at various phases of stem cell transplantation. These antibodies were used either alone or in combination with various chemotherapeutic agents, targeted small molecules or as immunoconjugates. Some of the side effect profiles of these antibodies were common and some were unique to the particular monoclonal antibody (MA). Unusual infections or organ dysfunctions were noted. Improved function of antibodies by protein engineering is also advancing rapidly. Dosage, frequency and route of administration depended on the convenience and condition for which the antibody is used.

Conclusion: Monoclonal antibodies (MAs) are going to stay for hematological practice. Some amount of familiarity with their usage, advantages, disadvantages and side effects are essential in clinical practice.

Keywords: Monoclonal Antibodies, Hematological Malignancies, Benign Hematological Disorders

INTRODUCTION

There has been tremendous advances in the therapeutics for hematological disorders over the last three decades, some of which has already been recorded elsewhere.[1,2] Nowadays many hematological disorders are treated with monoclonal antibodies (MAs) either alone or in combination with other drugs. Monoclonal antibodies (MAs) have found its use in hemato-oncology, red cell disorders and thrombotic disorders as well as in hereditary bleeding disorders. Every year a large number of monoclonal antibodies (MAs) enter the modern therapeutics and it is not easy to keep track with all these therapeutic antibodies. The present review has been planned to discuss commonly used monoclonal antibodies (MAs) in hematological practice. Broadly these antibodies are directed to various surface antigens of different cell types, i.e. lymphoid, myeloid, platelet, etc, or directed towards various adhesion molecules, soluble effectors like various

enzymes, activated complement components or may act like coagulation proteins or against various cytokines which drives in a dysregulated form in various hematological disorders. Therapeutically used monoclonal antibodies (MAs) are humanized or are chimeric so that these antibodies when used as therapy rarely elicit any immune reaction to produce anti-monoclonal antibodies (MAs). These monoclonal antibodies (MAs) may act directly through various mechanisms or they may act indirectly through immune or other effecter system or else they can be conjugated with various cytotoxic compounds or with various radio nuclides for targeting the cells or molecules of interest.

The story of successful application of monoclonal antibodies (MAs) in hematological disorders started with Rituximab in 1997. This is a chimeric monoclonal antibody (MA) against CD20 antigen of B lymphocytes.[3] The present review is focused on monoclonal antibodies (MAs) which are or has been in clinical use for hematological disorders either alone or in combination with other chemotherapeutic or other agents. These monoclonal antibodies (MAs) have been used against red cells, white cells and platelets. Some of them have been used for management of autoimmune disorders and in stem cell transplantation (SCT) either for the preparation or prevention of graft versus host disease (GVHD). Some of the antibodies have been successfully used to prevent cytokine storms associated with different hematological and non-hematological conditions and some have been used for congenital coagulation disorders in a way similar to coagulation factors.

The data for this review was culled from several databases like 'Pubmed', 'Scopus', 'IndMed' and others. Following monoclonal antibodies (MAs) have been used in hematological practice; some extensively and some sparingly. **Table 1** provides the list, dose and few of the main uses of monoclonal antibodies (MAs) used in hematological practice.

DESCRIPTION AND USES OF MONOCLONAL ANTIBODIES

1. Rituximab (MabThera^{R}, Rituxan^{R}): This is one of the first and most successful genetically engineered chimeric murine/human monoclonal antibody (MA) directed against the CD20 antigen on B lymphocytes. This antibody has been successfully used in combination with chemotherapy for various B cell non-Hodgkin lymphomas (NHLs) including follicular (FL) and diffuse large B lymphocytic lymphoma (DLBCL).[3,4] In addition, it has been used successfully with other immunomodulator like lenalinomide in the management of follicular lymphoma.[5] Moreover, this antibody has been used successfully in many autoimmune/alloimmune disorders as well as chronic graft versus host disease (GVHD) and B cell ALL.[6,7,8] In relapsed CLL, the antibody has been used with other therapy for longer disease control.[9] The drug has been used in subcutaneous mode also that has eased and simplified its administration on outpatient basis.[10] Since its induction in the market till today, PubMed recorded more than 20,000 references on the use of this antibody. It has also been used to prevent post stem cell transplantation Epstein–Barr virus disease in pediatric patients.[11] Quite a few allergic, infectious and non-infectious side effects have been recorded. Side effects and complications in using this antibody has been extensively reviewed.[3,12]

2. Daratumumab (Darzalex^{R}): The ligand for this human monoclonal antibody (MA) is expressed strongly on plasma cells and myeloma cells as CD38 antigen. Hence, this antibody is used for treatment of multiple myeloma (MM) patients. Initially used for treatment of refractory, stem cell transplantation (SCT) ineligible patients and now it is increasingly used with bortezomib, Imids and steroid along with other chemotherapy agents as a frontline.[13-15] This has been used also alone to maintain long-term disease control in multiple myeloma (MM). A variant of this molecule (Isatuximab) has also been used as a toxin conjugated cytotoxic therapy for myeloma cells.[15,16] As red cells also express this antigen, there could be difficulty in cross matching for red cell transfusion post Daratumumab therapy. Cytomegalovirus activation is also an important complication of this therapy.[17] Hemophagocytic syndrome has also been reported with its use. Like Rituximab this can also be given by subcutaneous route without losing its efficacy.[18] In addition to myeloma, the antibody has also been used AL amyloidosis with success.[19]

3. Belantamab: This afucosylated humanized monoclonal antibody (MA) is directed against BCMA (B Cell Membrane Antigen) and is being tried for relapse and refractory multiple myeloma (MM) particularly when the myeloma is resistant to Daratumumab; this product is used as an antibody toxin conjugate (Belantamab Mafadoxin).[20] Corneal deposit is one of the important side effects of the drug; hence regular eye examination is warranted.

4. Brentuximab (Adcetris^{R}): This chimeric (mouse/human) monoclonal antibody (MA) used as a complex with a toxin vedotin (MonoMethyl Auristatin E). The antibody is directed to CD30 antigen, a member of the TNF receptor family and is expressed in several types of cell. The drug is used in relapsed/refractory Hodgkin's lymphoma (HL), patients relapsing after autologous stem cell transplantation (SCT), for those relapsed/refractory patients who are ineligible for autologous transplantation or are at a high risk of relapse following transplantation.[21] Similarly, it has been used in peripheral T-cell lymphoproliferative disorders, Cutaneous T-lymphoproliferative disorders and in anaplastic large cell lymphoma.[22-23] CD30 expression in the malignant cell is a requirement for its use. This medicine should not be used simultaneously with bleomycin. Fatigue, fever, nausea,

Table 1: List of monoclonal antibodies (MA) used in hematological practice.

Sl. No.	Name	Specificity	Cell/Ligand	Dosage (IV)	Used in Diseases/Conditions
1.	Rituximab	CD20	B cell	375 mg/M^2	B-NHL, B-ALL, cGVHD, Auto-/alloimmune conditions
2.	Daratumumab	CD38	Plasma Cell	16 mg/kg	Multiple myeloma.
3.	Belantamab mafodotin	BCMA	B cell/plasma cell	2.5 mg/kg	MM Refractory to Daratumab
4.	Brentuximab vedotin	CD30	T cell	1.2–1.8 mg/kg	CD30 positive ALCL, PTCL, HD*
5.	Gemtuzumab Ozogomicin	CD33	Myeloid Cell	3 mg/M^2	Refractory AML
6.	Eculizumab	C5	Activated complement.	900 mg/2 wks	PNH, aHUS
7.	Alemtuzumab	CD52	T / B/ NK cell, Monocytes	3–30 mg	Refractory CLL, AA, GVHD, refractory Sezary syndrome
8.	Denosumab	RANK-L	T cell/ B cell osteoblast	60–120 mg$^+$/sc	MM (osteolytic lesion)
9.	Nivolumab.	PD-1	Lymphoid differentiation	480 mg	Refractory cHD failed on 3 therapy including Brentuximab. Relapsed/Refractory AML.
10.	Pembrolizumab	PD-1	as above	200–400 mg	Refractory cHD, MM, Follicular lymphoma.
11.	Ipilimumab.	CTLA4	T lymphocytes	3 mg/kg	MDS refractory to HMA & Post BMT relapse
12.	Milatuzumab	CD74	Blymphocyte	8 mg/Kg	Refractory B-NHL
13.	Blinatumumab	CD3/ CD19	Bispecific	28 ugm/24 h	Refractory ALL & CD19+ve malignancies
14.	Inotuzumab & Epratuzumab	CD22	Blymphocyte	0.8–1.2 mg/M^2 360 mg/M^2	Refractory B-NHL & Refractory B-ALL.
15.	Lumiliximab	CD23$^{\$}$	Blymphocyte	500 mg/M^2	Refractory CLL.
16.	Zanolimumab	CD4	T lymphocyte	980 mg/wk	Refractory PTCL, Sezary syndrome.
17.	Mogamulizumab	CCR4	T Lymphocyte	1 mg/kg/wk	Relapsed/Refractory Sezary syndrome
18.	Abciximab	GpII	Platelets	0.25 mg/kg, followed by max. 10 ug/min.	Angioplasty.
19.	Bevacizumab	VEGF-A	Endothelial cell	5–12 mg/ kg	Refractory HHT.
20.	Concizumab	TFPI	Coagulation Cascade.	0.15–0.25 mg/kg (SC)	Hemophilia A/B with inhibitors
21.	Emcizumab.	F VIII mimetic	Coagulation Cascade.	1.5 mg/kg/wk (SC)	hemophilia A with or without inhibitors
22.	Crizanlizumab	P Selectin	adhesion mol	5 mg/kg/bi-wkly	Sickle cell disease, IMF

Abbreviations used: AA – Aplastic anemia; aHUS – Atypical hemolytic uremic syndrome; ALCL – Anaplastic large cell lymphoma; ALL – Acute lymphoblastic leukemia; cHD – Classical Hodgkin's disease; cGVHD – Chronic graft versus host disease; CLL – Chronic lymphocytic leukemia; HMA – Hypomethylating agents; HHT – Hereditary hemorrhagic telangiectasis; IV – Intravenous route; IMF – Idiopathic myelofibrosis; NHL – Non–Hodgkin's lymphoma; MM – Multiple myeloma; PNH – Paroxysmal nocturnal hemoglobinuria; PTCL – Peripheral T-cell lymphoma; SC –Subcutaneous route; VEGF-A – Vascular endothelial growth factor alpha

vomiting, peripheral neuropathy and prolonged cytopenia are common side effects.

5. Gemtuzumab (Mylotarg^R): There had been no major advances in chemotherapy for AML since mid-70s when '3 + 7' therapy incorporating daunorubicin and cytosine arabinoside was initiated. Minor modifications including addition of etoposide or 6-thioguanine was not considered a major advance. CD33 antigen is generally expressed on most AML blast cells as well as on healthy myeloid cells. Gemtuzumab, the humanized monoclonal antibody (MA) against CD33 was covalently linked with a cellular toxin Calcheamicin. This antibody drug conjugate was called gemtuzumab ozogomicin (GO) and was introduced initially for elderly AML or high-risk elderly MDS patients where chemotherapy could not be used effectively. However, this drug was withdrawn from the market in 2010 because of high risk of developing veno-occlusive disease (VOD) of liver and other complications. The drug was reintroduced in 2018 as an important addition to AML therapy after it was found that veno-occlusive disease (VOD) incidence is dose related and rise sharply at or over 6 mg/M^2 dosage. At present recommended dosage (3 mg/M^2) the drug is a useful addition for AML patients particularly those with core binding factor mutation, APML patients where arsenic is contraindicated and as frontline therapy of

AML. It has also been used in relapse refractory AML for getting them into remission before stem cell transplantation (SCT). It should not be used with thioguanine as it increases veno-occlusive disease (VOD) incidence several folds.[24-25] As CD33 is also expressed over healthy myeloid cell and myeloid stem cells, this drug may produce prolonged neutropenia.

6. Eculizumab (Soliris®): This humanized monoclonal antibody (MA) against complement component 5(C5) from mouse has been very successfully used for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS) and neuromyelitis optica.[26,27,28] Bacterial, i.e. neisserial and meningococcal meningitis is one of the important side effects of this therapy; hence, all patients on this medication as chronic therapy must receive meningococcal vaccination[29] Once started for paroxysmal nocturnal hemoglobinuria (PNH), this therapy should not be suddenly stopped as the complement sensitive red cells which accumulates during the therapy may hyper-hemolyse in the absence of this inhibitor with attendant complications.

7. Alemtuzumab (Campath®, Lemtrada®): This is a humanized rat monoclonal antibody (MA) directed against common lymphocyte antigen CD52. This product has been used for refractory, resistant CLL, T cell malignancies, refractory Sezary syndrome, aplastic anemia unresponsive to anti-lymphocytic globulin and for graft versus host disease when other treatment fails.[29-32] This antibody is a strong immunosuppressant and has been associated with activation of CMV and other infections. Thrombo-hemorrhagic stroke and dissection of cervicocephalic blood vessels are also its important complications. The antibody has important use for conditioning before stem cell transplantation (SCT).

8. Denosumab (Xgeva®, Prolia®): This is a human monoclonal antibody (MA) directed to RANKL (Receptor Activator of NFk Ligand) and interferes its interaction with RANK (Receptor Activator of NFk) on osteoclast to prevent osteoporosis. This antibody is used in multiple myeloma (MM) and other malignancies to prevent osteoporosis where bisphosphonates are proven ineffective. It is given subcutaneously once in 4–6 weeks.[33] Increased osteonecrosis and osteomyelitis has been reported with its use.

9. Nivolumab (Opdivo®): It is a fully human IgG4 human antibody which blocks PD-1 (Programmed Death-1) receptors on activated T-and B-cells and rescues autoreactive T and B cells from apoptosis to act against tumor cells. Many other autoreactive T and B cells are generated with this drug explaining their large number of side effects which are mainly directed to different endocrine glands.[34] This antibody is a broad spectrum antitumor agent and has been successfully used in relapsed/refractory Hodgkin Disease which has become refractory to previous three management modalities including Brentuximab therapy, relapsed after autologous stem cell transplantation (SCT) and did not respond to Brentuximab.[35] This antibody has been tried in similar situation in Multiple Myeloma and in certain subsets of refractory/relapsed lymphoma.[36] The antibody is often used with ipilimumab (anti CTLA4) for stronger response when required.[37]

10. Pembrolizumab (Keytruda®): This humanized monoclonal antibody (MA) blocks attachment of PD-1 ligand to PD-1 receptor on hemopoietic or other malignant cells like nivolumab as described above and has similar complications and has been used for similar indications. This drug in combination with other imids or alone should be used under clinical trial conditions for relapse refractory multiple myeloma.[38] However, in relapse/refractory Hodgkin's disease it was found similarly useful as Nivolumab and has been approved by FDA for the use.[39] This drug has been associated with various hematological disorders like TTP (Thrombotic Thrombocytopenic Purpura) and autoimmune hemolytic anemia.

11. Ipilumab (Yervoy®): A fully humanized mouse monoclonal antibody (MA) directed against CTLA4 antigen (an inhibitory costimulator on T cells) and has been used alone or with PD1/PDL1 inhibitors for various solid tissue tumors but its role in hematological disorders except for refractory Hodgkin's disease in association with PD1 antibody is not established. A small subset of MDS patients responded to this therapy.[40]

12. Milatuzumab: A humanized monoclonal antibody (MA) directed to CD-74; linked with doxorubicin as the payload has received orphan drug status from FDA for the treatment of refractory multiple myeloma, refractory CLL and refractory non-Hodgkin lymphoma (NHL). It has also been used in combination with rituximab for refractory/resistant NHL.[41,42]

13. Blinatumumab (Blincyto®): This is an engineered humanized monoclonal novel class of antibody where one antibody with its two antigen detecting limb has two different sites to engage two different types of cells, i.e. malignant B cell and reacting normal T cells bringing T cell in close apposition of malignant B cell activating cytotoxic effect of T cell. This antibody is also called Bispecific T-cell engaging molecule (BiTe). The antigen on B lymphocyte detected by this antibody is universal CD19 antigen and the CD3 is the antigen detected on T cell. Blinatumumab is indicated in relapse/refractory Philadelphia negative ALL and also Philadelphia positive ALL which has become refractory to treatment.[43] About 19 percent patients developed manageable cytokine storm and the therapy does not preclude subsequent CAR-T cell therapy and has been successfully used as a bridge for allogenic stem cell transplantation (SCT).[44]

14. Inotuzumab (Besponsa®) & Epratuzumab (LymphoCide®): These two humanized monoclonal antibodies (MAs) are directed towards CD22 antigen on B lymphocytes and can be combined with toxin or other payloads for effective

therapy. Inotuzumab has calcheamicin (ozogomicin) as its toxic payload and has been used successfully in relapsed/refractory ALL while, epratuzumab and inotuzumab both have been used for refractory diffuse large B lymphocytic lymphoma (DLBCL).[44,45] These antibodies have also been tried to modulate immune response in various autoimmune disorders like SLE. Epratuzumab has also been tried for refractory CLL and follicular lymphoma.[46,47]

15. Lumiliximab: Chimeric human/macaca monoclonal antibody (MA) Lumiliximab is directed to CD23 antigen on B lymphocyte and has been used for refractory CLL /Follicular lymphoma.[46,47] It was not found to give significantly better results when combined with FCR (Fludarabine, cyclophosphamide and Rituximab) than FCR alone in CLL.[48]

16. Zanolimumab (Humax-CD4®): This is a human monoclonal antibody (MA) directed towards CD4 antigen of T lymphocytes. This antibody has been used for resistant cutaneous T cell lymphoma/mycosis fungoides and Sezary syndrome and proved quite effective in these conditions.[49] Recently the company discontinued the marketing of this drug for portfolio adjustments.

17. Mogamulizumab (Poteligeo®): This humanized afucosylated antibody directed towards CCR-4(chemokine receptor) receptors on regulatory effector T cells has been successfully used for peripheral adult T cell leukemia/lymphoma and refractory mycosis fungoides.[50,51]

18. Abciximab (Reopro ®): This Fab fragment of chimeric mouse/human antibody directed against the beta3 integrin GPII of platelets has been used in myocardial ischemia/infarction of Kawasaki disease.[52] This product interferes with platelet function for up to five days after a single injection. Some patient on this treatment may develop immune thrombocytopenia 16–20 days after treatment.

19. Bevacizumab (Avastin®): It is a mouse monoclonal antibody (MA) humanized through recombinant DNA technology against vascular endothelial growth factor–A (VEGF-A). By neutralizing this growth factor and preventing it to attach to its cognate receptors, this antibody prevents angiogenesis of various kinds and has been used for many solid tumors along with chemotherapy or other targeted therapies. In the field of hematology, it has found its usage to treat extensive hereditary hemorrhagic telangiectasia involving liver and lungs causing significant shunting of blood and mass lesion.[53,54] Currently this antibody is also being evaluated with other antibodies for immunotherapy of refractory multiple myeloma.[55] Because of its angiogenesis inhibitor effect it can cause innumerable side effects like gut perforation, non-healing ulcers and hypertension to name a few.

20. Concizumab: This is a humanized monoclonal antibody (MA) directed against tissue factor pathway inhibitor (TFPI); activates blood coagulation by increasing factor Xa and by doing so helps in congenital coagulation disorder like hemophilia A and B. However, in-appropriate activation of coagulation can also cause thrombosis and this has been one of the complications of this therapy. This antibody is to be given by subcutaneous route and it describes one of the novel ways of treating hemophilia without replacement of missing factor by relevant concentrates. After a single dose, this lasts in the system for more than two weeks, thus has the convenience of once in a fortnight or once in a month therapy. However, this product at present is not available in the market as it has some issues with dosage and inappropriate thrombosis which is being looked into in EXPLORER trials.[56,57]

21. Emcizumab (Hemlibra®): Like blinatumumab (where two different antigenic determinants carrying molecule on two different cells was brought together by a bispecific antibody), this humanized antibody brings factor-IXa and factor-X in very close proximity and this way it mimics (functions like) factor VIII. Hence, this product is used for congenital factor VIII deficiency (severe hemophilia A) with or without inhibitors. As it is a non-factor concentrate antibody molecule and has long half-life it can be used as once fortnightly or monthly dose given by subcutaneous route in contrast to factor VIII concentrates.[56,58] This is now one of the most successful product in the market for management of hemophilia A but unlike concizumab it cannot be used for hemophilia B. This product has also been successfully used for acquired hemophilia A.[59]

22. Crizanlizumab (Adakveo®): This humanized monoclonal antibody (MA) is directed towards P selectin on endothelial cells and has been successfully employed to treat vasoocclusive crisis in Sickle cell disease for which FDA has approved the product.[79,80] It has also been tested with Ruxolitinib for idiopathic myelofibrosis.[61].

23. Tocilizumab(IL-6, Actemra®), Infliximab(TNFα, Remicade®), Omalizumab (IgE, Xolair®) , Mepolizumab (IL-5, Nucala®) , Caplacizumab (VwF, Cablivi®): The series of monoclonal antibody (MAs) and nanobody (Caplacizumab) are directed against various cytokines, Ig E and Vwf. Tocilizumab and infliximab are largely used for hypercytokinanemia in different hematologic or non-hematologic autoimmune disorders like refractory graft versus host disease (GVHD), refractory lymphohystiocytosis syndromes and in dysregulated cytokine storm of CAR-T cell therapy.[62-65]. Omalizumab is used in disorders of basophils and mast cells and in allergic conditions to prevent Ig E mediated side effects.[66] Mepolizumab has been used for subsets of hypereosinophilic syndrome driven by IL-5.[67] Caplacizumab is single domain hypervariable region antibody (nanobody) which is being tested for acquired TTP.[68] It is directed against A1 domain of Von Willebrand protein and prevents adhesion of platelet with Von Willebrand factor hence can also be used as a novel antiplatelet agent.

MODIFICATIONS

Monoclonal antibodies (MAs) originally produced mainly in mouse and rats have been modified using recombinant DNA technology to modify its immunogenicity by various levels of humanization so that some antibodies are chimeric that is part human part mouse, some are humanized and some are fully human. These modifications change the immunogenicity of the product.

Monoclonal antibodies (MAs) can also be dissected into minimal binding sites (VH fragments, variable region) and they may be used in dimerised, multimerised states to produce nanobody and minibodies of varying affinity to the target. Moreover, being very small in size these antibody fragments can easily bind to those sites where normal antibody cannot access it due to steric hindrance.

Bispecific antibodies are another novel way of bringing two targets in close proximity for novel function. Here the two binding sites of the antibody have different target specificity like blinatumumab where malignant B-cell having CD19 antigen is brought in very close proximity to a cytotoxic CD3 positive T-cell by having anti CD19 and anti CD3 activity in two different limbs of the antibody resulting in cellular T-cell mediated cytotoxicity against malignant B cell. In a similar way, a product called Emicizumab can bring in close proximity factor IXa and factor X of coagulation system activating factor X and triggering blood coagulation.

Therapeutic antibodies may be tailor-made by removing Fc fragment (Abciximab) or by augmenting Fc domain-Fc receptor interaction by defucosylation or recombinant insertion of a different amino acid with different affinity or by alternative glycosylation for increasing its stability, biodistribution, etc.

Antibody drug conjugates or antibody conjugated with toxins or radioisotopes are also novel ways of increasing cytotoxic effects of antibodies without increasing the side effects. The conjugation of the antibodies with drugs/ toxins/ isotopes uses different types of linkers depending on how the target antigen-antibody complex is processed by the malignant cell. In a likewise manner, the antibodies may be coated with polyethylene glycol or liposome or may be attached to different nanoparticles for its improved performance as a therapeutic agent. These processes (**Table 2**) have been reviewed in several places.[69-71]

Table 2: Structure of conjugated monoclonal antibodies (MAs).

A. Nature of Conjugates:
- **a. Toxins:** Calcheamicin (from Micromonospora), Diphtheria exotoxin, Pseudomonas exotoxin A, Auristatin E (Dolabella auricularia, Sea Hare), Maitansine & Mayitansin derivatives (Maytenus serrata, Ethiopian plant).
- **b. Cytotoxic Drugs:** Doxorubicin, Paclitaxel.
- **c. Cytokines:** IL-2, IL-7, IL-15, IL-18, IL21, TNFα, Interferon α, GM-CSF.
- **d. Nano particles:** Albumin and other Biocompatibles
- **e. Oligonucleotides:** Si-RNA, Mi-RNA, Aptamers, Immunostimulatory, Noncleavable, Anti-sense and splice switching nucleotides.
- **f. Radioisotopes:**
  Beta emittrers: ^{131}I(Iodine), ^{90}Yt(yttrium). ^{153}Sm(Sammarium)
  Alpha emitter: ^{149}Tb(Terbium), ^{211}At (Astatine), ^{213}Bi (bismuth)
  Positron emitter: 152 Tb (Terbium).
  Gamma emitters are generally avoided for therapy because of their long path of ionization.

B. Nature of Linkers:
- **a. Non Cleavable:** Thioethers
- **b. Cleavable:** Hydrazone, Peptide, Disulfide, β Glucuronide bonded.

Biosimilars

Many different industrial houses produce monoclonal antibodies (MAs), as a result there could be multiple monoclonal antibodies (MAs) produced against the same antigens and may have similar activities or they may have been produced against different epitopes of the same antigens. These antibodies when produced against same epitope of same antigens are called biosimilars. However the efficacy, safety and quality of these products may differ. Unlike the small chemical molecules used in pharmacology where the chemical structure of the drug largely defines its pharmacology, the same cannot be said for large protein molecule like antibodies hence there is some reluctance of accepting biosimilars as of similar efficacy and toxicity. However, cost of biosimilar antibodies could be far less and may have wider applicability if harmonization is possible.[72] Rituximab has now largest number of biosimilars available in the market and some of them have been evaluated also. Biosimilar of rituximab has been available in India for some time and its result in lymphoma is encouraging.[73]

Several antibodies directed towards different epitopes of CD20 antigen have been developed and they are being evaluated for different malignant B-cell disorders and in autoimmune disorders, e.g. Ocrelizumab, Obinutuzumab, Ofatumumab, Ibritumomab tiuxetan, Tositumomab and Ublituximab. These are all active agents in the treatment of B cell lymphomas, leukemias, and B cell-mediated autoimmune diseases. They are monoclonal antibodies (MAs) which is human or humanized but all are directed towards CD20 epitope of B cells.[74]

Mechanism of Action

Monoclonal antibodies (MAs) have diverse mechanisms of action. For certain cytokines and complement activation

product, VwF neutralization or blockade etc. of the epitope is the clear and simple mode of action. For coagulation promoting activity the mechanism has been described under individual antibodies. For various anti-neoplastic functions when the antibody is just used as targeting molecules with cytotoxic payloads, radioisotopes, toxins, cytokines, etc. they produce cytotoxicity because of the payloads. These immune-conjugate antibodies are important areas of monoclonal antibody (MA) therapeutics.[70] These antibodies are attached to different kinds of payloads and have different kind of linkers to optimize the release of payloads at relevant site for minimizing the effects through its action on distant sites (Table 2). When antibodies themselves are used to kill malignant cells they do so by several mechanisms, i.e. complement mediated cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP) and antibody dependent apoptosis (ADA) and non-apoptotic cell death.[75] Monoclonal antibodies (MAs) involving check point inhibitors, i.e. those directed against PD-1/PDL-1 functions by activating body's own immune system to destroy malignant cells in the same way bispecific T-cell engagers destroy malignant cells through body's own T lymphocytes induced cytotoxicity. Certain monoclonal antibodies (MAs) like bevacizumab interferes with angiogenesis hence its direct use in HHT but vasculature is also a part of microenvironment whether hemopoietic malignancy or other solid tumors; hence this antibody is also used to control various tumors by manipulating its microenvironment and such compounds are increasingly being explored for hematological malignancies.[76,77]

Uses

Various protocols are used with different types of monoclonal antibodies (MAs). Some are used as the sole therapeutic agent like those used for nonmalignant hematological disorders. Some are used in various combinations with cytotoxic drugs/targeted therapy, etc. Generally monoclonal antibodies (MAs) are used by intravenous route but some of them like emcizumab are used subcutaneously and subcutaneous route for many standard monoclonal antibodies (MAs) like rituximab is increasingly used for ease of administration and convenience.

Side Effects

Some of the side effects are common and relate to hypersensitivity reaction to a protein and complement activation. This side effect is universal and is taken care of by slow infusion, paracetamol and prior corticosteroid and anti-allergic medications. These reactions are immediate. Some reactions, particularly in malignant hematological disorders depend on malignant cell load; higher the load more severe is the reaction. Tumor lysis syndrome as seen with chemotherapy may also be seen with monoclonal antibodies (MAs). Cytokine release syndrome (CRS) due to killing or immune activation of cells is also seen with several antibodies. Antibodies which suppress immune function can precipitate various types of infections specially CMV, herpes virus activation or progressive multifocal leucoencephalopathy. Check point inhibitors in addition produce other side effects specific to endocrine system due to autoimmune endocrinopathies. Hence, for each monoclonal antibody (MA) there could be specific side effects and hypersensitivity reaction. These drugs should be handled carefully and not only detailed knowledge and experience for its use is required but also understanding of so many biosimilars and new antibodies hitting the market every year are required. The package insert should also be carefully read before using them. The safety and side effects of monoclonal antibodies (MAs) has been reviewed elsewhere.[12,17,78] Antibody immunoconjugates produce additional and peculiar side effects.[70] Some of the antibodies have ophthalmic, cardiac, hepatic and hematological side effects.

DISCUSSION

In the present review some of the commonly used monoclonal antibodies (MAs) in hematological practice have been discussed. The area is ever expanding and with biosimilars, conjugates, engineered antibodies and with repurposing of the antibodies for many other conditions than the original ones for which the product was discovered makes this field of hemotherapeutics a rapidly progressive area.[71,79-80] Monoclonal antibodies (MAs) produce a different set of side effects compared to many other types of drugs used in hematology. Hence, they can be combined with various other types of therapies with significant improvement in outcome without increase in one type of side effects. Biosimilar antibodies put the hematologists and oncologists in a dilemma; many times the cost of therapy with biosimilar antibodies are two-to-three times less but results of robust trials with biosimilars are not always available.[81] One of the challenges of use of monoclonal antibodies (MAs) as against some of the targeted therapies is that the target may not be reachable due to the size of the antibody or if the target is intracellular then the bigger molecule that the antibody is composed of cannot be expected to enter the cell. To this effect various protein engineering techniques are being used to develop only variable part of the antibody molecule as nanobody, minibody, etc.[82,83] In addition to direct targets, monoclonal antibodies (MAs) are being developed to treat diseases through its interaction to surrounding stroma.[84] Every year many new monoclonal antibodies (MAs) with improved function or against newer antigens or epitopes are produced for novel use in hematological disorder and many antibodies similar to other antibodies existing for similar applications are developed. Details of these antibodies are regularly published in literature.[85]

CONCLUSION

Large numbers of monoclonal antibodies (MAs) are used in hematology practice. Some familiarity of them as to their usage is required for all practicing clinicians even if it is outside the scope of their own day-to-day practice. Moreover, how modern biotechnology and antibody engineering is changing the facet of this therapy is also worthy of understanding.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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