Monoclonal Antibodies (mAbs) Application in Cancer Immunotherapy

Subjects: Primary Health Care

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Clinical application of monoclonal antibodies (mAbs) immunotherapy to treat and manage many cancers has been successfully established in recent years. Primary solid tumors have been effectively treated and managed with antibody-chemotherapy conjugates. The development and establishment of therapeutic monoclonal antibodies require a complete understanding of tumor heterogeneity, intra-tumoral factors, protein engineering, and the interaction between cancer cells and the immune system. Researchers have now developed mAbs that target specific antigens in cancer cells and inhibit signals responsible for tumor growth and invasion. Monoclonal antibodies are simply synthetic proteins employed as immunotherapies to treat and manage some, but not all, cancers. Monoclonal antibodies are produced in four different forms, including murine, chimeric, humanized, and human.

Keywords: cardiomyocyte ; heart failure ; heart failure with preserved ejection fraction (HFpEF)

1. Development of Therapeutic mAbs

The production of mAbs uses hybridoma by coupling myeloma cells with desired antibody-producing B-cells, typically from murine protein sources (-omab) [1][2]. From hybridoma, clones based on antigen specificity and immunoglobulin class are screened and selected to produce a single epitope. However, mAbs derived from mice are restricted owing to the generation of the innate immune response in humans. Therefore, steps were taken to generate humanized antibody by chimeric fusion of part mouse and part human proteins (-ximab), by a small portion from mouse and a major portion of protein from human (-zumab), or fully human antibody by using only human proteins (-umab) to overcome deficiencies in the mouse immune system. Around 5% of humanized mAbs contains mouse-derived antigen-binding factor, and this portion of humanized mAbs is generally engineered from human sources. However, mAbs generated from hybridomas of human or humanized mouse origin systems using high-throughput immunoassays have the strongest affinities to antigens [3].

2. Types of mAbs

Three types of monoclonal antibodies are employed in clinics to treat cancer patients to boost their immune system includes (1) Naked mAbs, (2) Conjugated mAbs, and (3) Bispecific mAbs. Naked mAbs are not conjugated with drug or radioactive material [4]. Conjugated mAbs are radiolabeled and chemolabeled antibodies [5]. Bispecific mAbs consist of parts of two different binding fragments of Abs, attaching two different proteins and bringing two cells in proximity to one another.

3. Mechanism of Action of mAbs in Cancer Treatment

Monoclonal antibodies target cancer cells in different and unique ways [6][7][8][9]. Naked antibodies function by themselves without any type of conjugated drug or radioactive materials. Most naked mAbs bind to antigen-bearing cancer cells, healthy cells, and free-floating proteins. Naked mAbs work by boosting the host immune system against cancer cells by binding to an antigen-presenting cancer cell. For example, alemtuzumab binds to the CD52 antigen in chronic lymphocytic leukemia patients and attracts immune cells to destroy lymphocytes. Alternatively, naked mAbs bind to immune checkpoint proteins, thereby stimulating the host immune response. The drugs pembrolizumab, Nivolumab, and Cemiplimab bind to PD-1 protein, while Atezolizumab, Avelumab, and Durvalumab bind to PD-L1 proteins to inhibit the evasion of cancer cells from host immune response. CTLA-4, also known as CD152, is a protein receptor that mediates immune checkpoint function and down-regulates immune responses. The mAb drug conjugate Ipilimumab binds to CTLA-4, blocking the inhibitory signal, facilitating the killing of tumor cells by cytotoxic T lymphocytes. In contrast, conjugated (tagged, labeled, or loaded) mAbs are combined with a chemotherapeutic drug or radioactive elements and function as a

homing signal to deliver these drugs, or elements, directly to the cancer cells. An interesting example of a similar mechanism of action is the mAb drug trastuzumab that inhibits breast and stomach cancer cell proliferation by binding with HER2. An example of a radiolabeled antibody is ibritumomab tiuxetan which binds to the CD20 antigen on the surface of B-cells and delivers both drug and radioactivity to kill specific cancer cells. Another example of chemolabeled mAbs is brentuximab vedotin. It binds to the CD30 antigen on the surface of B-cells and attaches to a chemotherapeutic drug called monomethyl auristatin E. The bispecific mAb blinatumomab binds to CD19 protein on lymphoma cells and CD3 protein on immune T-cells, thus triggering T-cell cytotoxicity against leukemic B-cells.

4. Monoclonal Antibodies (mAbs) in Cancer Treatment and the Development of Cardiac Toxicity

Myocarditis is an inflammation of the heart muscle. ICIs causes myocarditis with the signs of dyspnea, fatigue, chest pain, palpitation, peripheral edema, or hypotension with elevated electrocardiogram and cardiac troponin (cTn) and sometimes no symptoms [10][11]. Similarly, ICIs can also cause inflammation of the pericardium, such as pericardial disease and pericarditis [12]. Monoclonal anti-CTLA-4 and PD-L1 are two major ICIs in immunotherapy. Monoclonal antibodies against PD-1 and PD-L1 are also an interventional therapy, as described in **Table 1** [13]. All immunotherapies have adverse side effects since activated immune responses can target nonspecific cancer cells, leading to frequent immune-related adverse events (IRAEs) or immune-related adverse reactions (IMARs) [14][15][16][17][18]. IRAEs can involve any organ in the gastrointestinal, hepatic, endocrine, pulmonary, cardiac, renal, ophthalmological, and nervous systems. IRAEs typically have delayed onset with prolonged low-grade symptoms that are, for the most part, treatable and reversible. However, some IRAEs can lead to permanent disorders among cancer patients. Monoclonal antibodies against CTLA-4, PD-1, and PD-L1 trigger IRAEs involving single organ systems, but they can simultaneously affect multiple organs in approximately <1% of patients [19]. The most common checkpoint-inhibitor-associated IRAEs are observed in the skin (34% of patients) with a rash over 30% of the patient's body. IRAEs can also affect the gastrointestinal tract, resulting in diarrhea or colitis occurring in 13% of cancer patients. Cardiotoxicity is rare, occurring in 0.04% to 1.14% of patients receiving immunotherapy. However, potentially fatal myocarditis and arrhythmias have been reported with a significantly higher associated mortality of 25% to 50%, indicating that cardiotoxicity must be a diagnostic/prognostic consideration as these therapies expand to meet the demand [20][21]. A meta-analysis for lung cancer that included 22 clinical trials of ICIs showed the incidence of other cardiovascular toxicities, including pericardial disease, myocardial infarction, stroke, cardiac failure, and cardiorespiratory arrest, ranging from 0.7% to 2.0%. Both cancer cells and cardiomyocytes express PD-L1, ICIs bind to cancer cells and as well as to non-target cardiomyocytes. ICIs bind to cardiomyocytes and modulates immune function, and promote muscle inflammation (autoimmune myocarditis) in heart muscle [22][23]. Additionally, ICIs can induce left ventricular hypertrophy and cause cardiac dysfunction [23][24][25][26]. However, the molecular and cellular changes during the development of cardiac dysfunction are yet to be systematically studied. Similarly, the mechanism underlying autoimmune myocarditis is not very clear. However, a shared antigen between tumor cells and cardiomyocytes could become the target for activated T-cells, leading to myocardial lymphocytic infiltration showing clinical manifestation of heart failure (HF) and cardiac conduction abnormalities [6]. PD-1 and PD-L1 are expressed in mouse and human cardiac myocytes. However, inhibiting CTLA-4 and deleting PD-l have led to autoimmune myocarditis, and several cases of HF have been reported in melanoma cancer patients treated with checkpoint inhibitors [13]. In a PD-1 knockout mouse study, an increase in autoimmune response was responsible for decreased left ventricular systolic function and wall thinning with dilated right ventricles, leading to increased mortality [3]. Moreover, diffused Immunoglobulin G antibody deposition was observed in cardiomyocytes of PD-1 knockout mice, suggesting an autoimmune response to the heart.

Table 1. Different ICI-induced Cardiac Toxicities in Different Cancers.

Cancer Type	mAb (ICI)	Cardiac Toxicity	Reference
Melanoma	Ipilimumab and Nivolumab	Myositis with rhabdomyolysis, early progressive cardiac electrical instability and myocarditis	[27]
Non-small cell lung cancer	Nivolumab	Massive pericardial effusion	[28]
Hodgkin's lymphoma	Pembrolizumab (KEYTRUDA)	Myocardial infarction, pericardial effusion, pericarditis, arrhythmia and cardiac tamponade	[29]
Kidney cancer	Nivolumab	Myocarditis	[30]
Advanced urothelial carcinoma	Pembrolizumab and Atezolizumab	Immune myocarditis	[31]
Merkel cell carcinoma	Nivolumab	Myocarditis	[32]

Cancer Type	mAb (ICI)	Cardiac Toxicity	Reference
Squamous cell neck cancer	Nivolumab	Myocarditis and ventricular arrhythmia	[32]
Squamous cell neck cancer	Pembrolizumab	Cardiac failure	[32]

5. Cardio-Oncology: Clinical Presentation, Diagnosis, and Management of Cardiotoxicity

Improvement in the mortality rate among cancer patients reflects better and more precise therapies. However, such therapies have also potentially increased risk factors for the cardiovascular system, resulting in long-term clinical adverse events following initial treatment. Current advancements in cardio-oncology involve highly specialized services for both cardiac health and cancer diseases. The National Institutes of Health have funded initiatives to study cardio-oncology that focus on (1) assessing cardiovascular (CV) clinical risk factors and presentation of clinical symptoms before and during cancer therapy, (2) introducing several precise cardioprotective interventions during cancer treatment, (3) balancing risk and reward as part of prescribing immunotherapy, and (4) managing post-treatment cardiotoxicity [16].

The clinical presentation of cardiotoxicity associated with immunotherapies has a spectrum of mild nonspecific symptoms to severe disease with symptoms of overt acute HF that requires inotropic support [33]. The reported clinical symptoms can be classified according to the recommendations of the American Society of Clinical Oncology clinical practice guidelines for the management of IRAEs. Life-threatening end-stage HF is the most reported contraindication in the literature, with most patients presenting a clinical syndrome of cardiogenic shock accompanied by severe conduction abnormalities, such as advanced atrioventricular blockage or ventricular tachycardia. The moderate clinical spectrum of disease ranges from chest pain, dyspnea, fatigue, peripheral edema, bilateral rales, and syncope to paroxysmal nocturnal dyspnea and palpitations [34][35]. Such clinical spectrum highlights the necessity of assessing CV risks in cancer patients to avoid fatal cardiotoxicity following the discontinuation of immunotherapy. It also provides a rationale for using immunosuppressive therapies to avoid such unnecessary discontinuation of effective anticancer treatments [21]. These assessments can also recognize early symptoms of hemodynamic instability that can persist during or after treatment.

Providing interventions during immunotherapy strongly depends on the diagnosis of the standard cardiac clinical manifestations as described above. Elevated serum troponin T levels are used to assess both prognosis and diagnosis of major adverse cardiovascular events, such as cardiovascular-related death, cardiogenic shock, cardiac arrest, or complete heart blockage as seen in myocarditis associated with immunotherapy. Similarly, along with the use of troponin, natriuretic peptides have also been proposed in screening and surveillance for higher-risk patients in the setting of immune checkpoint inhibitor-related myocarditis. Several professional societies, including the American Society of Clinical Oncology [36], Heart Failure Association of the European Society of Cardiology [37], European Society of Medical Oncology [38], the American Society of Echocardiography, and the European Association of Cardiovascular Imaging [39], have outlined guidance for an integrated approach combining ECG, echocardiography, and biomarkers in predicting cancer immunotherapy-related cardiac failure [40][41]. However, all these suggestions are based on anecdotal data since the available peer-reviewed literature is limited, and clinicians have reached no consensus about the timing of cardiotoxicity onset, thus hindering accurate clinical diagnosis. Therefore, the researchers look to more standardized patient profiling against to apply triple diagnostic scheme, e.g., before, during, and after immunotherapy, as follows: (1) definite symptoms, including abnormal echocardiography, positive biomarker and positive ECG; (2) probable clinical symptoms; and (3) possible symptoms with elevated biomarkers, but normal hemodynamic functions [19][39]. Immunosuppression is the major course of action to reduce drug-mediated cardiotoxicity with a high dose of prednisone [14]. Higher doses of steroids have not improved the outcomes of autoimmune cardiotoxicities. For stable patients in whom symptoms often appear while exercising or under stress but disappear after medication, diuretics and HF drugs should be provided until symptoms resolve. However, close monitoring needs to be done for arrhythmic patients with a low-threshold pacemaker to prevent complete heart blockage [15]. For unstable and highly symptomatic patients, immunotherapy should be stopped immediately and indefinitely until resolving IRAEs and associated cardiotoxicity [20]. Conventional cardiac failure therapies, such as β-blockers, calcium channel blockers, and renin-angiotensin system inhibitors, can be applied for severe and unstable patients who will show symptoms at any time, even at rest [14].

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