Chapter

Therapeutic Applications of Monoclonal Antibodies in Urologic-Oncology Management - An Update

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Abstract

The idea of utilizing immunotherapy for the treatment of cancers has been appealing to scientists and clinicians for over a several decades. Immunotherapy for cancers encompasses knowledge gained from a wide range of disciplines and has the potential to procure the 'magic bullet' for the treatment of cancer. Monoclonal antibody-based treatment of cancer has been recognized as one of the most successful therapeutic strategies for both hematologic malignancies and solid tumours in the last 20 years. The discovery of hybridoma technology in late 1975 and the development of chimeric, humanized, and human antibodies have increased the availability and utility of immunotherapy for the treatment of cancer. Metastatic or recurrent cancer continues to be the bane of the urological oncologist. Despite recent improvements in therapeutic management and outcomes for clinically localized disease overall survival rate in patients with the majority of metastatic and recurrent genitourinary malignancies remains relatively unchanged. By targeting tumours through specific or associated antigens, it is possible to selectively eliminate tumour cells and maintain an acceptable toxicity profile. Therapeutic antibodies that target immune cells are also being developed with the goal of breaking local tolerance and stimulating the patient's anti-tumor immune response. As with other treatment modalities, immunotherapy is far from perfect and requires additional study to optimize clinical response and overcome therapeutic resistance. Modern advances in the field of immunotherapy hold the promise of providing the clinical urologist/oncologist with new tools to fight urological cancer. However, the literature on monoclonal antibody-based immunotherapy with a particular emphasis on target antigens, monoclonal antibody design and potential applications in the field of urology is limited. Hence, the present chapter focuses on the applications of Immunotherapy using monoclonal antibodies for urologic oncology settings such as prostate, bladder, renal, testicular and penile with a hope to highlight its clinical efficacy and also its mechanisms of action in each of these cancer types.

Keywords: Monoclonal antibodies, Immunotherapy, Applications, Urologic-oncology

1. Introduction

Modern advances and a quantum leap in the field of cancer therapy has been promising to oncologists with new tools to fight many cancers. The immune system has multifunctional units referred to as antibodies, mostly polyclonal which facilitate humoral and cellular reactions to antigens [1]. However, it is possible to produce large quantities of an antibody from a single B-cell clone which are called as *Monoclonal Antibodies (MAbs).* Using these antibodies for therapeutic purposes is termed as Immunotherapy. Immunotherapy in recent times has been propitious across a number of cancer types. Stimulating results with MAbs directed towards both established and emerging targets indicate its potential key role as a therapeutic agent [2]. These are being tested in early- and late-stage clinical trials. In the last 35 years over 100 Monoclonal Antibodies have been considered potential as drugs and many have been approved. The usage of the monoclonal antibodies in cancer therapy requires the understanding of the biological role of various antigens involved in tumor growth [3]. In cancer patients' immunity system is often altered. The purpose of immunotherapy with monoclonal antibodies is to interfere with synergic activity of immunosuppressive environment created by T cells, cytokines, interleukins and tumor growth factor [4]. In many cancer treatments, the monoclonal antibodies have been robust enough, however in some, combinatorial treatments including monoclonal antibodies, chemotherapy and vaccines have been successful thereby bringing together cancer immunologists and clinicians required for the management of cancer in the near future [5]. This chapter will focus on Immunotherapy using Monoclonal antibodies for many urologic oncology types such as prostate, renal, bladder, testicular and penile with a hope to highlight its clinical utility and also its mechanisms of action in each of these cancer types.

2. Types of monoclonal antibodies and their mode of action

There are several ways by which the mAbs are made. They are as follows:

- Human: Theses are derived from the human source. Called as 'umabs'
- Murine: These are derived from mouse. Called as 'omabs'
- Humanized: Here the mouse proteins are attached to the human protein. Called as 'zumabs'
- Chimeric: variable regions are from humans and constant regions are from mouse. Called as'ximabs'

Following are the types of Monoclonal antibodies:

1. **Naked monoclonal antibodies**

   a. These are the most common types of antibodies which are not attached to the radioactive material or any chemotherapy drugs. They act independently and have been extensively used to treat cancer. They attach themselves to antigens on cancer cells, or even non cancerous cells and other free-floating proteins. They can also act as immune checkpoint inhibitors [6]

   b. E.g., alemtuzumab. This is used in the treatment of multiple sclerosis and leukemia (CLL).

c. E.g., trastuzumab is a monoclonal antibody that acts against the HER2 protein and used in the treatment of carcinoma of the breast in which this protein is expressed in larger amounts on the surface of the cancer cells. It thereby causes the inactivation of the protein by blocking it [7].

2. **Conjugated monoclonal antibodies**

As the name suggests these are in combination with the chemotherapy drugs or radioactive materials. These are referred to as tagged or labeled mAbs. They directly deliver the therapy to the target cells causing minimal damage to the normal cells surrounding them after precisely identifying them [8]. It then delivers the toxic substance where it is needed most. They can be of the following types;

a. **Radiolabeled antibodies:** These are conjugated with radiolabeled particles. An excellent example is Ibritumomab tiuxetan which works against the CD20 antigen found on B lymphocyte cells. It is made up of radioactive substance (Yttrium-90). The mAb works on the target cancer cells and then the radioactive materials target the destined cells and also the nearby cell. *Radioimmunotherapy* (RIT) is the name used for this type of treatment [9].

b. **Chemolabeled antibodies:** These mAbs have chemotherapy drugs attached to them. Eg: Ado-trastuzumab emtansine, an antibody that targets the HER2 protein (breast cancer). It is covalently linked to the cytotoxic agent DM1

3. **Bispecific monoclonal antibodies**

These can attach to 2 different types of antigens at the same time, these have also been explored in cancer therapy and drug delivery. Example is blinatumomab, used in the treatment of acute lymphoblastic leukemia. It works by directing the body's T-cells (part of the immune system) to target and bind with the CD19 protein on the surface of B-cell lymphoma cells [10].

3. Monoclonal antibodies and prostate cancer

Prostate cancer is one of the most common cancers with its incidence being high in Americans but lesser in the Asian population. It develops within the prostate gland that is responsible for the production of seminal fluid. Cancer therapy considered for prostate cancer includes radical prostatectomy, radiation therapy, chemotherapy, brachytherapy and hormone therapy [11]. The role of mAbs in Prostate cancer treatment has not been very successful. Several trials have been carried out to check for its efficacy, the details of which have been mentioned below.

Ipilimumab was the first immune checkpoint inhibitor which received FDA approval for the treatment of metastatic melanoma. It worked as the anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4). This stimulated its exploration for the treatment of prostate cancer. Use of this mAb in conjugation with radiation therapy did show antitumor activity in the form of decreasing PSA levels. This was a phase 1 trial. Hence, phase 3 clinical trials were conducted for further evaluation where subjects were randomized to ipilimumab after chemotherapy or radiation therapy. These trials did show progression free survival but missed its endpoint of overall survival [12].

Clinical trials on another mAb Nivolumab remains under investigation. In a first of its kind combination immunotherapy using monoclonal antibodies, Ipilimumab

plus nivolumab has been gaining responses as being reported in a phase 2 trial on metastatic castration resistant prostate cancer. Pembrolizumab is also an immune checkpoint inhibitor [13]. It has received approval from FDA for the treatment of prostate cancer. In these solid tumors, microsatellite instability (MSI) and mutations in mismatch repair genes (MMR) has been observed. Pembrolizumab is evaluated for in a patient after other effective treatments (such as sipuleucel-T, abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223, etc.) has been ruled out [14]. Combination therapies either with multiple immunotherapies or with immunotherapy and chemotherapy/RT, are currently being evaluated in prostate cancer. The optimal timing of immunotherapy in prostate cancer also remains unclear. Although much work remains to be done, the promise of prostate cancer immunotherapy remains unclear. There have been modern advances in the treatment of prostate cancer, however there is no curative treatment option once prostate becomes metastatic.

4. Monoclonal antibodies and renal cell carcinoma

Renal cell carcinoma is one of the urologic cancers that has lower incidence rates and poor prognosis. About 30% are diagnosed in their metastatic stage. It is a type of cancer that originates in the PCT. Therapy considered for this form of cancer include nephrectomy, radiation therapy, chemotherapy and embolization. The role of mAbs in Renal cell carcinoma is undertaken and studied in clinical trials treatment has not been very successful. Several trials have been carried out to check for its efficacy the details of which have been mentioned below as renal cell carcinoma (RCC) is a largely chemotherapy-resistant disease. It is immune responsive disease; therefore, checkpoint inhibitors can be considered as agents for the treatment of RCC [15].

The pivotal drug trial Checkmate 214 showed good objective responses in case of poor and intermediate risk patients in combination immunotherapy (Nivolumab/Ipilimumab) vs. the tyrosine kinase inhibitor sunitinib and can be considered as a first line treatment in these subjects for RCC. However, for favorable high-risk patients, the single agent sunitinib showed more response rate. Survival rates were similar in both arms. In another clinical trial Keynote 426, Pembrolizumab (anti-PD-1) plus axitinib, the responses were good and this led to its approval by leading to Food and Drug Administration (FDA) first line treatment. In another trial named, Javelin 101 Renal, avelumab (anti-PD-L1) plus axitinib vs. sunitinib the OS was not significantly different between the two arms [16].

In addition to this, there are many clinical trials that are underway for RCC (**Table 1**). Nivolumab was approved advanced clear-cell RCC by the FDA and is under investigation as pre- and postoperative therapy in mRCC. Combinatorial treatments with various drugs are also being studied in various clinical trials. Atezolizumab phase I trial involving 17 mRCC patients showed promising results as 7 had stable disease for more than 24 weeks. In another phase Ia study, of the 63 patients with clear-cell RCC whose OS was 28.9 months. Pembrolizumab is currently being investigated in two randomized phase II trials of mRCC patients. It has been found to be acceptable for safe use [17]. Several trials evaluating pembrolizumab in combination with various agents are also undergoing. Avelumab showed an acceptable usage when used in patients with advanced solid tumors and safety profile. Two ongoing trials are still being evaluated for avelumab in combination with axitinib Durvalumab. There are ongoing trials evaluating durvalumab in combination with other drugs, including tremelimumab for patients with advanced malignancies including RCC. Ipilimumab: Phase-II studies have been undergoing and the results are found to be partial response with adverse events being reported. In addition, Ipilimumab and nivolumab is being investigated and found to be favorable [18].

mAbs	Targeted therapy	Phase	Population
Nivolumab	Sunitinib Pazopanib	I	Advanced RCC, prior cytokine therapy allowed
Atezolizumab	Bevacizumab	Ib	Untreated, advanced clear cell RCC
Nivolumab	Bevacizumab	Neo-adjuvant pilot	Metastatic clear cell RCC, prior therapy allowed
Nivolumab	Temsirolimus	Ib/II	Metastatic RCC, prior therapy allowed
Pembrolizumab	Pazopanib	I/II	Untreated, advanced clear cell RCC
Pembrolizumab	Axitinib	Ib	Untreated, advanced clear cell RCC
Pembrolizumab	Bevacizumab	Ib/II	Metastatic clear cell RCC treated with failure of at least one prior therapy
Pembrolizumab	Aflibercept	I	Metastatic RCC treated with at least one prior VEGF TKI
Avelumab	Axitinib	Ib	Untreated, advanced clear cell RCC
Atezolizumab	Bevacizumab	III	Untreated, advanced clear cell RCC
Avelumab	Axitinib	III	Untreated, advanced clear cell RCC
Pembrolizumab	Axitinib	III	Untreated, advanced clear cell RCC

RCC: Renal cell carcinoma; VEGF: Vascular Endothelial Growth Factor; TKI: Tyrosine kinase inhibitors.

Table 1.
List of the Clinical trials that are underway for RCC.

5. Monoclonal antibodies and bladder cancer

Bladder cancer is one of the common cancers which develop in the tissues of the bladder. It is a type of Urolethial cancer. There are several methods which have been developed as a cancer therapy for bladder cancer and the most common being the, Bacillus Calmette-Guerin which has a very high success rate. The role of immuno-therapy in Bladder cancer has been detailed in a number of case report and clinical trial studies [19]. The incidence of Bladder cancer is comparatively found to be higher in America when compared to other forms of malignancy.

Here are the various monoclonal antibodies that have been considered as a cancer therapy for the bladder cancer. 2016-Atezolizumab, was the first mAb to be approved by the FDA and also accepted by the European Association of Urology (EUA) as second-line therapy for patients with advanced Bladder Cancer. It is a PD-1/PD-L1 checkpoint inhibitor It has been used for subjects even with metastatic or advanced bladder cancer. 2017-Avelumab was also approved by FDA for urothelial cancers. It acts against PD-L1. A phase Ib clinical trial had been carried out with metastatic urothelial cancer which showed inconvincing results. However in the phase II trial, avelumab exhibited a good antitumor response in patients with advanced urothelial cancer whose tumors progressed during or after platinum-based chemotherapy 2017-Durvalumab has also received approval by FDA for the treatment of Bladder cancer. Studies in phases I and II patients have confirmed the effectiveness of dur-valumab: It has shown responses in a number of clinical trial studies. It is a drug that acts against the PD-L1. 2017-Nivolumab is a FDA and EUA approved human mAb that acts against the PD-1. It was accepted on the basis of a single-arm phase trial for 270 platinum pretreated patients. The result has been 20% response rate [20].

Nivolumab was also tested on advanced or metastatic Bladder cancer subjects. In this study many adverse events were reported. Unlike the above mentioned

mAbs,PD-L1 overexpression among patients was not significant. In another phase II clinical trial with subjects also receiving platinum-based chemotherapy showed a two-month progression-free period. In patients with PD-L1 overexpression compared to patients with low-expression, a difference in drug effects was observed. Many subjects did show adverse events [21].

Pembrolizumab has been showing positive responses in cases of advanced bladder cancer. It is a humanized monoclonal antibody used in the treatment of bladder cancer and is approved by the FDA and EAU. In a study conducted by on pembrolizumab by Bellmunt et al., it was observed that this mAb showed lower adverse events and longer survival by about 3 months which was significant when compared to chemotherapy drugs such as docetaxel and paclitaxel [22]. In a case report mentioning the treatment with pembrolizumab as reported by McDermott et al., it was observed that adverse events were not observed after 8 months and hence suggested that pembrolizumab can be considered as a PD –I inhibitor [23]. In patients with DNA repair defects, pembrolizumab can also be considered for treatment. This drug not only reduced the risk of developing newer cancers but also prevented premalignant hyperplastic lesion. This shall be a rational therapy. Pembrolizumab is also shown better survival rates when compared to chemotherapy as mentioned farina and his colleagues.

A novel murine monoclonal antibody KMP1 has been studied by cheng and his colleagues [24]. The study was conducted both in vitro and in vivo settings It identified the CD44 epitope on bladder cancer cells and bound to it due to O-linked glycosylation and thereby exhibit antitumor potential in both settings. Future studies may be recommended to understand the exact glycolsylation mechanism also produce humanized forms and also conjugate types for better therapeutics. Enfortumab vedotin delivers toxic drugs to tumors. It is an antibody-drug conjugate that targets the Nectin-4 pathway, it has been approved for further study in case of bladder cancer. Immunotherapy has significantly reduced the risk of recurrence for bladder cancer while also increasing the percentage of patients who see a complete response post-surgery. Investigational bladder cancer immunotherapies also have the capacity change the outcomes positively for patients with this disease.

6. Monoclonal antibodies and testicular cancer

Testicular cancer is a disease of the male organ, testicles that produces the male hormones and sperms. Approximately 90% of testicular cancer start in the germ cells which make the sperm and are referred to as the Germ cell tumor (GCT). They are of two types: seminomas and non-seminomas. The testicular cancer are the solid tumors that can be treated by chemotherapy even in the metastatic condition. However, the role of immunotherapy is still under investigation. The incidence of Testicular cancer has observed an increasing trend in both America and Europe [25].

6.1 Testicular cancer

There are several trials that have been directed towards the Testicular cancer. Several of these trials are against the Immune check point inhibitors. Many case studies have reported immune checkpoint inhibition efficacy in refractory GCTs. However, the mechanism by which this occurs is not clear. Trials have been conducted with mAbs, nivolumab or pembrolizumab (both anti-PD-1 agents) on subjects with refractory GCT. The results are very inconvincing on a phase II trial of Adra et *al*. [26] who administered pembrolizumab to 10 refractory

GCT patients. Despite of the PD-L1 status there were no responses and hence this led to the termination of the trial. Although three of seven patients with refractory germ cell tumors treated with nivolumab or pembrolizumab did show response, there was partial remission. Some case reports did mention about the rapid progression of the disease with pembrolizumab on single dose and some 40% response with single dose of nivolumab. In a case study reported by Chi and Schweizer, treatment response to nivolumab was observed hence, use of single checkpoint inhibitors have been unstable in nature [27]. No responses were observed by nadal et al. for a case report on a study conducted using Nibolumabwith cabozantini and bipilimumab [28]. Due to inefficacy of single agent durvalumab, the monotherapy arm was closed for a study conducted by Raggi et al. [29] Hence the results of immune checkpoint inhibitor monotherapy studies are disappointing and hence need more evaluation in many more clinical trials that shall be planned for future.

7. Monoclonal antibodies and penile cancer

Penile Cancer is a disease in which a tumor growth occurs in the tissues of the Penis. Although the localized penile cancer can be treated by penectomy, the metastatic forms need better strategies to deal with such as the standard Chemotherapy or the novel Immunotherapy. About 95% of the penile cancers are squamous cell carcinomas and other forms include the sarcoma, melanomas and the basal cell carcinoma. Most of the penile cancer is caused by HPV (human papilloma virus) infection. Although the incidence of Penile cancer is only about 1 in every 1,00,000 individuals I America and Europe, several Immunotherapy drug trials are underway to strategize its importance.

Epidermal growth factor receptor is usually overly expressed in Penile squamous cell carcinoma. EGFR amplification has been observed and thereby reported in a number of studies on primary penile squamous cell carcinoma. This amplification has been observed with poor prognosis in patients with penile squamous cell carcinoma and increased risk of recurrence. Considering this aspect, it has been chosen for treatment of systemic penile cancer. Immunotherapy towards EGFR target, includes monoclonal antibodies cetuximab and panitumumab [28]. In a study considering cetuximab either alone or with cisplatin, there was partial response. In another study considering cetuximab, panitumumab, and nimotuzumab about 50% of the patients showed response to treatment. However, this was a second line of treatment.

In addition to anti-EGFR therapy, immune checkpoint inhibitor drug trials of avelumab and pembrolizumab are under progress. These drugs are evaluating the role of PD- L1 and PD-1 inhibition with the above mentioned mAbs respectively, exclusively in penile carcinoma. The combination of PD-1 and cytotoxic T lymphocyte protein 4 (CTLA4) blockade might improve antitumour activity across multiple malignancies, including PSCC. However, the majority of the trials with patients suffering from penile carcinoma are basket trials that include because incidence of penile squamous cell carcinoma is very low [30]. In addition, Cetuximab, a chimeric monoclonal antibody is an epidermal growth factor receptor (EGFR) inhibitor and has still not received FDA approval for the treatment of penile cancer. Phase I trials of Nivolumab are also underway which is a conjunction of chemotherapy and lymphokine working against the HPV. As the frequency of this disease is very low, it has been difficult to conduct many trials. However, continual progress in the area of Immunotherapy with fewer trials has still been gaining approvals and success.

8. Conclusion

Immune status modification as strategy of cancer therapy does hold a significant place. Although, the conventional cancer treatments such as surgery, chemotherapy, and radiotherapy are still being referred to as the prominent ones, for some cancer types, immunotherapies are considered as first-line of treatment. One of the most important discoveries in the last several years in immunotherapy has been the development of immune checkpoint inhibitor, monoclonal antibodies that promote antitumor activity. T cells are a form of lymphocyte which are produced within the thymus and performs a crucial function in stimulating body's immune reaction to combat most cancers. They apprehend the overseas particles (antigens) with the aid of using particularly variable T cell receptor. Unlike antibody, the TCR cannot bind antigen and as a substitute it wishes to have peptides of the antigen proven to it with the aid of using an antigen presenting cell (APC). The molecules at the APC that gift the antigen are called as major histocompatibility complexes (MHC). Many stimulatory alerts also are wanted at this time. B7 is a form of peripheral membrane protein observed on activated antigen-providing cells (APC). This B7 on an APC can bind to cytotoxic T-lymphocyte-related antigen 4 (CTLA-4) developing an inhibitory sign and TCR activation. Once the activated T-cell receptor is within the tumor surroundings it is able to apprehend the antigen supplied with the aid of APC within the tumor. At this time, the programmed cell death protein 1 (PD-1) receptor also sends an inhibitory signal to the T-cell when the receptor binds to programmed cell death 1 ligand 1 (PD-L1), that's regularly expressed on tumor cells. Monoclonal antibodies act by inhibiting the binding PD-1 to PD-L1 and thereby boost body's immune response against the tumor cells.

Checkpoint inhibitors specifically goal PD-1/PD-L1) and CTLA4 Immune checkpoint efficacy is stricken by diverse factors, among which are tumor genomics, host germline genetics, PD-L1 levels, and intestine microbiome. Generally, in tumors, mutated or incorrectly expressed proteins are processed through the immunoproteasome into peptides which can be commonly loaded onto MHC molecules, which similarly now no longer usually are capable of eliciting CD8+ T cell reaction. This may also cause producing MHC-supplied immunogenic neoepitopes. It turned into proven, that after the intratumor heterogeneity rises, neoantigen-expressing clones emerge as greater homogenous with the differential expression of PD-L1.

There are number of FDA approved monoclonal antibodies, that are considered for the treatment of Urology oncology. These have been detailed in the **Table 1** and include FDA-approved PD-1 inhibitors such as nivolumab, pembrolizumab, cemiplimab, and FDA-approved PD-L1 such as atezolizumab, avelumab, and durvalumab. But all the open literatures do believe that combinatorial strategies with immune checkpoint therapies may provide a better survival benefit which have been demonstrated in various clinical trials. These can be in combination with radiation therapy, tyrosine kinase inhibitors and also many chemotherapeutic drugs. However, the response to immunotherapy with monoclonal antibodies varies subjectively and hence research into PD-L1 expression, gene signature expression, messenger RNA subtype, mutational and neoantigen load is essential to determine the varying response to monoclonal antibody immunotherapy. Although older modalities of treatment for cancer, has been extensively exploited, array of new drugs that offer hope of not only prolonging life but also curing significantly more patients in the future bring a ray of hope to the scientific world.

Conflict of interest

The authors declare conflict of interest as None.

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