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Research Article

MONOCLONAL ANTIBODIES FOR NON-SMALL CELL LUNG CANCER TREATMENT

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ABSTRACT

The most common therapeutic approach for the treatment of non-small cell lung cancer includes surgical resection, chemotherapy and radiotherapy. A recent advance with targeted therapies such as monoclonal antibodies and biological inhibitors has emanated potent and efficacious results. This mainly includes cetuximab, panitumumab, bevazicumab and ramucirumab. Several targeted therapies are under trial. Endothelial growth factor receptor inhibitors include cetuximab, panitumumab, necitumumab, vascular endothelial growth factor inhibitors such as bevacicumab, vandetinib, angiogenesis inhibitors such as ramucirumab, programmed death ligands such as nivolumab. Pembrolizumab are the effective targeted therapies. Eventhough these targeted therapies have been proved to increase the overall survival rate and specificity, the success still requires profound researches and auxillary controlled trial experiments to evaluate the overall benefits and toxicity.

KEYWORDS: *Monoclonal Antibodies, Anaplastic Lymphoma kinase, Endothelial growth factor receptors, Vascular, Janus kinase.*

INTRODUCTION

Non- small cell lung cancer (NSCLC) is a type of cancer that comes to about 85% of all lung cancers. It can be further divided into squamous cell carcinoma and adeno carcinoma [1]. The most common signs and symptoms include dyspnoea, wheezing, chest pain, and recurrent infections such as bronchitis, pneumonia. This can further cause bone pain, weakness of limbs, seizures, spinal cord impingement etc. NSCLC are sensitive to chemotherapy [2]. Now a days targeted therapies have paved the way for sparkling results in both adeno carcinoma and squamous cell carcinoma. These includes drugs that target angiogenesis, drugs that target epidermal growth factor receptors, Drugs that target Anaplastic lymphoma kinase (ALK) gene changes, BRAF changes and so on. Cytotoxic drugs and radiation therapy have been proved to improve the survival rate and quality of life of patients with lung cancer, but they have diminished patient survival rate and yield many toxic results.

Conventional treatment:

Non small cell lung cancer accounts to a majority of diagnosed cancers. The survival rate of lung cancer is very less. Radiation therapy and chemotherapy plays a pivotal role for the treatment and survival of non small cell lung cancer. With the advancement of genetics and molecural biology, several targeted treatments were introduced for NSCLC. These were highly beneficent and had fruitful results because of reduced toxicity and improved survival rate in patients. The major targeted therapies include molecule kinase inhibitors including monoclonal antibodies. These monoclonal antibodies are proteins that bind to the same epitope unlike polyclonal antibodies. They are highly homogenous and are specific in their action.

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Their mechanism of action is by binding to the molecular targets. Because of the predominant pharmacodynamics and pharmacokinetic properties they are widely used in bio genetics and immune pharmacology. More over their frivolous and trivial side effects makes them highly reliable and dependable compared to other treatment options. Before ten years only one monoclonal antibody was available. But now the system has changed, today six highy specific and reliable monoclonal antibodies are now available which is now approved by US Food and Drug Administration (FDA).

Monoclonal antibodies:

Inhibitors of Endothelial growth factor receptors:

Endothelial growth factor receptors (EGFR) are highly expressed in non small cell lung cancer. Therefore inactivating those receptors are the main treatment option [8]. This can be done either by inhibitors of EGFR or Tyrosine kinase inhibitors. EGFR'S along with 1st line chemotherapy can be considered as a predominant treatment method in NSCLC [9].

Epidermal growth factor receptor directed monoclonal antibodies combined with platinum based chemotherapy have shown positive results in clinical trials [10]. When cetuximab was used along with platinum compounds such as cisplatin/ vinca alkaloids, it was found to be far better than chemotherapy alone [11]. Most of the studies have shown that cetuximab has explicit response as targeted therapy. In NSCLC with high EGFR expression the death rate was far more less, when cetuximab was used along with chemotherapy than chemotherapy alone. Among patients with low EGFR expression there was no significant difference in survival rate [12]. This concludes that EGFR expression plays a significant role for the treatment with cetuximab. Cetuximab shows predictive role when EGFR expression level is high. The efficacy of cetuximab was also measured by combining it with a JAK-2 inhibitor, CYT387. Cetuximab suppresses JAK STAT (Janus Kinase) - signal transducer and transcription pathway. Xenograft animal models were used for the study. Results showed that cetuximab alone or CYT387 alone has efficacy lower when combined with CYT387. The study concludes that CYT387 has an indirect anti- tumor activity as well as shows profound increase in activity when used with cetuximab [13]. The increase effectiveness of the combination of EGFR monoclonal antibody with chemotherapeutic regimen is noteworthy. The patients treated with chemotherapy alone are compared with those given a combination of monoclonal antibody and chemotherapy. The results

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obtained were amalgamated using significant statistical tools. The primary end points were overall survival, progression free survival, response rate and disease control rate. The study concludes that more beneficial effects are seen in combination part. However the use of monoclonal antibody has developed trivial ADR's such as infusion reaction, rashes etc [16]. Morover the risk of toxicities such as neutropenia, leucopenia was greater when monoclonal antibodies were used. However compared to high beneficial results of EGFR-mAb combination, these toxicities are bearable.

The role of panitumumab as targeted therapy is quite notable. Panitumumab was randomly given to patients at a dose of 9mg/kg in combination with pemetrexed 500mg/m3 and cisplatin 75 mg/m3. Another group received pemetrexed /cisplatin alone. The primary end points were progression free survival, overall survival and quality of life. The study finalize that Panitumumab combination is less effective than control group of cisplatin/ pemetrexed because of decreased progression free survival rate, overall survival and decreased QOL [14].

Another predominant monoclonal antibody with affirmative effect is Necitumumab. It is mainly used a combination with gemcitabine and cisplatin for squamous cell carcinoma. Studies based on safety and efficacy of necitumumab are in progress and that shows paramount results in overall survival and progression free survival in non-squamous and non-small cell lung cancer. Eventhough the trial shows trivial adverse events such as diarrhea, infusion reaction, hypo magnasemia, dermatological toxicities,etc. The safety and efficacy of necitumumab bring it to the forefront in therapy for NSCLC. However cost of the drug is more and it shows added toxicity when combined with gemcitabine and cisplatin [15].

Vascular endothelial growth factor inhibitors:

Immune checkpoint inhibitors and molecular targeting drug are the main treatment option for NSCLC. Bevacizumab is a US FDA drug which is used for advanced Non squamous NSCLC. It is a monoclonal anti VEGF antibody used in combination with platinum based chemotherapy. In order to improve the safety, efficacy and progression rate to lessen the disadvantages bevazicumab can be combined with other immunotherapies and targeted molecules [16]. A study known as ARIES (Avastin regimen investigation of effectiveness and safety) was conducted inorder to assess the safety and efficacy profile of Bevazicumab. The study could establish that the progression and survival rate is high when Bevazicumab is used along with chemotherapy. The combination of EGFRs along with vascular endothelial growth factor inhibitors have shown improved resistance and synergestic effect. Vandetenib is another drug which is used as a cytotoxic agent for non small cell lung cancer. The pharmacodynamic profile and least toxic effects bought it to the forefront among targeted agents [17].

Role of Angiogenesis inhibitors:

Ramucirumab is the first anti- angiogenic drug approved by US FDA for NSCLC. Angiogenesis plays a fundamental role in tumor development and its metastasis. This is mainly carried out by vascular endothelial growth factor and its signaling pathway. Pamucirumab is VEGF 2 receptor inhibitor. These drugs block the interaction of VEGF 2 and VEGF ligands and further endothelial proliferation and migration. Recently a study named REVEL was conducted to evaluate the overall safety and efficacy of ramucirumab when it is used along with docetaxel. REVEL was carried out in more than 1250 patients and random selection was done. The patients were either treated with ramucirumab and docetaxel or placebo and docetaxel. The result showed prominent survival rate among patients treated with ramucirumab and docetaxel [18].

Programmed death ligand (PDL -1) Inhibitors in NSCLC:

The discovery of immunotherapy has bought a drastic change in the overall survival rate and quality of life in oncology. Nivolumab, Pembrolizumab, and Atezolimumab are some of the major FDA approved drugs which has PDL-1 inhibitory action. Several studies have shown satisfactory results using monoclonal antibodies against PDL1 [19].

Azetolizumab:

Azetolimumab was the first FDA approved programmed death ligand inhibitor. Their approval was based on mainly two studies namely POPLAR and BIRCH studies. These were multi centric phase 2 trials which were conducted in both NSCLC patients with squamous and non squamous pathology. Azetolizumab was compared with docetaxel and was found to have improved overall survival rate and progression free survival rate. From the POPLAR and BIRCH studies it was concluded that side effects and toxic rate was less in azetolizumab when compared to docetaxel [21].

Nivolumab:

There are several proofs to show that the overall survival rate of Nivolumab is far more superior to several other drugs. A randomized controlled trial was conducted using Nivolumab: docetaxel in the ratio 1:1. The results showed that the overall survival rate of Nivolumab was 51% when compared to docetaxel which has 39%. Nivolumab is also found to have significant effects in Hodgkins lymphoma, renal carcinoma and bladder cancer. Eventhough Nivolumab shows cardinal responses in PDL 1 positive patients it also shows response to PDL 1 negative patients [23].

Pembrolizumab:

Pembrolizumab is another FDA approved agent IgG 4 antogonist which act as PD –L1 inhibitor. The FDA approval of pembrolizumab was obtained by using KEYNOTE trials which were conducted in 495 patients. The study concluded that the overall survival rate and progression free survival rate was very high. Several studies are also conducted using pembrolizumab in combination with platinum/ pemetrexed doublet chemotherapy patients and platinum/ pembrolizumab/ pemetrexed triplet therapy. The overall survival rate was the primary end point of the study. The results concluded that the overall survival rate of triplet therapy was substantially high when compared to doublet therapy [24].

HER family for NSCLC:

Patritumab:

HER class of drugs has a foremidable action for Non Small cell lung cancer. The expression of HER subfamily has a supreme pharmacological action against tyrosine kinase inhibitors. The safety and efficacy of patritumab in combination with erlotinib was found to be predominantly high in early phase clinical trials [26].

Patritumab is an immunomodulatory agent which has promising actions in NSCLC, gastric cancer, breast cancer, colorectal cancer, and pancreatic cancer [17]. The mechanism lies in the action against HER 3. HER3 heterodimerizes with HER 1 and HER 2 .The overall survival rate, progression rate and safety of Patritumab are significantly greater especially when used along with erlotinib [28].

Anti Insulin like growth factor 1 receptor Antibodies:

Dalotuzumab:

Dalotuzumab is an anti- IGFR 1 which has notable activity for NSCLC. Dalotuzumab is an igG 1 kappa antibody which targets insulin like growth factor 1 receptors [29]. Progression free survival and overall survival rate were the primary end points. Progression free survival and overall survival rate was more in the group given with erlotinib compared to other given with erlotinib in combination with dalotuzumab. Both the groups showed ADR s such as dehydration, asthenia etc [30].

CONCLUSION

Monoclonal antibodies have a promising effect in the treatment of non- small cell lung cancer patients. They are very much distinctive and they require tumor cells to express the target antigen. This occurs because they can activate numerous mechanism concerned with immune response like apoptosis induction and cell growth blockage. The targeted therapies such as cetuximab and bevacizumab are highly specific in nature and shows highly beneficial effects in improving the overall survival rate. Inorder to elaborate the proper use of these molecules, their advantage and adverse effects in the long term targeted therapies requires extensive research and randomized control trials.

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