REVIEW

Libri Oncol. 2017;45(2-3):60–64

IMMUNOTHERAPY IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER

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Summary

Lung cancer is leading cause of death among malignant disease Worldwide and it is responsible for more than 1, 5 million deaths each year. Lung cancer is divided in two major groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Despite significant improvements, for vast majority of patients chemotherapy still remains the treatment of choice in the first line setting. Progress over the last decade has led to the recognition of immunoevasion as of the leading hallmarks of cancer development. Clinical development was focused on immune checkpoint inhibitors, cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) and programmed death (PD1/PD-L1) pathway. Programmed death 1 protein is another T-cell coinhibitory receptor with a structure similar to that of CTLA-4 but with a distinct biologic function and ligand specificity and it is stimulated with PD-L1. PD-1 or PD-L1 blockade with drugs like nivolumab, pembrolizumab or atezolizumab resulted in superior efficacy comparing to standard chemotherapy in first-line setting. In patient with high PD-L1 expression (50% or more) pemborlizumab should be treatment of choice in first-line setting. PD-L1 expression is at the moment only available biomarker who can predict response to immune checkpoint inhibitors.

KEY WORDS: *lung cancer, checkpoint inhibitors, immunotherapy*

IMUNOTERAPIJA U TRETMANU NE-SITNOSTANIČNOG RAKA PLUĆA

Sažetak

Karcinom pluća vodeći je uzrok smrti od malignih bolesti te je odgovoran za više od 1,5 milijuna smrti. U većine bolesnika osnovu liječenja karcinoma pluća čini kemoterapija temeljena na platini. Unazad desetak godina, brojna se istraživanje provode o ulozi imunološkog sutava u karcinogenezi. Tumori uspjevaju izbjeći nadzor imunološkog sustava te tako rasti i metastazirati. Koncpet aktivacije imunološkog sutava iznimno je zanimljiv te se pokazalo da blokatori kontrolnih točaka pokazauju dobro učinkovitost u liječenju solidnih tumora poput melanoma ili bubrega. U zadnjih pet godina, inhibitori kontrolnih točaka nivolumab, pembrolizumab i atezoilizumab pokazali su se kao iznimno učinkoviti lijekovi u liječenju bolesnika s karcinomom pluća ranije liječenih klasičnom kemoterapijom. Pembrolizumab se također pokazao kao iznimno učinkovit u liječenju bolesnika sa visokom PD-L1 ekspresijom (PD-L1≥50%) u prvoj liniji liječenja. Ono što je nužno je pronaći biomarker koji bi ukazivao koji će bolesnici regirati na liječenje imunoterapijom. Danas znamo da što je viša ekspresija PD-L1 bolji je odgovor na imunoterapiju, ali i negativni bolesnici mogu odgovoriti na liječenje. Imunoterapija inhibitorima kontrolnih točaka danas je standard u drugoj liniji liječenja karcinoma pluća malih stanica, te je pembrolizumab najbolja opcija za liječenje visoko pozitivnih PD-L1 bolesnika u prvoj liniji liječenja.

KLJUČNE RIJEČI: *karcinom pluća, inhibitori kontrolne točke, imunoterapija*

INTRODUCTION

Lung cancer is leading cause of death among malignant disease worldwide and it is responsible for more than 1, 5 million deaths each year (1). In 2012, lung cancer was the most common cancer and leading cause of cancer deaths among men, and leading cause of death among females in developed countries, and second most common cause of cancer deaths in less developed countries (1). In European Union there is a trend of decreasing lung cancer mortality among men, and at the same time, increasing mortality was noticed among females (2). Lung cancer is divided in two major groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for around 85% of all cases, while incidence of SCLC is decreasing (3). NSCLC is further divided into adenocarcinoma, squamous carcinoma and large cell carcinoma; adenocarcinoma is the most common subtype of NSCLC. For decades, platinum based chemotherapy doublets were cornerstone of treatment of advanced and metastatic NSCLC (4). During the last decade, discovery and introduction of targeted therapies for tumours harbouring activating mutations such are EGFR mutations and EML4-ALK translocation were a significant step forward in treatment of lung cancer, but EGFR and ALK activating changes in the genome are present in around 20% of NSCLC patients (5,6). Despite significant improvements, for vast majority of patients chemotherapy still remains the treatment of choice in the first line setting. Therefore, further treatment options are needed to improve survival of patients with lung cancer.

Immunotherapy

Progress over the last decade has led to the recognition of immunoevasion as of the leading hallmarks of cancer development. Cancer cells are thought to escape immune destruction by disabling components of the immune system that are suppose to eliminate them (7). Tumor immune escape mechanisms include the loss of major histocompatibility complex antigen (HLA) expression, activation of regulatory T cells, upregulation of immune checkpoints and immunosuppressive cytokines (8). Therefore, activation of the immune system against cancer represents an attractive treatment approach. However, until recently, antitumor effects of immunotherapy among solid tumors were limited to melanoma, renal and prostate cancers (9).

The goal of immunotherapy is the induction of a humoral or cellular immune response against cancer. Clinical development of immunotherapy for NSCLC has involved three broad classes of agents: nonspecific immune stimulants, vaccines and immune checkpoint inhibitors (9).

Unfortunately, vaccines and nonspecific immune stimulants did not show efficacy in lung cancer patients. Clinical development was then focused on immune checkpoint inhibitors, cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) and programmed death (PD1/PD-L1) pathway.

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) protein is expressed on the surface of T cells. It is acting as suppressor of T-cell activation by competing with CD28 for B7 binding in an inhibitory fashion. CTLA-4 inhibitors are among the earliest immune checkpoint inhibitors in clinical development. Antibodies to CTLA-4 block the inhibition of CD28/B7 T-cell activation and stimulate antitumour activity (10). Ipilimumab, a fully humanized monoclonal antibody that binds to CTLA-4 and prevents it from binding to its ligand, was tested in combination with chemotherapy on phase II trial in patients with NSCLC (11). Combination treatment improved progression-free survival (PFS) compared to chemotherapy alone. Better responses were seen in patients with squamous cell carcinoma, so this subgroup was selected for phase III trial (11). Unfortunately, phase III trial was stopped prematurely due to detrimental effect of combination of ipilimumab and chemotherapy compared to chemotherapy alone.

Programmed death 1 protein is another T-cell coinhibitory receptor with a structure similar to that of CTLA-4 but with a distinct biologic function and ligand specificity and it is stimulated with PD-L1 (12). Interrupting this pathway, either by blocking PD-1 or by blocking PD-L1, showed excellent results.

Nivolumab is fully human, PD-L1–specific, IgG monoclonal antibody that inhibits the binding of PD-L1 to both PD-1 and CD80 (13). It was first tested in phase I trial in different tumor types, including NSCLC. In heavily pretreated adenocarcinoma and squamous cell carcinoma patients, objective response rates of 8% and 16%, respectively, were noticed (12). Promising results of phase I

trial lead to starting phase III trials in second-line treatment of nivolumab against docetaxel.

CheckMate – 024 was phase III trial which compared efficacy of nivolumab against docetaxel in patients with squamous cell lung cancer who progressed after first-line standard platinum-based doublet. Novolumab significantly improved PFS (3.5 months with nivolumab versus 2.8 months with docetaxel (hazard ratio, HR) for death or disease progression, 0.62; 95% CI, 0.47 to 0.81; P<0.001). What was more important, nivolumab significantly improved overall survival (OS) to 9.2 months with nivolumab versus 6.0 months with docetaxel. The risk of death was 41% lower with nivolumab than with docetaxel (hazard ratio, 0.59; 95% CI, 0.44 to 0.79; P<0.001) (14).

Similarly, CheckMate-057 phase III was conducted in patients with non-sqamous NSCLC. Interestingly, PFS did not favor nivolumab over docetaxel (mPFS 2.3months vs 4.2 months), the rate of progression-free survival at 1 year was higher with nivolumab than with docetaxel (19% and 8%, respectively). Overall survival was longer with nivolumab than with docetaxel. The median overall survival was 12.2 months in patients tretated with nivolumab and 9.4 months in patients treated with docetaxel (hazard ratio for death, 0.73; 96% CI, 0.59 to 0.89; P=0.002) (15). Positive results of this two trials has lead to approval in USA and Europe of nivolumab in patients with either squamous or non-squamous cell lung cancer in patients who progressed after first-line treatment.

Pembrolizumab, a highly selective, humanized monoclonal IgG4 kappa isotype antibody against PD-1 was tested in a large phase I (495 patients) KeyNote 001 in NSCLC patients. The median PFS was 3.7 months, and the median OS was 12.0 months. Among patients with a proportion score of at least 50% in the validation group, the response rate was 45.2%. Among all the patients with a proportion score of at least 50%, median PFS was 6.3 months; median OS was not reached (16).

KeyNote – 010 was large phase III trial which compared pembrolizumab to docetaxel in second-line treatment of patients with NSCLC who are showed PD-L1 positivity of 1 or more percent. Two doses of pembrolizumab, 2 mg/kg and 10 mg/kg were tested. Both doses showed significant improvement in PFS and OS compared to docetaxel. There was no significant difference between different doses of pembrolizumab, so dose of 2 mg/kg was registered in USA and Europe for second-line treatment of PD-L1 (PD-L1≥1) positive patients with NSCLC (17).

Atezolizumab, a humanised anti-programmed death-ligand 1 (PD-L1) monoclonal antibody that inhibits PD-L1 and programmed death-1 (PD-1) and PD-L1 and B7-1 interactions was tested in phase III OAK trial against docetaxel in second-line setting in patients with NSCLC previously treated with standard chemotherapy. Overall survival was improved with atezolizumab compared with docetaxel (medianOS was 13·8 months vs 9·6 months; hazard ratio [HR] 0·73, p=0·0003). Results of this trial have lead to approval of atezolizumab regardless of PD-L1 expression in second-line setting of NSCLC patients.

First line-setting

Promising and encouraging results of second-line trials gave a lot of enthusiasm to investigators and two large phase III trial in PD-L1 highly positive NSCLC patients were conducted (18).

Pembrolizumab was investigated in first-line setting against standard platinum-based chemotherapy in phase III KeyNote-024 trial in highly (PD-L1≥50%) positive patients. Median progression-free survival was 10.3 months in the pembrolizumab group versus 6.0 months in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68; P<0.001). The estimated rate of overall survival at 6 months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; P=0.005). The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%). These astonishing results resulted in approval of pembrolizumab in first-line setting in highly (PD-L1≥50%) positive treatment – naïve NSCLC patients (19).

Similary designed CheckMate – 026 phase III trial compared nivolumab and standard chemotherapy in first-line setting in highly positive (PD-L1≥10%, different test and cut-off values used). The trial was negative with no statistical significant difference in OS (mOS 14.4 months with nivolumab (20).

PD-L1 expression

In patients with activating mutations like EGFR and ALK, molecular diagnostics of these

changes is crucial for selection of patients who are candidates for targeted treatments. In patients who harbour activating mutation treatment with targeted agents' like EGFR tyrosine kinase inhibitos or ALK inhibitors can prolong PFS and even OS (5,6). A search for biomarker who can predict long-term responders is ongoing. From phase III trial we know that 20-30% of all patients have durable and ongoing responses to immunotherapy treatment (14,15,17,18). At the moment, we are not quite sure what the best biomarkers which could predict response to immunotherapy agents are. Currently, the best biomarker we have is PD-L1. PD-L1 expression can predict response to immune checkpoint inhibitors. The higher expression is, the better is response to the treatment (14,15, 16,17,18). Still, there are patients who benefit from treatment with immune check point inhibitors despite they are PD-L1 negative (15,18). That means that PD-L1 is not the most appropriate biomarker but at the moment is the best we have.

CONCLUSION

Progress over the last decade has led to the recognition of immunoevasion as of the leading hallmarks of cancer development. However, until recently, antitumor effects of immunotherapy among solid tumors were limited to melanoma, renal and prostate cancers. Recent achivemtns have shown that immunotherapy has promising results in patients with non-small cell lung cancer. Immune checkpoint inhibitors which bloc either PD-1 or PD-L1 like nivolumab, pembrolizumab and atezolizumab showed superiority over chemotherapy in second-line setting. Whereas, nivolumab and atezolizumab are approved in second-line setting in treatment of NSCLC regardless of PD-L1 status, pembrolizumab is approved in second-line setting in patients who are PD-L1≥1% positive(21). In first line-setting, pembrolizumab is treatment of choice in NSCLC patients who are PD-L1≥postive and at the same time EGFR, ALK and ROS1 negative (23).

Immune checkpoint inhibitors offers a new hope to non-small cell lung cancer patients and combinations of immunotherapy and other treatment approaches like chemotherapy, radiotherapy and targeted agents are under investigation.

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