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Review Article

Selection of chemotherapy for non-small cell lung cancer is facilitated by new therapeutic strategies

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Abstract: Nowadays, advanced non-small cell lung cancer is still an incurable disease. Recent researches have led to considerable progress in the treatment of non-small cell lung cancer. This article reviews the main studies on chemotherapy on non-small cell lung cancer and discusses the new therapeutic strategies available to date. Stable disease (SD) is necessary in chemotherapy for tumor. The proportion of population with responders or SD basically maintained similar regardless of regimens. The overall survival after chemotherapy for patients with SD was lower than patients with responders, and higher than patients with progressive disease. Greater benefits could be achieved in patients with effective induction chemotherapy using chemotherapeutic agents for maintenance therapy, whereas the benefits were relatively small for patients with SD. It has been found that epidermal growth factor receptor (EGFR) mutation status had certain correlation with the efficacy of chemotherapy. First-line chemotherapy has shown advantages in effective rate and progression free survival on EGFR mutant. EGFR mutation produced significant effects on the efficacy of postoperative adjuvant chemotherapy. Patients with EGFR mutation had a higher effective rate than wild-type EGFR patients, and patients with responders had a greater benefit in progression free survival from maintenance therapy. However, it is still necessary to carry out more careful and deeper studies and analyses on traditional cytotoxic chemotherapy, to further optimize cytotoxic chemotherapy and to use molecular targeted agents with different mechanisms.

Keywords: Advanced disease, stable disease, overall survival, epidermal growth factor receptor

Introduction

Lung cancer is a worldwide leading cause of cancer deaths. Approximately 75% of non-small-cell lung cancers (NSCLC) are at stage IIIB or IV when diagnosed. Cytotoxic chemotherapy and molecular targeted therapy are main therapeutic methods. Epidermal growth factor receptor (EGFR) is a protein involved in an important signaling pathway that regulates the development, growth and apoptosis of tumors. Numerous studies demonstrated that NSCLC with EGFR mutations showed unique clinical characteristics and course of development. Unlike traditional cytotoxic chemotherapy, tyrosine kinase inhibitors (TKI) that target EGFR, such as gefitinib and erlotinib, can significantly prolong progression free survival (PFS) and overall survival (OS) in patients with advanced NSCLC, and is an essential therapy for patients with EGFR mutations. Although remarkable achievements were obtained in using TKI to treat patients with EGFR mutations, traditional cytotoxic chemotherapy is still of importance. In traditional platin-based first-line combination chemotherapy, the effective rate is 20-40% and tumor control rate is 70-80%, with a short PFS of only 3-5 months and a median overall survival of 7-12 months [1, 2]. Therefore, means to further improve the PFS and the median overall survival of chemotherapy is attracting more and more attentions in recent years.

With the discoveries of new chemotherapeutic agents of low toxicity and high efficacy and new molecular targeted agents, maintenance chemotherapy is becoming an important pattern for treating advanced NSCLC. In the mean time, the discoveries of EGFR sensitive genes and new targeting agents such as anti-angiogenic drugs, and more thorough clinical studies have brought more and more new challenges for the optimal application of cytotoxic chemotherapy. In this article, we will perform an analysis on

how to better understand and optimize traditional cytotoxic chemotherapy according to the currently new therapeutic strategies for advanced NSCLC.

Stable disease (SD) is necessary in chemotherapy for tumor

Despite decades of continuous studies and updates, the change of solid tumor size from pre-treatment to post-treatment is still the primary endpoint for efficacy evaluation in previous WHO evaluation criteria and the Response Evaluation Criteria in Solid Tumors (RECIST) widely used since 2000 [3, 4]. There may be some remarkable defects in actual clinical application using this system, among which the difficulty to reflect the change of tumor cell activity is a critical aspect, as this change is always associated with clinical development of tumor and therapeutic benefits. For example, some lesions may be bleached or have cavity without significant size change through chemotherapy or molecular targeted therapy. These patients may always have good clinical benefits, although SD is defined here according to efficacy evaluation criteria.

Therefore, it is not exactly accurate to seek tumor shrink overwhelmingly and to consider that only tumor shrink can prolong survival and demonstrate clinical benefits of systemic therapy. Actually, a small proportion of patients with advanced NSCLC may have tumor shrink after platin-based chemotherapy, but more patients have SD or progression. In recent years, the relationship between SD and therapeutic benefits is attracting more concerns and becoming an important parameter for clinical therapeutic strategies.

Proportion of population with SD maintained similarly regardless of chemotherapy regimens

In a large random study on traditional platin-based chemotherapy for 1155 naïve patients with NSCLC of stage IIIB/IV conducted by the Eastern Cooperative Oncology Group (ECOG) in 2002, the efficacy of cisplatin plus paclitaxel, cisplatin plus gemcitabine, cisplatin plus docetaxel and carboplatin plus paclitaxel was compared. There was no significant difference between the effective rates of the four regimens, with an overall effective rate of 19%, a SD rate of 21%, a progressive disease rate of 45% and the undetectable disease rate of 15% [5].

There were no significant changes in the effective rate and SD rate in cytotoxic chemotherapy used according to pathological type. In 2012, Paz-Ares and colleagues reported the outcome of first-line chemotherapy by pemetrexed and cisplatin in 939 patients with advanced non-squamous type NSCLC, in which the effective rate was 30%, the SD rate was 44.0% and the progressive disease rate was 23.1% [6].

Vascular endothelial growth factor (VEGF) enhances tumor angiogenesis and plays a critical role in the development of tumor. It has been confirmed that the combination of chemotherapy with Bevacizumab, a humanized anti-VEGF monoclonal antibody, could improve progression-free survival (PFS) in nonsquamous type NSCLC. In a random clinical trial of 1043 first-treated patients with advanced nonsquamous type NSCLC [7], the effective rate was significantly increased from 20.1% to 34.1%, after being treated by Bevacizumab (7.5 mg/kg) combined with cisplatin and gemcitabine ($P < 0.0001$). However, analysis by traditional efficacy evaluation criteria still indicated that cytotoxic chemotherapy-based regimen was effective for only a small proportion of patients.

In summary, despite development of over 10 years, the proportion of population with responders or SD basically maintained similarly regardless of regimens selected according to pathohistological type or combined with monoclonal antibodies. Studies on stable patients should be further intensified while actively seeking for efficacy.

The overall survival after chemotherapy for patients with SD was lower than patients with responders, and higher than patients with progressive disease

Although there are currently few deep studies on the characteristics of tumor cytology in patients with SD, a few retrospective studies have shown that stability obtained in first-line chemotherapy was beneficial for survival. In phase III clinical studies comparing the effects of pemetrexed and docetaxel in patients with previous chemotherapy failures for advanced NSCLC, pemetrexed had a median survival time

of 8.3 months, which was similar to the median survival time of 7.9 months for docetaxel. The 1-year survival rate was 29.7% [8].

Multivariable analysis showed that the efficacy of second-line therapy was significantly affected by gender, stage at diagnosis, performance status and efficacy of first-line therapy [9]. The OS of second-line therapy using pemetrexed and docetaxel for patients who received effective first-line therapy was up to 15.8 months calculated from the start of second-line therapy, while the OS was 10.5 months for patients with SD and 4.6 months for patients with progressive disease ($P < 0.001$) [9].

Lara Jr and colleagues [10] analyzed the correlation between the efficacy and survival in three platin-based random clinical studies (S9509, S9806 and S0003) conducted by the Southwest Oncology Group (SWOG) on 984 patients with advanced NSCLC. The median overall survival in the studies S9509, S9806 and S0003 was 8.6 months, 8.9 months and 9.2 months, respectively.

Analysis of patients' status at Week 8 after registration showed an effective rate of 12%, a SD rate of 50% and a progressive disease rate of 37% [10]. The median overall survival for patients with responders, SD and progressive disease was 14.7 months, 12.0 months and 6.4 months, respectively [10]. The median overall survival for patients with responders was significantly superior to that for patients with SD ($P = 0.03$), whereas the median overall survival for patients with SD was significantly superior to that for patients with progressive disease ($P < 0.0001$) [10]. The survival curve for patients with SD was closer to that for patients with responders.

Patients with SD have smaller benefits than patients with effective induction chemotherapy using chemotherapeutic agents for maintenance therapy

Maintenance therapy is a new therapeutic strategy in which non-platin single agents are used to continue treatment or drugs are changed for the maintenance in patients with controlled tumor after 4-6 cycles of first-line chemotherapy with double platins. The aim of maintenance therapy is to achieve prolonged progression free survival and OS by increasing the exposure of effective treatments to the maximal extent and maximizing the efficacy of anti-tumor agents. It is normally used for patients with controlled tumor, or patients with responders and SD in first-line chemotherapy. Recent results from maintenance therapy studies indicated that the clinical course had certain effects on the benefits of maintenance therapy strategy on patients with responders and SD in first-line chemotherapy.

PFS of patients with responders and SD in first-line chemotherapy

Few studies have investigated the difference in PFS between patients with responders and SD in first-line chemotherapy during the observation periods. The study PARAMOUNT conducted by Paz-Ares [6] in 2002 showed some implications for this aspect. PARAMOUNT is a double-blind, phase III, and randomly controlled study, in which the effects of pemetrexed and placebo were compared in maintenance therapy after 4 cycles of first-line chemotherapy with pemetrexed and cisplatin were applied on 1022 patients with advanced NSCLC, including 939 patients who entered induction chemotherapy stage. The results indicated that the PFS for the pemetrexed maintenance therapy group was 4.1 months for patients with effective induction chemotherapy or SD, with hazard ratios (HR) of 0.48 (95% CI 0.34-0.67) and 0.74 (0.53-1.04), indicating that pemetrexed had greater benefits for patients with effective induction chemotherapy. The PFS for the placebo group was 2.6 months and 3.0 months for patients with effective induction chemotherapy or SD, respectively, indicating a relatively low rate of tumor progression despite a relatively low response to first-line chemotherapy in patients with effective induction chemotherapy.

Efficacy of maintenance chemotherapy for patients with SD in induction chemotherapy

It is always expected to shrink tumor as much as possible and to seek maximal effective rate through systemic therapy. However, results from maintenance therapy studies indicated that the effective rate was basically comparable to second-line therapy for NSCLC, although change of drugs could achieve a slightly higher effective rate than continuous maintenance therapy with the same agent. Therefore, it is not appropriate to consider the improvement of

effective rate in induction chemotherapy for patients with SD to be an important study parameter.

In the study conducted by Fidias [11] in 2009, 563 stage IIIB/IV NSCLC patients with SD or responders were given docetaxel for maintenance therapy after 4 weeks of chemotherapy with gemcitabine combined with carboplatin (GC regimen). The effective rate of maintenance therapy reached 11.7%. In addition, the effective rate was 6.8% and 11.9% in drug change maintenance therapy by pemetrexed and erlotinib, respectively [12, 13]. The effective rate was 12.2% and 3% in the same drug maintenance therapy with gemcitabine and pemetrexed, respectively [6, 14].

Previous studies on second-line therapy showed that the effective rate of pemetrexed, docetaxel, erlotinib and gefitinib were ranged from 8.2% to 12.0% [15]. Maintenance therapy is comparable with second-line therapy for effective rate in advanced NSCLC, whereas the former is efficacious for SD and the latter is efficacious for progression. Therefore, it is not appropriate to use effective rate to judge whether maintenance therapy is reasonable.

The effectiveness of induction chemotherapy is helpful for drug selection in maintenance therapy

Recent studies indicated that maintenance chemotherapy could achieve greater benefits for patients with effective induction chemotherapy than those with SD. The results demonstrated that the PFS for the pemetrexed maintenance chemotherapy group was significantly higher than that for the placebo group (6.9 months [95% CI 6.2-7.5] and 5.6 months [5.5-6.0] from the start of induction chemotherapy) (HR 0.59, 95% CI 0.47-0.74; log-rank P < 0.0001). Subgroup analysis was performed for stage, effectiveness of induction chemotherapy, performance status, smoking, gender, age and histological type. The results showed certain variance in the degrees of benefits, although benefits were achieved in all the subgroups. The median PFS of patients with effective induction chemotherapy was 4.1 months (95% CI 3.1-6.0) for the pemetrexed group and 2.6 months (1.6-2.9) for the placebo group (HR 0.48 [95% CI 0.34-0.67]), whereas the median PFS of patients with SD was 4.1 months (95% CI 3.0-4.6) for the pemetrexed group and 3.0 months (2.8-4.1) for the placebo group (HR 0.74 [0.53-1.04]).

Similar results were obtained in drug maintenance therapy using gemcitabine. Pe'rol *et al.* [16] administered 4 cycles of induction chemotherapy with the combination of gemcitabine and cisplatin to 834 naïve patients with advanced NSCLC. The patients with controlled tumor were randomly assigned in the ratio of 1:1:1 into three groups: observation group (placebo-control group), maintenance therapy group with gemcitabine, and maintenance therapy group with erlotinib. It appeared that PFS benefit for patients with effective first-line induction chemotherapy was greater than that for patients with SD, with the HR of 0.47 (0.47-0.96) and 0.67 (0.34-0.67) compared with placebo group, respectively. There was also a trend of prolonged OS for patients with effective induction chemotherapy: the OS for the maintenance therapy group with gemcitabine was 15.2 months and the OS for the placebo group was 10.8 months (HR 0.72 [95% CI, 0.51-1.04]). No prolonged OS was observed in patients with SD compared with patients in the placebo group (HR 1.13 [0.79-1.62]).

In summary, current maintenance therapy studies showed that greater benefits could be achieved in patients with effective induction chemotherapy using chemotherapeutic agents for maintenance therapy, whereas the benefits were relatively small for patients with SD. This provides a useful implication for optimizing maintenance therapy in clinical practice.

EGFR mutation enhances the efficacy of cytotoxic chemotherapy

It has been demonstrated that EGFR mutation is a potent predictive factor for the efficacy of TKI [17]. TKI has a significantly higher effective rate and PFS than chemotherapy for patients with EGFR mutation, which is in contrast to those for patients with wild-type EGFR. In addition, it was found that EGFR mutation status had certain correlation with the efficacy of chemotherapy.

First-line chemotherapy has advantages in effective rate and PFS on EGFR mutant

Iressa Pan-Asia Study (IPASS) is a multi-center, random, phase III clinical study investigating

clinical efficacy of first-line therapy with gefitinib or carboplatin plus paclitaxel for advanced pulmonary adenocarcinoma. In this study, 1217 patients were randomly selected, among which 437 patients received EGFR tests [17]. 261 out of the 437 patients had positive EGFR mutation (59.7%), whereas 176 patients had wild-type EGFR (40.3%). The effective rate of chemotherapy was 47.3% and 23.5% for mutant and wild-type EGFR, respectively; the PFS was 6.3 months and 5.5 months for mutant and wild-type EGFR, respectively [17, 18].

In a retrospective analysis conducted by Kalikakia [19], the correlation between the efficacy of first-line chemotherapy and mutation status in EGFR and K-RAS was investigated on 162 patients with advanced NSCLC, in which 96 patients received regimens with platin and 66 patients received regimens without platin. The effective rate was 55.6% in EGFR mutant group and 21.8% in wild-type EGFR group (P = 0.023), whereas the effective rate in regimens with platin was 62.5% and 23.9% for mutant EGFR group and wild-type EGFR group, respectively (P = 0.021). Multivariate analysis showed that EGFR mutation was an independent predictive factor for the efficacy of first-line therapy (wild-type vs. mutant: HR = 4.85; 95% CI: 1.13-20.83; P = 0.034). The PFS was 4.2 months in both of the groups with 6.1 months and 4.1 months for mutant EGFR and wild-type EGFR, respectively. However, no statistically significant difference was found (P = 0.81). In the study on 105 patients with advanced NSCLC conducted by Lin *et al*. [20], the effective rate was 47.5% in the 56 patients with EGFR mutation and 30.6% in the 49 patients with wild-type EGFR. However, no statistically significant difference was found (P = 0.162). The PFS for mutant and wild-type EGFR was 6.6 months and 6.1 months, respectively, without statistically significant difference.

Studies on the correlation between EGFR mutation status and first-line chemotherapy are mainly retrospective analyses or subgroup analyses, performed on a relatively small number of patients. Chemotherapy has shown advantages in effective rate and PFS on EGFR mutant, but larger, random, and prospective clinical trials are still needed for further investigations.

Second-line chemotherapy was more efficacious for EGFR-mutant patients than for wild-type EGFR patients

Few studies were reported on the correlation between EGFR mutation status and second-line chemotherapy the Iressa NSCLC Trial Evaluating Response and Survival Versus Taxotere (INTEREST) study [21] is a random, phase III clinical study aiming at comparing the OS of the second-line therapy with gefitinib and docetaxel for advanced NSCLC. A total number of 1466 patients were enrolled and evenly divided into two groups. Results showed that the improvement in PFS, effective rate and tumor-related symptoms was similar for all patients. A better improvement in tolerability and quality of life was caused by gefitinib. 297 patients received EGFR tests, among which 44 patients had positive EGFR mutation and 253 had wild-type EGFR [21]. The survival time was 6.4 months and 6.0 months for wild-type patients in the gefitinib and docetaxel groups, respectively, whereas EGFR-mutant patients had a longer survival time of 14.2 months and 16.6 months, making the survival time of all the studied patients to be 7.6 months and 8.0 months in the gefitinib and docetaxel groups, respectively [21]. The effective rate and PFS of gefitinib were both significantly higher than that of docetaxel for EGFR-mutant patients. For patients with mutant and wild-type EGFR in the gefitinib group, the PFS was 7.0 months and 1.7 months, and the effective rate was 42.1% and 6.6%, respectively [21]. For patients with mutant and wild-type EGFR in the chemotherapy group, the PFS was 4.1 months and 2.6 months, and the effective rate was 21.1% and 9.8%, respectively [21]. This indicated that second-line chemotherapy was more efficacious for EGFR-mutant patients than for wild-type EGFR patients.

EGFR mutation produced significant effects on the efficacy of postoperative adjuvant chemotherapy

Recently, some retrospective studies were carried out to explore the correlation of EGFR mutation status with postoperative survival and efficacy of adjuvant chemotherapy in patients with NSCLC. In 2011, Tsao [22] retrospectively analyzed 482 patients with NSCLC of stage T2N0 and T1-2N1, who received total

Table 1. Treatment duration and PFS of chemotherapy and TKI in various studies

Studies	Treatment duration		PFS (months)	
	Chemotherapy	TKI	Chemotherapy	TKI
OPTIMAL [24]	10.4 weeks	55.5 weeks	4.6	13.1
IPASS [17, 18]	3.4 months	6.4 months	6.3	9.5
NEJ002 [27]	4 cycles	308 days	5.4	10.8
WJTOG3405 [28, 29]	64 days	165 days	6.3	9.2

resection and postoperative adjuvant chemotherapy with the combination of vinorelbine and cisplatin (NP regimen), or only observation. In the observation group of 221 patients, the number of EGFR mutant patients was 27, and the number of wild-type patients was 194. The OS and disease free survival (DFS) of EGFR mutant patients were higher than patients with wild-type EGFR. The death and recurrence risks of EGFR mutant patients were reduced by 32% and 17%, respectively (HR 0.68 [95% CI: 0.34-1.36, P = 0.28] and 0.83 [95% CI: 0.44-1.56, P = 0.56]), indicating that patients with EGFR mutant had a better postoperative survival compared with wild-type EGFR patients [22]. All patients with mutant and wild-type EGFR could benefit from adjuvant chemotherapy, but those with mutant EGFR had better benefits. The HR was 0.76 (95% CI: 0.56-1.04, p = 0.08) and 0.65 (95% CI: 0.20-2.14, p = 0.48) for wild-type and mutant EGFR patients, respectively, but without statistically significant difference (P = 0.50) [22]. This study was a retrospective investigation on a small number of samples, and it was yet difficult to determine the correlation of EGFR mutation status with postoperative survival and the efficacy of adjuvant chemotherapy, but the results still provided knowledge necessary for further investigations [22].

In 2013, Sun *et al*. [23] evaluated the correlation of the efficacy of postoperative adjuvant chemotherapy with EGFR expression status in 150 patients with stage IIIA-N2 NSCLC after total resection. Paclitaxel or vinorelbine in combination with carboplatin was used as the regimen for postoperative adjuvant chemotherapy. 43 out of 150 patients had EGFR mutation, including 25 patients in the observation group and 18 patients in the chemotherapy group. There were a total number of 71 patients in postoperative observation group, including 25 patients with mutant EGFR and 46 with wild-type EGFR. The DFS for EGFR mutant patients was 49 months and that for patients with wild-type EGFR was only 14 months, with statistically significant difference (P < 0.001). In the 43 patients with EGFR mutation, the DFS was 49 months in the observation group and 30 months in the chemotherapy group, with no statistically significant difference (P = 0.195). However, a better DFS trend for EGFR mutant patients was observed, compared with wild-type EGFR patients, whose DFS was 14 months in the observation group and 32 months in the chemotherapy group (P < 0.001). In the observation group, the OS of EGFR mutant patients was 59 months and that of wild-type EGFR patients was only 17 months, with statistically significant difference (P < 0.001). For the 43 patients with EGFR mutation, the OS was 59 months and 33 months for the observation group and chemotherapy group, respectively (P = 0.050); For patients with wild-type EGFR, the OS was 17 months and 32 months for the observation group and chemotherapy group, respectively (P < 0.001). The results strongly suggested that EGFR status was closely correlated with postoperative survival, producing a significant effect on the efficacy of postoperative adjuvant chemotherapy.

New topics are emerging in the postoperative adjuvant chemotherapy for NSCLC with the development of molecular markers, as well as the use of EGFR on the treatment and prognosis of NSCLC. However, larger, random, and prospective clinical studies are still needed to further understand how to use adjuvant chemotherapy more reasonably according to EGFR mutation status.

Effect of EGFR mutation status on maintenance therapy strategy

For patients with EGFR sensitive mutation, multiple random studies confirmed that the PFS in first-line use of TKI is significantly superior to chemotherapy although no significant difference was observed for the OS [17, 18, 24-29]. Notably, the administration time of TKI was significantly longer than that of chemotherapy in these first-line therapies targeting EGFR mutant NSCLC (**Table 1**). It has been confirmed that prolonged administration of cytotoxic chemotherapy with the same drug for maintenance

could definitely enhance PFS, even in advanced NSCLC with unknown EGFR mutation status.

IFCT-GFPC 0502 [16] study is a phase III clinical study aiming at observing the value of gemcitabine or erlotinib for maintenance therapy for patients with advanced NSCLC after 4 cycles of induction chemotherapy with gemcitabine and cisplatin until progressive disease or intolerable toxicity. Maintenance therapy with gemcitabine resulted in longer PFS than the observation group (3.8 months and 1.9 months, respectively) ($P < 0.001$). In PARAMOUNT (6) study, after 4 cycles of chemotherapy with pemetrexed and cisplatin, patients with stage IIIB/IV non-squamous-type NSCLC and controlled disease continued the administration of pemetrexed for maintenance or placebo for observation. This study was divided into two stages, the first stage was nonrandom induction chemotherapy and the second stage was the induction of patients with controlled disease into pemetrexed or placebo maintenance treatment in the ratio of 2:1. Results showed that pemetrexed significantly prolonged PFS compared with placebo (6.9 months and 5.6 months from the start of induction, respectively, with statistically significant difference ($P < 0.0001$); HR 0.59 [5% CI 0.47-0.74]). The PFS for maintenance chemotherapy was 4.1 months and 2.8 months, respectively ($P < 0.0001$) (HR 0.62 (95% CI 0.49-0.79)). The emerging anti-angiogenesis targeted agents and profound clinical studies provide more clinical options for further improving PFS in patients with first-line therapy, as well as new thoughts for strategies to further utilize first-line therapy.

Bevacizumab is a valued monoclonal agent that targets VEGF and significantly improves the effective rate and PFS for patients with NSCLC in combination with chemotherapy. Eastern Cooperative Oncology Group (ECOG) [30] randomly administered the combination of first-line paclitaxel and carboplatin or the combination of paclitaxel and bevacizumab to 878 patients with stage IIIB/IV NSCLC. Results showed that the effective rate of simple chemotherapy was increased from 15% to 35% after the addition of bevacizumab ($P < 0.001$), the PFS was increased from 4.5 months to 6.2 months ($P < 0.001$), and MST was increased from 10.3 months to 12.3 months ($P = 0.003$). Bevacizumab also showed a good application perspective in maintenance therapy studies. AVAPERL [31] is a phase III, open-label, random, multi-center study to investigate the benefits of bevacizumab in combination with pemetrexed or alone for maintenance therapy after first-line induction chemotherapy. 253 out of 376 patients with stage IIIB/IV non-squamous NSCLC had controlled tumor after 4 cycles of chemotherapy with pemetrexed and cisplatin, and then received 1:1 bevacizumab monotherapy 7.5 mg/kg once every 3 weeks or bevacizumab 7.5 mg/kg in combination with pemetrexed 500 mg/m^2 for maintenance therapy, until tumor progression or intolerable toxicity. Results showed that the PFS was 6.6 months and 10.2 months from the start of induction, and the progression risk was reduced by 50% ($P < 0.001$).

It has been demonstrated that first-line application of TKI is more advantageous than cytotoxic chemotherapy for patients with EGFR sensitive mutation, and it has become an essential consensus that TKI is preferred for these patients, but the following aspects should still be noted in prolonging PFS of first-line therapy in patients with EGFR mutation: i) maintenance therapy should not be used in comparing first-line TKI and chemotherapy for patients with EGFR mutation; ii) maintenance chemotherapy could prolong PFS, while the EGFR status in patients with maintenance chemotherapy was currently unknown; iii) it was shown in most studies that patients with EGFR mutation had a higher effective rate than wild-type EGFR patients, and patients with responders had a greater benefit in PFS from maintenance therapy; iv) the PFS reached 10.2 months in maintenance therapy with pemetrexed in combination with bevacizumab, which was almost two-fold of that in chemotherapy and was comparable to that of TKI in the comparative study of first-line TKI and chemotherapy in patients with EGFR mutation. Therefore, it is necessary to further study how maintenance chemotherapy alone or the combination of maintenance chemotherapy and bevacizumab correlates with continuous administration of TKI, and to further determine PFS and OS status for first-line therapy for patients with EGFR mutation.

Summary

With the development of molecular biology of NSCLC in recent years, significant changes have taken place in the therapeutic strategies for NSCLC. The proposal of the concept that advanced NSCLC is transformed into a chronic

disease, as well as the arrival of the era of molecular targeted treatment, brought about a lot of new challenges, including the effect of EGFR mutation status on cytotoxic chemotherapy, and the promotion of chemotherapy by maintaining the new pattern of therapies. Therefore, it is necessary to carry out more careful and deeper studies and analyses on traditional cytotoxic chemotherapy, to further optimize cytotoxic chemotherapy and to use molecular targeted agents with different mechanisms based on molecular markers.

Disclosure of conflict of interest

None.

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