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Short Review of "Phase II Study of Erlotinib Plus Gemcitabine in First-Line Treatment of Poor Prognosis, Advanced Non-Small Cell Lung Cancer(NSCLC) Patients"- 8 Years Letter

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***Abstract*—Chemotherapy of patients with advanced NSCLC and poor performance status remain a challenge for clinicians and researchers. After 8 years from the beginning of our study"Phase II study of erlotinib plus gemcitabine in first-line treatment of poor prognosis, advanced non-small cell lung cancer (NSCLC) patients", the things are not enough clear regarding the combination of target therapy or immunotherapy for patients with advanced NSCLC. This review tries to discuss some important meth-analysis and some important study which give us more information and solutions to resolve this matter. Conclusion is that some of results of our study remain valuable and more efforts should be done to find the best combination and sequentially between TKI and chemotherapy and between immunotherapy and chemotherapy. In the same spirit we consider and the challenge of studying the combination of targeted therapy and immunotherapy.**

***Index Terms*— Chemotherapy, non small cell lung cancer, Tyrosine kinase inhibitors, Immunotherapy.**

I. Introduction

Studies on first-line systemic treatment in non small cell lung cancer (NSCLC) in patients with poor performance status ECOG II are few in medical literature in the field.

It was 8 years after first enrolling a patient in our study and three years after publication. In this period occurred more tyrosine kinase inhibitors (TKI) of new generation and have made progress in defeating the resistance in these therapeutic agents.

We propose in this "Follow up" of our study to analyze several meta-analyzes which were concerned of TKIs combination with chemotherapy. Some of individual studies have tried to find the optimal combination of chemotherapy with TKIs.

Great lack of our study is the fact to not tested for economic reasons, the genetic mutation of EGFR, but considering that a certain group of the population has more frequent mutation presence (namely female gender, adenocarcinoma, non-smokers etc.) we can make some judgments and draw some conclusions.

Neither in our days is not unanimity regarding how to combine chemotherapy with TKIs, some studies showing that sequential therapy would give the best results, bringing arguments against other studies of the advantages of concomitant therapy.

Cytotoxic drugs association with TKIs remains valid a theory and we still presuming that this combination can overcome acquire resistance to TKIs.

The first studies that dealt with combination of TKIs with chemotherapy were negative. Some elements were foreseen therapeutic success in these studies such as that in adenocarcinomas combination of TKIs and chemotherapy resulted in a better response than in the general population. (TRIBUTE study) [1].

A meta-analysis published in 2015 performed on six studies that met inclusion criteria. Six clinical trials including 4675 patients were enrolled in this systematic review [5]–[8].

There were 2679, 1864 and 132 patients who were randomized to receive chemotherapy concurrently with EGFR TKI, chemotherapy or EGFR TKI alone, respectively [2].

Another meta-analysis reveals some benefit but it seems that the combination of patient survival was not influenced. Using combinations of chemotherapy and TKI remains controversial. In this meta-analysis was compared the combination of EGFR- TKIs with chemotherapy or EGFR–TKIs monotherapy. Authors hazard ratios (HRs), if available or other survival data published. Eight trials entered into this meta-analysis, including 4585 patients. This meta-analysis show that the combined regimen significantly delayed disease progression (HR=0.81, 95% CI 0.69–0.95, P=0.01); "subgroup analysis showed significantly higher progression free survival advantages in Asian patients (P<0.001), with sequential combination of TKIs and chemotherapy (P=0.02). In selected patients by EGFR-mutation, both mutation positive (HR=0.48, 95% CI 0.28–0.83, P=0.009) and negative (HR=0.84, 95% CI 0.72–0.98, P=0.02) patients gained progression free survival benefit from the combined regimen, albeit the magnitude of benefit was marginally larger in mutation positive patients (*P*=0.05). The combined regimen had no significant impact on overall survival, irrespective of ethnicity, dose schedules or EGFR-mutation status". Anorexia (RR=2.01, 95% CI 1.11–3.63; *P*=0.02) and diarrhea (RR=2.70, 95% CI 1.94–3.76; *P*<0.001) were more frequent in the combined regimen arm [3].

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II. RESULT

The results of FASTACT, a randomised, placebo-controlled, phase 2 study,and FASTACT-2, a phase 3 study, in a similar patient population, showed that intercalated chemotherapy and erlotinib significantly prolonged progression-free survival (PFS) in patients with NSCLC.

In FASTACT-2 patients with untreated stage IIIB/IV NSCLC were randomly assigned in a 1:1 to receive six cycles of gemcitabine (1250 mg/m(2) on days 1 and 8, intravenously) plus platinum (carboplatin 5 × area under the curve or cisplatin 75 mg/m(2) on day 1, intravenously) with intercalated erlotinib (150 mg/day on days 15-28, orally) or placebo orally and the some chemotherapy like in the first arm every 4 weeks. The result was a significantly prolonged PFS with chemotherapy plus erlotinib versus chemotherapy plus placebo.PFS was (median PFS 7·6 months [95% CI 7·2-8·3], vs 6·0 months [5·6-7·1], hazard ratio [HR] 0·57 [0·47-0·69]; p<0·0001). Treatment benefit was noted only in patients with an activating EGFR gene mutation. Toxicity was similar in the two arms of the study. The authors concluded that chemotherapy and erlotinib could be an option for first-line treatment for patients with NSCLC with EGFR mutation-positive or for selected patients with unknown EGFR mutation status [4].

An other meta-analysis with , intercalated administration of chemotherapy and erlotinib, included nine randomized controlled trials with a total of 3599 patients were included. Compared chemotherapy plus erlotinib versus chemotherapy alone, chemotherapy plus erlotinib was superior in PFS. Among patients with EGFR mutant tumors, chemotherapy plus erlotinib demonstrated significant improvements in PFS.Patients with EGFR wild-type tumors had no improvement of PFS. In combination chemotherapy and erlotinib could be a good option for NSCLC, especially for patients who never smoked and patients with EGFR mutation-positive disease [5].

In "Tarceva Lung Cancer Investigation Trial " Erlotinib with concurrent cisplatin and gemcitabine showed no survival benefit compared with chemotherapy alone in patients with chemotherapy-naïve patients with advanced NSCLC [6].

Acquired resistance to gefitinib or erlotinib occurs in almost all patients with EGFR-mutated NSCLC . For patients with acquired resistence the posible therapy is platinum doublet chemotherapy. Third-generation TKIs specific for the T790M resistance mutation are other possibility of treatment. The combination of afatinib and cetuximab demonstrated that it can defeat acquired resistance [7].

A phase II study should be mentioned having similarities with our trial except that we have not analyzed the EGFR mutation. In this study patients with advanced non-squamous, EGFR-mutant NSCLC were randomly assigned to receive in first line treatment either a concurrent or a sequential alternating regimen with gefitinib (250 mg) and carboplatin/pemetrexed [area under the curve (AUC) = 6 and 500 mg/m2; 3-weekly. An important finding in our opinion was that concurrent regimens (used also in our study) might provide better OS [8]).

One last study that I want to present is a retrospective study which try to verify the assumption that EGFR addiction persists after development of TKI acquired resistance. For that reason many clinicians recommend to continue TKI with subsequent chemotherapy. In our opinion this approach has not been studied in enough. This study demonstrated that continuation of EGFR TKI with chemotherapy in patients with acquired resistance improves outcomes compared with chemotherapy alone [9].

Because of a veritable cascade of the new drugs (small molecules, immunotherapeutic agents) the combinations of chemotherapy with TKIs agents was in our opinion neglect and the final results wait to be find. The incentive combinations are now cytotoxic agents with immunotherapy or targeted therapy with immunotherapy[10].

All the combinations are promising we think yet we think that the first-line combination of an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) and platinum-based doublet chemotherapy has not been sufficiently evaluated for patients with EGFR-mutant non-NSCLC in first line or for non EGFR mutant in second line.

Another idea that remains today is that studies should be made for patients with a poor performance status, these patients are numerous in advanced NSCLC and for this patients our study remains valid.

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