



Treatment of induction in resectable NSCLC with chemotherapy, followed by surgery and erlotinib

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Comment on: Cascone T, Gold KA, Swisher SG, *et al.* Induction Cisplatin Docetaxel Followed by Surgery and Erlotinib in Non-Small Cell Lung Cancer. *Ann Thorac Surg* 2018;105:418-24.

Submitted Aug 31, 2018. Accepted for publication Sep 12, 2018.

doi: 10.21037/atm.2018.09.38

View this article at: <http://dx.doi.org/10.21037/atm.2018.09.38>

We have carefully read the article by Dr. Cascone *et al.* in which they report the results of a phase 2 study evaluating the role of the induction therapy with cisplatin plus docetaxel, followed by a surgery and erlotinib in patients with resectable non-small cell lung cancer (NSCLC). This study has been registered as NCT00254384 and the data presented in the aforementioned article correspond to long-term efficacy results (1).

We know that the limited stages of NSCLC comprise a miscellany of diseases with a diverse biological behaviour and with wide differences in terms of survival according to the stage of the disease at the moment of diagnosis. Several studies have shown that adjuvant chemotherapy (CT) provides a survival benefit in patients with completely resected NSCLC (2-6). Furthermore, the LACE meta-analysis analysing data from 5 studies confirms the improvement in survival in patients treated with platinum-based CT. This meta-analysis, which includes more than 4,500 patients, with a median follow-up of 5.2 years, shows a decrease in the risk of death of 5.4% at 5 years in patients treated with CT compared to those who did not receive it (HR 0.89). However, this benefit is statistically significant only in the subgroup of patients with stage II and IIIA of the disease (HR 0.83) (7).

In the case of induction therapy, there is not as much data as in the adjuvant treatment in these patients. However, comparative analyses seem to indicate that there are no differences in overall survival (OS), although it can improve the results of surgery and allow less extensive resections (8-10).

In the Dr. Cascone's study a total of 47 patients were

included and started the CT induction treatment. Only 13 of them had histological confirmation of mediastinal lymph node involvement. The majority of the patients had good tolerance to the treatment and less than 15% of them required a reduction of the CT dose. Seventy-nine percent of the patients treated with neoadjuvant CT were operated and the most performed intervention was lobectomy (66%), followed by pneumonectomy (9%). However, only 3% of the complete pathological responses (pCR) and 19% of the major pathological responses (MPR) were conformed (3 cases in patients with stage I, 3 in stage III and only one case in stage II). Only 57% of patients started the adjuvant treatment with erlotinib and only 12 of them managed to complete the 12-month adjuvant period. The OS at 5 years was 51.9% for stage I patients, 55.5% for stage II and 21.1% for stage III. The relapse rate throughout the follow-up was 57%.

The analysis of the results in terms of survival does not provide any benefit with respect to historical controls, compared to the patients treated exclusively with induction CT (based on platinum). On the other hand, the addition of the adjuvant erlotinib to the treatment not only does not provide any survival benefits, but also carries the risk of compromising the quality of life due to some associated adverse events. These data are consistent with the results of the RADIANT study that included 973 patients (11). This study evaluated the role of the adjuvant treatment with erlotinib without finding any benefit in survival in these patients. In addition, the pathological analysis of the surgically treated patients does not show any differences in the pCR or MPR rates with respect to those, described in

the previous series (12). Even the MPR, a survival surrogate in patients with NSCLC treated with neoadjuvant CT, is lower in this study (19%) compared to previous studies in which it was around 22% (12).

One of the aspects to consider while analysing the results of this study, is that the recruitment was done a decade ago and therefore the application of the data is limited. One of the reasons is that in recent years the impact of immunotherapy (IO) has been demonstrated in patients with advanced NSCLC both in the first-line of treatment and in later lines (13-16). These treatments, used in monotherapy or in combination with other immunotherapeutic drugs or CT, have shown significant response rates, as well as a benefit in survival and quality of life. However, if IO is effective in patients with metastatic disease, it is likely that there is a potential activity which improves the results of induction treatments in patients with potentially resectable disease. Actually, there are currently 3 clinical trials evaluating the role of IO in this group of patients with NSCLC.

The first study, published by Forde PM in May 2018, evaluates the use of neoadjuvant nivolumab at a dose of 3 mg/kg every 2 weeks in patients with NSCLC stages I-IIIa (NCT02259621) (17). From all 21 patients included, 20 were subsequently operated. The MPR rate was 45% and the tolerance to the treatment was excellent. Another of the neoadjuvant studies in NSCLC stages I-IIIa with IO is the CheckMate816 which is the ongoing phase 3 trial. This study includes 3 treatment arms: nivolumab plus ipilimumab vs nivolumab plus CT vs. CT alone. And finally the NADIM study of the Spanish Lung Cancer Group (SLCG), which is an exploratory phase 2 study, evaluating the efficacy of the combination of CT + IO with carboplatin plus paclitaxel plus nivolumab (18). This study is designed for patients with resectable NSCLC (stage IIIa) and has already closed its recruitment. The partial data, presented at ASCO 2018 with a total of 43 patients recruited and 22 of them already operated, show an overall response rate of 78% (pCR: 60% + MPR: 18%). Therefore, although the results of induction studies in potentially resectable NSCLC whose protocols include IO are promising, they are still immature but probably in a short period of time they will become a new standard of treatment.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Franco F, Provencio M. Treatment of induction in resectable NSCLC with chemotherapy, followed by surgery and erlotinib. *Ann Transl Med* 2018;6(Suppl 1):S31. doi: 10.21037/atm.2018.09.38