Consolidation Chemotherapy after Concurrent Radiochemotherapy in Locally Advanced Non–small-Cell Lung Cancer May Have Been Beneficial if We Only Knew Where It Have Worked

To the Editor:

In a recent article by Tsujino et al.[1] pooled the data from the literature investigating the effectiveness of consolidation chemotherapy (CHT) after concurrent radiochemotherapy (RT-CHT) in locally advanced non–small-cell lung cancer (NSCLC). They found no difference (survivals, toxicity) between RT-CHT followed by consolidation CHT and exclusive RT-CHT, adding to previous observations that concurrent RT-CHT is the standard treatment in locally advanced NSCLC.[2–4] Another recent data[5] showed that concurrent RT-CHT can also be considered as one of standards in clinical stage IIIA NSCLC patients.

Although reasons for inefficiency of consolidation CHT may be multiple, it is challenging to disclose some aspects that may have adversely influenced the outcome. Although these studies presented very detailed pattern of failure in general, this was done for the whole time period of the study (treatment plus follow-up). This way we only learned about the total patterns of failure and not about which type of failure was observed when, that is, after concurrent or after consolidation part, and particularly in which patients.

Why exact pattern of failure is so important? First, there are several types of patients after the initial (concurrent) part of RT-CHT and they can easily be separated regarding the response. Although it is extremely unlikely that those achieving a stable disease would benefit from the consolidation CHT, those with either a complete response (CR) or a partial response (PR) seem as likely candidates (although not all of them) to benefit from the consolidation CHT. Therefore, separation of pattern of failure occurring in likely (CR and PR) and unlikely (stable disease) candidates could be used for further studies using similar design with respect to, for example, eligibility criteria. Second, and more importantly, among likely candidates (CR and PR) to benefit from consolidation CHT, a distinction should be made between those achieving CR and those achieving PR after concurrent RT-CHT. This is so because different mechanisms (precisely, different location) of action of consolidation CHT would be expected. In the CR patients, consolidation CHT would target only a microscopic disease both intrathoracically and extrathoracically, whereas in the PR patients, it would have also to address clinically overt intrathoracic disease. Pattern of failure in these two distinct groups of patients would then clearly show how and where consolidation CHT actually acts and to what extent (clinical versus subclinical). In addition, we would be able to investigate the determinants of treatment outcome such as cross-resistance between drugs or drugs and RT.

Although identifying pattern of failure in patients achieving different response after concurrent RT-CHT would place additional burden on investigators and hospitals, this effort would be eventually rewarding. This way we would be able to identify different patient subsets and different options and to proceed (or not) with a consolidation CHT, an approach which would ultimately lead to a better patient-tailored treatment sequence, a must for a future clinical research in lung cancer.

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Role of Consolidation Chemotherapy after Concurrent Chemo-Radiotherapy in Locally Advanced Non–Small-Cell Lung Cancer

In Response:

We thank Dr. Jermic for giving us an opportunity to express our

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views in our study. Our pooled analysis failed to show the efficacy of consolidation chemotherapy (CCT) in terms of survival prolongation for patients with locally advanced non–small-cell cancer (LA-NSCLC). This negative result should carefully be assessed because, as Dr. Jermic suggested, our study has several limitations which might affect our study result.[1] In particular, as our study was performed on a publication basis, we could not assess the heterogeneity at the individual patient level. It is important to identify the characteristics of patients who could benefit from CCT. However, we could not carry out subgroup analyses based on the patterns of treatment failure or responses to initial chemo-radiotherapies as our analysis did not use individual data of each trial.

Another important factor that may affect our study result is the diversity of CCT regimens among trials. We evaluated the effectiveness of CCT by dividing it into two patterns: continuous CCT, which continues chemotherapy with agents given in the induction therapy, and switch CCT (SCCT), which switches chemotherapy to different agent(s) in the consolidation phase. SCCT might be more promising than continuous CCT because it is expected to effectively eradicate tumor cells resistant to the induction chemo-radiotherapy. Although our analyses failed to show the efficacy of SCCT, it was probably because of the small number of trials: only four trials were designed for SCCT. Further clinical trials on SCCT will be warranted to answer these queries.

Finally, our pooled analysis failed to provide evidence that CCT yields significant survival benefit for LA-NSCLC patients. However, we believe that the findings of this study are relevant because it reminds us that there is currently no sufficient evidence to support CCT for LA-NSCLC patients, and that current recommended treatment for LA-NSCLC patients remains concurrent chemo-radiotherapy. Little progress in treatment strategies for LA-NSCLC patients has been observed in the last 20 years,[2] and it is urgent to seek new treatment options/strategies to improve this. Further studies, for example, individual patient-based meta-analyses or prospective studies focusing on patterns of treatment failure or responses to initial chemo-radiotherapy are needed to establish how to use CCT appropriately to improve survival of LA-NSCLC patients.

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Lung Adenocarcinoma with Ipsilateral Pleural and Breast Metastases

To the Editor:

We congratulate Huang et al.[1] for their elegant description on how lung adenocarcinoma cells may metastasize to the ipsilateral parietal pleura, invade the chest wall lymphatic vessels which drain to the ipsilateral axillary lymph nodes, retrogradely spread to the intramammary lymphatics, and finally establish ipsilateral breast metastasis. It is plausible that the presence of the clinical triad of ipsilateral pleural effusion or thickness, enlarged ipsilateral axillary lymph nodes that are palpable or evident on computed tomography (CT), and ipsilateral breast metastasis provides support for this proposed mechanism for ipsilateral breast metastasis from lung cancer. In addition, the presence of intact fat planes between the chest wall and breast tissue on CT scan excludes direct tumor invasion of the breast from the ipsilateral parietal pleural metastasis as a less likely mechanism.[1]

We also like to add that the absence of enlarged mediastinal (N2 or N3 disease) and ipsilateral supraclavicular (N3 disease) lymph nodes on CT scan and the latter also on palpation is needed to discount the other possible mechanism of lymphatic spread to ipsilateral axillary lymph nodes from mediastinal lymph nodes, through intercostal lymphatics[2] or retrogradely through supraclavicular nodes.[3]

Whatever the mechanism of spread to the axillary lymph nodes, breast metastasis is an infrequent manifestation of advanced disseminated lung cancer and is associated with an extremely poor prognosis and a short survival.[4,5]

As Huang et al.[1] has stated, differentiating primary from metastatic breast carcinoma is of great clinical importance

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