Chemotherapy regimens for metastatic nonsmall cell lung cancer: Generating good quality data is important before challenging evidence

Sir,

It was interesting to read the study by Kamath *et al.* on their experience with etoposide-cisplatin (Eto-Cis) in metastatic nonsmall cell lung cancer (NSCLC).[1] The authors concluded that this regimen had a substantial "pharmacoeconomic benefit" in patients belonging to "lower socioeconomic group." However, there are several flaws in the design and statistical analysis of this paper due to which the above-mentioned conclusion may not necessarily by valid.

Of the several major issues, the first is the use of mean for depicting and comparing survival (overall survival [OS] as well as progression free survival [PFS]) between different groups. The mean survival time is highly affected by censorings, cannot estimate survival reliably and is in fact rarely reported.[2,3] If one looks at the median PFS values, patients treated with Eto-Cis in fact had a lower PFS (6.0 months) as compared to those receiving any of the other regimens which ranged from 8.75–9.0 months. However, the Kaplan–Meier survival curves, as well as 95% confidence intervals, are overlapping and the log-rank test, which is traditionally used for comparing the median survival times, does not show any statistical difference.

The second issue is of that related to reporting and comparison of toxicity profiles. Typically toxicities are graded and the common toxicity criteria is a very useful tool for comparing adverse events from any given drug or drug combinations.[4] Herein, each toxicity is graded from a scale of 1–5 wherein Grades 1–2 represent mild to moderate toxicity while Grades 3 or higher are indicative of severe to very severe toxicity. It is also equally important while assessing the toxicity profile of different chemotherapy regimens to know not just the frequency of any grade toxicity but also the frequency of severe toxicity (Grade 3 and higher). Moreover, toxicities have been reported for only 59.1% (78 of 132) of patients receiving Eto-Cis, 65.9% (56 of 85) of those receiving paclitaxel-platinum, 46.2% (12 of 26) of patients receiving gemcitabine-platinum and 63.9% (39 of 61) of patients receiving pemetrexed-platinum. To have an accurate idea of the frequency of any grade toxicity and severe (Grade 3 or higher) toxicity from any given regimen, one needs to have all the number of patients who received one cycle or more as the denominator. This also leads one to wonder whether the frequencies of different toxicities from the four chemotherapy regimens shown in Table 4 represent under-estimates or over-estimates of their respective actual occurrences and for this reason a comment on their similarities and differences, as has been done by the authors, namely "highest incidence of hepatotoxicity from gemcitabine-platinum" is not warranted.

The third issue is that given the data provided by the authors in the manuscript, we performed a simple comparative (Chi-square) analysis and found that the percentage of patients completing $\geq$3 cycles was significantly lower with Eto-Cis (80.3%; 106/132) as compared to either pemetrexed-platinum (95.0%; 58/61; $P = 0.008$) or gemcitabine-platinum (100.0%; 26/26; $P = 0.013$) whereas it was similar to that with

paclitaxel-platinum (83.5%; 71/85; $P = 0.550$). It is possible that this could be due to either higher frequency of disease progression with Eto-Cis (something that has not been commented on by the authors) or due to greater toxicity with this regimen (something which is not possible to infer given the missing number of patients for whom toxicity has not been reported – a flaw already eluded to by us in the paragraph above). The authors herein have also stated that the median duration of hospitalization for management of major chemotherapy related toxicities with the Eto-Cis regimen was the highest (5 days) as compared to the other regimens and being least for pemetrexed and gemcitabine-containing regimens (3 days each).

Finally, the fourth issue is that pharmacoeconomic analysis generally requires much more than calculation of direct costs and indirect costs and often involves use of specialized statistical tools and methods such as Markov model, incremental cost-effectiveness ratio, net benefit approach, and assessment of cost-effectiveness at various willingness-to-pay levels.[5-7]

Apart from this, there are a few other minor statistical errors in the manuscript that perhaps need clarification [Table 1], the use of Chi-square for a 1×2 analysis (distribution of smokers and nonsmokers in the patient population).

Eto-Cis continues to be the standard regimen used for small cell lung cancer and one of the preferred regimens to be used in combination with radiation for patients undergoing concurrent chemoradiation for unresectable Stage III NSCLC.[8,9] However, there is overwhelming evidence to indicate the superiority of pemetrexed-platinum combination for nonsquamous NSCLC for all clinically relevant endpoints (OS, PFS, objective radiological responses and toxicity profile).[10-13] In the case of squamous cell carcinoma of the lung, gemcitabine-platinum remains the preferred chemotherapy regimen although the evidence comparing different third-generation chemotherapeutic agents is more balanced and taxane-platinum doublet is equally acceptable.[14,15] One also needs to consider the ease of administration of the different chemotherapy regimens. All the three regimens other than Eto-Cis are administered as outpatient (daycare) since they are all D1 only regimens. On the other hand, Eto-Cis being a D1–D3 regimen makes it inconvenient for patients coming from distant places and mandates either admission for administering chemotherapy as inpatients or for them to find other places to stay near the hospital/day care centre and thus in turn increases the indirect costs related to this particular chemotherapy regimen.[16]

Although we fully understand the importance of considering socioeconomic background and cost of therapy while taking decisions for lung cancer patients in resource-constrained settings such as ours, it is equally prudent to understand that cheaper regimens are not necessarily better and that one has to individualize the decision for every given patient presenting to us in our clinic and sometimes this involves trading off between using a relatively more expensive but more effective and better-tolerated drug like pemetrexed/gemcitabine versus using a more affordable drug like paclitaxel or even for that matter etoposide.[16,17] Ultimately, all of us wish to do the best for our patients despite the limitations binding us and for this purpose, there is little to achieve by going against conventional wisdom and challenging strong evidence with something contrary unless we have sufficient grounds to do so and that comes only by being able to generate good quality data first.

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Conflicts of interest
There are no conflicts of interest.

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