Reviewer's report

Title: The effect on survival of continuing chemotherapy to near death

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Reviewer: Alvin Wong

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1. The main point for the reviewer here is whether the study is just stating the obvious. To say that ‘chemotherapy in the last 2 weeks of life’ is not associated with prolongation of survival could be interpreted as a mere re-statement of its own definition. If some patients died soon after chemotherapy, then these are patients ultimately did not do so well and their survival was obviously not more prolonged. ‘Aggressive chemotherapy’ here is defined based on the outcome (death) that has already occurred. It is thus not clear what the study is trying to show, and this begs an explanation from the authors.

2. Ultimately, the category ‘chemotherapy in the last 2 weeks of life’ exists only in retrospect. While the senior author has presented the case for the usefulness of retrospective studies in this area, one assumption is that ‘physicians usually know when their patients are nearing death’.1 There is, however, a difference to describing the fact that some patients die within 2 weeks of chemotherapy, and implying that chemotherapy is knowingly given to patients who will die in 2 weeks regardless of the treatment. The controversy is furthered by:

   a. Studies showing that physician estimates can be inaccurate in predicting the time of death. In fact, they tend to overestimate the time remaining for patients who actually die soon.

   b. Other studies showing that oncologists tend not to treat patients whom they think are about to die, or have the same approach to end of life care as generalists. This study itself reports that 85% of patients who died within 3 months of diagnosis did not receive any chemotherapy.

   c. The fact that unexpected deaths occur, for example, due to treatment related toxicity.1

It is a difficult point to prove that oncologists are over-aggressive in prescribing chemotherapy at the end of life from a ‘prospective’ point of view. Retrospectively one could describe the fact that some deaths occur close to the last chemotherapy. However, a similar pro-active approach in chemotherapy prescribing could have resulted in the prolonged survival for the other group of patients – at least, one cannot rule this out. In fact, the survival in both ‘standard’ and ‘aggressive’ chemotherapy groups was better than the ‘no chemotherapy’ group. Other factors may contribute substantially to the phenomenon of chemotherapy close to the end of life, such as the inaccurate prediction of patients’ survival, or the inability to foresee fatal toxicities in a particular patient.
The discussion in this paper is somewhat brief and should touch more on these areas in order to give a more balanced approach.1

3. This study was done on lung cancer patients who received chemotherapy in the 1990’s. Much has changed in recent years with the development of lower toxicity targeted therapy, especially in non-small cell lung cancer. Inoue et al gave gefitinib to poor performance status lung cancer patients whose tumors contained sensitizing EGFR mutations and showed dramatic turnaround in their clinical status, prompting Langer’s editorial on the “Lazarus’ effect”.2,3 Even if their contention were true, that chemotherapy is given aggressively and excessively close to the end of life in patients who seem to already have a poor prognosis, the authors may like to mention the point that anti-cancer treatment in the targeted era may justifiably modify the threshold for aggressive treatment.

References: