

The latest meta-analysis on the use of erythropoiesis-stimulating agents in chemotherapy induced anaemia brings new light on the safety

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In this current issue of Lung Cancer, Vansteenkiste *et al.* (1) report the results of 2 meta-analysis on the benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients. This is a welcome manuscript that comes to clarify some of the safety concerns the medical community had on the use of ESAs in cancer. It is well established that ESAs reduce the requirements of blood transfusions and improve quality of life. However, over the last few years results from several controlled ESAs trials and from meta-analysis of these trials brought a safety concern that lead to a FDA alarm on the use of ESAs. This action was triggered by the negative outcome observed in patients from some trials in the ESAs arm compared to the placebo arm. Interestingly, only one of such studies was in lung cancer, EPO-CAN-20 (2). In that particular trial patients were not receiving chemotherapy and the study was terminated prematurely when only 70 patients were recruited. This happened at the peak of the FDA alarm. Retrospectively, this study should never have been closed. Several evaluations on the potential causes for such negative outcomes observed in a minority of clinical trials, compared to more than 60 trials conducted on ESAs in cancer where no alarm signal was identified, have concluded that in all of these trials the use of ESAs was off-label. Patients received only radiotherapy, anemic cancer patients received ESAs on no cancer treatment and, finally cancer patients received ESAs in an anemia prevention protocol, clearly neither one of these situations was indicated,

The current manuscript (1) reports the results of two meta-analysis, one at the study-level and the other at the patient level in lung cancer patients on chemotherapy receiving ESAs and in particular darbepoetin alfa (DA).

In the study-level meta-analysis, 9 studies were included with 2,342 patients enrolled. Results showed an odd ratio (OR) of 0.87 for mortality, an OR of 0.84 (in only 5 studies analyzed) and, an OR of 0.34 for transfusion incidence. As per the patient-level study, 4 studies were included with 1,009 patients recruited. The results here are favourable for the use of ESAs when compared to placebo. Patients in the DA arm the survival time was 41 *vs.* 34 weeks for the placebo arm. During the combined study, the authors observed 80% mortality for patients in the placebo arm *vs.* 74% in the DA arm. In their final analysis, overall mortality for the DA arm was 84% while it was 87% for the placebo arm. The authors concluded that for patients with lung cancer receiving chemotherapy, who become anemic the use of ESAs reduces the blood transfusions requirements by 19% compared to 43% for the placebo arm. More importantly, the authors did not observed any safety alarm in neither one of the studies but a clinical benefit.

The unexpected results from the study by Littlewood *et al.* (3) in 2001 showing a better survival of almost 6 months in the arm of epoetin alfa compared to the placebo arm brought an outburst of studies on the field trying to prove that ESAs may be working as an universal adjuvant but improving tissue oxygenation and leading to better responses and to better outcomes. Recent publications by several authors as well as several meta-analysis on the use of ESAs in cancer patients show a neutral effect of the ESAS and no alarm signal has been reported (4-6).

Two ongoing prospective studies have disease progression and mortality as their primary end-points, one in breast cancer (epoetin alfa) and the other in lung cancer (DA). Until the results of these definitive studies become available,

the results by Vansteenkiste *et al.* (1) are encouraging and reassuring of the safety of DA and of all epoetins in cancer patients treated with chemotherapy. It is fair to say in light of results from this publication in lung cancer and several others published recently that the use of ESAs reduces the requirements for blood transfusions, improve quality of life and very important, their use is safe providing they are used according to registry specifications.

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