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PROSTATE CANCER

Mixed responses to ipilimumab

Prostate cancer seems to have an immune component, but therapies targeting antitumour immunity have had a limited impact on patient management. Now, the first phase III trial of ipilimumab—an antagonist of the immune checkpoint inhibitor cytotoxic T-lymphocyte antigen 4—in metastatic castration-resistant prostate cancer (mCRPC) has produced mixed results, but provides at least a glimmer of hope for this approach.

Kwon *et al.* enrolled 799 men with at least one bone metastasis and disease progression after docetaxel therapy. “We designed the study such that radiotherapy, which might stimulate the immune system to attack cancer cells (the abscopal effect), was given just before the men were randomized to either 3-weekly ipilimumab (10 mg/kg) or placebo, with the goal of potentiating the immune response,” says Kwon.

“Although the study did not meet its primary end point of an improvement in overall survival at the interim analysis, there was evidence of activity with ipilimumab in this population of patients with advanced mCRPC,” says Kwon. Indeed, overall survival was 11.2 months and 10.0 months, in the ipilimumab and placebo groups, respectively, and the effect of ipilimumab on survival was close to significant ($P=0.053$). “In particular, prespecified and exploratory subgroup analyses suggest the possibility that ipilimumab is most active in patients with favourable prognostic factors for CRPC.” For example, in patients with no visceral metastases and mild or no elevation in alkaline phosphatase levels, and without anaemia, median overall survival in the ipilimumab group was 22.7 months versus 15.8 months in the placebo cohort ($P=0.0038$).

Progression-free survival was also improved in the ipilimumab group compared with the placebo cohort (median of 4.0 months versus 3.1 months; $P<0.0001$). However, in an accompanying commentary, Chris Parker, of the Royal Marsden Hospital, expresses concern over the value of this finding. He points out that the end point used to define progression, clinical deterioration, is relatively subjective and, in the context of potential unblinding due to the distinctive pattern of toxic effects associated with ipilimumab, might be a source of bias. Of note, the rates of ipilimumab-related adverse events (75%) and immune-related toxicity (63%) were high. Indeed, Parker also questions the safety of ipilimumab therapy. As defining the cause of death in patients with mCRPC can be difficult, he highlights the rate of fatal reactions to ipilimumab (1%), in particular, as a potential underestimation—especially considering the higher rates observed in studies in melanoma, in which lower doses of ipilimumab were used (3 mg/kg) and patients tended to be younger.

The study findings, nevertheless, demand further investigation; indeed, “ipilimumab is currently being evaluated in a phase III trial (CA184-095) involving patients with asymptomatic or minimally symptomatic mCRPC, excluding patients with visceral metastases,” states Kwon. “While CA184-095 was designed independently of our trial, it will enable testing of important hypotheses generated by our results,” he concludes.

David Killock

Original article Kwon, E. D. *et al.* Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol.* doi:10.1016/S1470-2045(14)70189-5