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LUNG CANCER

Maintenance chemotherapy—a stitch in time saves nine?

Until recently, patients with non-small-cell lung cancer (NSCLC) had very few therapy options. For the three-quarters of patients who presented with locally advanced (stage IIIb) or metastatic (stage IV) disease, the treatment recommendation was platinum-based first-line therapy, with an alternative therapy offered as a second-line treatment on disease progression. The response rates to the first-line treatment were 20–40% and patients had an overall survival of 7–12 months. In addition to this poor overall survival, patients experience pronounced symptoms, including pain, fatigue, cough, shortness of breath, and loss of appetite and weight. The identification of the antimetabolite pemetrexed as a drug that extended survival in these patients when used as maintenance therapy following first-line chemotherapy has opened up new options. Two recent trials have now revealed that maintenance pemetrexed is efficacious when used following a first-line therapy that included pemetrexed, and also that maintenance pemetrexed is not detrimental to the quality of life of those patients receiving it.

The trial that assessed the efficacy of pemetrexed was conducted by a team led by Luis Paz-Ares. This phase III, double-blind, placebo-controlled trial enrolled 539 patients with advanced-stage non-squamous NSCLC who had received four cycles of cisplatin–pemetrexed combination as induction (first-line) treatment and not experienced disease progression. On completion of their first-line regimen, the patients were randomly assigned to pemetrexed maintenance or placebo, and all patients additionally received best supportive care. Paz-Ares explains the rationale behind the trial, "at the initiation of our trial it was unclear if pemetrexed maintenance therapy would further enhance efficacy after four cycles of pemetrexed and cisplatin. It was hypothesized that the administration of a treatment demonstrated to be effective and well tolerated during the induction regimen as a maintenance therapy would combine the advantage of continuing beneficial therapy with the improved safety of a single agent."

The primary end point of this trial (PARAMOUNT) was progression-free survival (PFS) in the intention-to-treat population. Paz-Ares points out, "PFS was selected as the primary end point because delaying progression is beneficial to patients. Furthermore, PFS has been shown to be a valid and reliable measure of clinical benefit in a pemetrexed trial." In PARAMOUNT, the treatment with maintenance pemetrexed was associated with a PFS of 4.1 months, which compared favorably with the PFS of 2.8 months for the placebo group. "These data are the first to show that pemetrexed in a continuation maintenance setting is beneficial to patients with locally advanced or metastatic NSCLC," states Paz-Ares.

Although an improved PFS is obviously an important end point for patients, it has been shown previously that most patients with NSCLC would choose a treatment that improved their respiratory symptoms—and thus their quality of life—but had no effect on overall survival over a therapy that prolonged survival for 3 months. This obviously leads us to the question of what effect maintenance pemetrexed has on the quality of life of patients, an aspect that has been addressed in the follow up report of the H3E-MC-JMEN trial. This phase III, placebo-controlled trial assessed maintenance pemetrexed in patients with advanced-stage NSCLC who had received four cycles of platinum-based induction therapy, and showed that this therapy significantly improved overall survival and PFS in this patient population.

The quality-of-life assessment was a prospective aspect of the study and involved the completion of the Lung Cancer Symptom Scale at predetermined points in the study. Using these self-reported measures, the investigators were able to show that the maintenance pemetrexed group had a very similar overall quality of life to those receiving placebo, with the only significant difference being a small increase in loss of appetite and a delay in the worsening of pain and hemoptysis.

Taking these data together, maintenance pemetrexed is well tolerated and results in survival improvements for patients. So it seems that the old wives tale is true in this case, maintenance (or a stitch in time) really is better than rescue therapy.

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Original articles Paz-Ares, P. *et al*. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol*. doi:10.1016/S1470-2045(12)70063-3 | Belani, C. P. *et al*. Quality of life in patients with advanced non-small-cell lung cancer given maintenance treatment with pemetrexed versus placebo (H3E-MC-JMEN): results from a randomised, double-blind, phase 3 study. *Lancet Oncol*. doi:10.1016/S1470-2045(11)70398-9