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Editorial

Pemetrexed re-challenge in pleural malignant mesothelioma: An option for a subset of patients initially treated with pemetrexed-platinum doublets in the first-line setting?

Malignant pleural mesothelioma (MPM) is a highly aggressive tumor that has become a very important problem in recent years. Asbestos exposure is the main factor involved in its pathogenesis, which can explain the rise in incidence of MPM since the late sixties. Although mesothelioma is rare in the general population, a prevalence of 100 cases per million individuals per year in asbestos-exposed individuals leads to an annual incidence of 10,000 cases in the industrialized countries where asbestos was widely used.

Taking account that this is a low incidence disease, a recent bibliometric survey found only 2559 published articles dealing with mesothelioma from 1987 to 2006 [1]. Less than 20 articles reported on controlled clinical trials during the last two decades, of which there were only five phase III trials with more than 200 patients recruited. Evidence-based mesothelioma medicine has therefore relied on low-level of evidence studies, retrospective series or registries, and guidelines from scientific societies based on expert consensus.

Until the early 2000s, first-line treatment was disappointing. Patients with early-stage MPM were thought to benefit from a radical surgical procedure, extra-pleural pneumonectomy (EPP), as a part of a multimodality therapeutic program, which included preoperative cisplatin-based chemotherapy, and was often followed by hemithoracic radiotherapy. Ninety-day mortality of such a procedure was high, from 7% to 11%, with major morbidities and long hospital stays often exceeding 30 days [2]. Data from North American surgical registries showed a 14–16-month median survival, only reaching 20 months for the clinical stage I patients [3,4]. Subsequently, phase II multimodality trials which employed pemetrexed-based chemotherapy confirmed a 16.8–18.4-month median survival for very highly selected stage I to III patients, of whom less than 2/3 were able complete the whole tri-modality sequence [5,6].

Poor results were also obtained with the older chemotherapy regimens of the 1990s, in patients considered not amenable for surgery. This is perfectly illustrated by the MS01 phase III trial from the Medical Research Council, which randomized 409 patients into a best supportive care (BSC) arm, compared to a triplet chemotherapy regimen of mitomycin, vinblastine and cisplatin, or weekly vinorelbine [7]. No improvement in quality of life or symptoms was observed with chemotherapy. Median overall survival was only 8.5 and 7.6 months in the pooled chemotherapy arms and the BSC arm respectively, and 1-year survival rates were abysmal, at 37% and 30%, respectively.

In the early 2000s, first-line chemotherapy with a combination of cisplatin/pemetrexed or cisplatin/raltitrexed was shown to be superior to cisplatin monotherapy [8]. With these new generation cisplatin and anti-folate-based doublets, median survival reached 13.3 months and one-year survival was 56% in patients receiving vitamin B_{12} and folic acid supplementation. Those results were strengthened by evidence that pemetrexed-cisplatin could improve quality of life and symptoms such as dyspnoea.

Recent phase II trials using pemetrexed-platinum doublets have been even more encouraging, consistently showing median survivals of 14–15 months for advanced-stage patients [9,10]. These results are close to those obtained with EPP-based multimodality treatment in selected early-stage MPM patients. Before regulatory approval of pemetrexed, an Expanded Access Program also confirmed in more than 3000 MPM patients that pemetrexed-platinum doublets can yield a 64% one 1-year survival in chemo-naive patients [11].

Thymidylate synthase (TS) is the main enzymatic target of pemetrexed. Retrospective studies have shown that TS may be a predictive biomarker in MPM patients who receive pemetrexed; in one recent study the subset of patients with low TS protein expression had a provocative 30-month median overall survival [12]. These data clearly suggest that pemetrexed could actually change the natural history of MPM, especially in patients with low TS protein expression.

All MPM patients ultimately progress on or after first-line treatment. Second-line therapies are being increasingly used since patients frequently remain in a good general condition at the time of disease progression. In the 189 patients who received post-study therapy in the pivotal phase III pemetrexed-cisplatin *vs.* cisplatin registration trial, second-line treatments were shown to produce a statistically significant impact on overall survival [13]. A randomized phase III trial comparing pemetrexed plus best supportive care with BSC in previously-treated, but pemetrexed-naive advanced MPM patients demonstrated that pemetrexed significantly delayed disease progression [14]. These studies collectively suggest that second-line treatment could influence overall survival, even though definitive evidence from a randomized trial is still lacking.

In a retrospective observational study published in this issue of *Lung Cancer*, Ceresoli and colleagues now provide some compelling arguments favoring re-challenging MPM patients previously treated with pemetrexed. During a five-year period,

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thirty-two PS 0-1 patients who did not progress for at least 3 months after first-line pemetrexed-based chemotherapy (PBC) were retreated with PBC as a second-, third- or even fourth-line therapy. Nineteen percent of these patients experienced an objective response to re-treatment, and 31% had stable disease. One-year survival from the first day of re-treatment PBC was 61.5% in patients treated in the second-line setting.

Patients retreated with PBC who had a PFS less than 12 months after first-line chemotherapy had a one-year survival of only 18.8%, while those who had a PFS greater than 12 months after initial PBC achieved a 54.1% one-year survival with retreatment. About 20–25% of MPM patients receiving pemetrexed-cisplatin front-line therapy fall into this subset. Overall, a median PFS of 3.9 months, and a median overall survival of 10.3 months from the start of PBC re-challenge was observed. In this series, only 3 patients had grade 3–4 hematological toxicity and only one patient experienced febrile neutropenia.

Because of the retrospective non-randomized design, these provocative results must be considered with caution, and should be hypothesis-generating. But these observations certainly deserve further study in a prospective trial. One could envision a study in which "pemetrexed-sensitive" patients who have a long PFS following front-line treatment are stratified by TS levels and are randomized to pemetrexed re-treatment, or a well-tolerated regimen with a different mode of action such as weekly vinorelbine, or placebo. In the absence of prospective randomized data to confirm Ceresoli's retrospective observation, re-challenging sensitive patients with pemetrexed-based therapy could be considered as an option for fit patients in whom no investigational treatment options are available.

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