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Original Research

Maintenance therapy with pemetrexed and bevacizumab versus pemetrexed monotherapy after induction therapy with carboplatin, pemetrexed, and bevacizumab in patients with advanced non-squamous non small cell lung cancer☆

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KEYWORDS
Bevacizumab;
Carboplatin;
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Non small cell lung cancer;
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Abstract ***Objectives:*** Single agent maintenance therapy is widely accepted for advanced non-squamous non small cell lung cancer (NSCLC). However, there is no consensus on the initial and maintenance phase regimens, and the clinical benefit of adding bevacizumab to cytotoxic drugs in the maintenance phase remains unclear.
Methods: Chemotherapy-naïve patients with non-squamous NSCLC were randomly assigned to maintenance therapy with pemetrexed and bevacizumab or pemetrexed alone, after achieving disease control after four cycles of induction therapy with carboplatin (area under the curve = 6), pemetrexed (500 mg/m^2), and bevacizumab (15 mg/kg). The primary end-point was 1-year progression-free survival (PFS) rate.
Results: One hundred ten patients were enrolled in the study, with 55 patients assigned to the two groups. The mean 1-year PFS rate was 43.9% (95% confidence interval [CI]: 29.6–59.2%) in the combination maintenance group and 35.2% (95% CI: 22.1–51.0%) in the pemetrexed maintenance group, and the difference was not significant (p = 0.433). Median PFS measured from enrolment was 11.5 months (95% CI: 7.1–19.0) in the combination maintenance group and 7.3 months (95% CI: 5.7–14.1, hazard ratio: 0.73, 95% CI: 0.44–1.19, log-rank p = 0.198) in the pemetrexed maintenance group. Nasal haemorrhage, hypertension, and proteinuria were significantly more frequent in the combination maintenance group, but they were mild and tolerable.
Conclusion: Both maintenance therapy with pemetrexed alone and pemetrexed and bevacizumab in combination were feasible in patients with non-squamous NSCLC who have achieved disease control after induction therapy with carboplatin, pemetrexed, and bevacizumab. According to the selection design, differences in the superiority between these maintenance therapies were not demonstrated.

Introduction

Lung cancer is a leading cause of cancer death worldwide [1,2]. In patients with advanced non small cell lung cancer (NSCLC), platinum-based combination chemotherapy has improved survival and quality of life [2,3]. Until recently, patients with advanced NSCLC who completed first-line chemotherapy were followed up without chemotherapy until disease progression, then second-line chemotherapy was administered when the patient exhibited adequate general health and organ function [3]. However, it has been reported that ≤50% of patients cannot receive second-line chemotherapy mainly because of deteriorating general health [4,5]. To increase the proportion of patients who can receive second-line chemotherapy, maintenance therapy, which is defined as the continuation of chemotherapy without interruption following effective first-line chemotherapy, has emerged as a novel strategy for the treatment of advanced NSCLC [2,6,7].

The high efficacy of first-line chemotherapy and maintaining good performance status are essential to receive maintenance therapy [2,8]. Pemetrexed is a multitargeted antifolate that has demonstrated efficacy for non-squamous NSCLC as first-line therapy combined with platinum agents or second-line therapy in single use [9,10]. In addition, maintenance therapy with pemetrexed after platinum-based chemotherapy prolonged survival [11,12]. Bevacizumab, an angiogenic inhibitor, is known to stabilise the tumour microenvironment and improve the drug delivery of anti-cancer agents to tumours, which work to enhance the efficacy of chemotherapy [13–16]. Sandler et al. reported that bevacizumab in combination with carboplatin and paclitaxel chemotherapy followed by bevacizumab maintenance prolonged survival compared with carboplatin and paclitaxel [17].

Maintenance therapy with pemetrexed or bevacizumab is widely accepted as a standard therapeutic option for advanced non-squamous NSCLC [2,6,18]. However, there is no consensus regarding the initial therapeutic regimens or the choice of chemotherapeutic agents in the maintenance phase [6,7,18]. In the AVAPERL trial, patients with non-squamous NSCLC who were receiving pemetrexed and bevacizumab maintenance therapy after pemetrexed, cisplatin, and bevacizumab induction therapy had significantly prolonged progression-free survival (PFS), compared with those treated with bevacizumab maintenance therapy [19]. The result confirmed the significance of pemetrexed in maintenance therapy after bevacizumab-containing platinum-based therapy; however, it is unknown whether the addition of bevacizumab to pemetrexed in the maintenance phase improves efficacy. In this study, we evaluated the efficacy and safety of maintenance therapy with pemetrexed alone or pemetrexed and bevacizumab following induction therapy with carboplatin,