



Original research article

Meta-analysis examining impact of age on overall survival with pemetrexed for the treatment of advanced non-squamous non-small cell lung cancer



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ARTICLE INFO

Article history:

Received 10 March 2016

Received in revised form 2 December 2016

Accepted 11 December 2016

Keywords:

Elderly

Meta-analysis

Advanced non-small cell lung cancer

Pemetrexed

Overall survival

ABSTRACT

Objective: In clinical practice, elderly patients are often undertreated relative to younger patients. This meta-analysis was designed to determine whether older patients with non-squamous non-small cell lung cancer (NSCLC) could derive an overall survival (OS) benefit from pemetrexed treatment comparable to that experienced by younger patients in the first-line, second-line, or maintenance settings.

Methods: Data from 2671 patients with non-squamous NSCLC participating in four pemetrexed phase III studies were included in a meta-analysis using a random-effects model. Studies included were: JMEI (second-line pemetrexed, N = 399); JMDB (first-line pemetrexed/cisplatin, N = 1252); JMEN (pemetrexed maintenance after non-pemetrexed/platinum doublet, N = 481); and PARAMOUNT (pemetrexed maintenance after first-line pemetrexed/cisplatin, N = 539). Patients were predominantly Eastern Cooperative Oncology Group performance status (PS) 0/1. The ratio of OS hazard ratio (HR) (pemetrexed versus control) for younger patients over that for older patients within each study was used as the measure of the differential effect of pemetrexed. Data were examined using age cutoffs of 65 and 70 years.

Results: Among the four studies, 32% of patients were aged ≥ 65 years and 14% were aged ≥ 70 years. The test of heterogeneity among studies was non-significant for subgroups defined by age 65 ($P = 0.083$) and age 70 ($P = 0.848$). The pooled ratio of the OS HR (pemetrexed versus control) in patients < 65 years to that in patients ≥ 65 years was 0.92 (95% confidence intervals [CI] 0.67–1.25). Similar results were seen for the analysis using the age 70 years cut-off (0.80 [95% CI 0.62–1.04]).

Conclusions: In patients with non-squamous NSCLC with good PS, the effect of pemetrexed on OS was not found to be different in younger and older patients undergoing treatment in the first-line, second-line, or maintenance settings.

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1. Introduction

The incidence of lung cancer increases with age and this rate is expected to continue to grow in the upcoming years as more people live longer. More than 50% of newly diagnosed cases of advanced

non-small cell lung cancer (NSCLC) occur in patients aged > 70 years [1], and Surveillance, Epidemiology and End Results (SEER) Program data in the United States show that patients ≥ 70 years account for 47% and patients ≥ 80 years account for 14% of all patients with lung cancer [2].

Despite the high incidence of lung cancer and its high mortality rate in elderly patients, the likelihood of receiving active treatment appears to decrease with increasing age [3,4]. Fit elderly patients with NSCLC are often undertreated in the clinic based purely on their age and physician perception that they would not be able to

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Table 1
Trials included in the meta-analysis.

Phase III trial	Pemetrexed treatment setting	Pemetrexed treatment arm regimen ^a	Control treatment arm regimen	Primary objective	N
JMDB [15]	First line (non-inferiority study)	500 mg/m ² IV q 21 days + cisplatin ^c × 6 cycles	1250 mg/m ² gemcitabine ^b IV q 21 days + cisplatin ^c × 6 cycles	OS	1252
JMEI [16]	Second line after chemotherapy (non-inferiority study)	500 mg/m ² IV q 21 days until disease progression	75 mg/m ² docetaxel IV q 21 days until progressive disease	OS	399
JMEN [17]	MTC after non-pemetrexed platinum doublet	500 mg/m ² IV + BSC q 21 days until disease progression	Placebo + BSC q 21 days until disease progression	PFS	481
PARAMOUNT [18]	MTC after induction pemetrexed + cisplatin	500 mg/m ² IV + BSC q 21 days until disease progression	Placebo + BSC q 21 days until disease progression	PFS	539

Abbreviations: BSC, best supportive care; IV, intravenously; MTC, maintenance; N, number of non-squamous patients in the pemetrexed + control arms of each trial; OS, overall survival; PFS, progression free survival; q 21 days = every 21 days.

^a All patients from all studies receiving pemetrexed also received supplementation with folic acid and vitamin B12 as well as dexamethasone (administered according to pemetrexed prescribing information).

^b 1250 mg/m² gemcitabine administered on days 1 and 8 of each cycle.

^c Cisplatin administration was 75 mg/m² IV q 21 days.

Table 2
Age groups and patient numbers.

Phase III trial	No (%) of patients non-squamous NSCLC in each age group			
	<65 years	≥65 years	<70 years	≥70 years
JMDB	841 (67)	411 (33)	1092 (87)	160 (13)
JMEI	295 (74)	104 (26)	342 (86)	57 (14)
JMEN	322 (67)	159 (33)	404 (84)	77 (16)
PARAMOUNT	350 (65)	189 (35)	447 (83)	92 (17)
Total, N (%)	1808 (68)	863 (32)	2285 (86)	386 (14)

Abbreviation: NSCLC, non-squamous non-small cell lung cancer.

tolerate aggressive chemotherapy [5]. Among more than 20,000 patients aged ≥65 years with newly diagnosed NSCLC, a larger proportion of patients with local disease aged 65–74 years (61%) were reported to receive guideline-recommended treatment than patients aged 75–84 years (44%) or patients aged ≥85 years (18%) [6].

Treatment of lung cancer in older patients may be complicated by several comorbid conditions and greater concomitant medication use compared with younger patients. Other factors such as sensitivity to the toxicity of chemotherapy may also require special consideration [7]. As a consequence, clinical data obtained in a younger population cannot be automatically extrapolated to the great majority of non-selected elderly patients with NSCLC [7]. These factors also mean that elderly patients, including those with a good performance status (PS), are often underrepresented in clinical trials [8,9]. Thus, many patients with advanced NSCLC may not receive available treatments solely because of their age, despite international treatment guidelines suggesting that elderly patients without major comorbidities and PS of 0 or 1 may benefit from platinum-based therapies and could be treated in a similar way to a younger population [1,10,11].

Retrospective analyses suggest that treatment with pemetrexed, a multi-targeted antifolate with well-established efficacy and tolerability in several treatment settings, may be a viable option for elderly patients with non-squamous NSCLC [12–14]. Analysis of individual trials in first-line (JMDB) [12], second-line (JMEI) [13] and maintenance (JMEN, PARAMOUNT) [12,14] settings showed similar survival (favoring pemetrexed over comparators) and toxicity profiles of pemetrexed in older and younger subgroups. This meta-analysis of the aforementioned four trials was designed to determine whether older patients with non-squamous NSCLC and a

good PS can derive an overall survival (OS) benefit from pemetrexed treatment comparable to that experienced by younger patients undergoing first- or second-line treatment, or maintenance therapy.

2. Materials and methods

2.1. Study design

Data from patients with non-squamous NSCLC participating in four pemetrexed phase III studies were included in this meta-analysis (Table 1): JMDB (NCT00087711); non-inferiority study, first-line pemetrexed/cisplatin versus gemcitabine/cisplatin, N=1252 [15]; JMEI; non-inferiority study, second-line pemetrexed versus docetaxel, N=399 [16]; JMEN (NCT00102804); pemetrexed maintenance after non-pemetrexed/platinum doublet, N=481 [17]; PARAMOUNT (NCT00789373); pemetrexed maintenance versus placebo after first-line treatment with pemetrexed/cisplatin, N=539 [18]. For each study, the protocol was approved by the institutional review board at each site and conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

2.2. Study population

The eligibility criteria for the individual studies have been described previously. [15–18] Studies enrolled patients with NSCLC with Eastern Cooperative Oncology Group (ECOG) PS 0 or 1, except for the JMEI trial in which 11% of patients had PS 2 [16]. Analyses were performed on the patients with non-squamous NSCLC randomized in each study.

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