Original Article

Maintenance gemcitabine versus best supportive care following platinum-paclitaxel chemotherapy for patients with advanced nonsmall cell lung cancer

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ABSTRACT

Background: Approximately two-thirds of all patients with newly diagnosed nonsmall cell lung cancer (NSCLC) have advanced disease (Stage IIIB or IV) that is only amenable to palliative chemotherapy. Switch maintenance therapy with a different active agent aims to hit clonal variants resistant to the first-line therapy before they have had time to increase in number. Based on this, we conducted a randomized Phase III study to compare gemcitabine (Gem) versus best supportive care (BSC) as maintenance therapy. **Methods:** Between July 2011 and January 2012, chemo-naive patients with Stage IIIB/IV NSCLC were initially treated with six cycles of cisplatin (40 mg/m^2 day 1, 2) and paclitaxel (175 mg/m^2 day 1) every 3 weeks. Subsequently, nonprogressors were randomized 1:1 to receive maintenance G (1000 mg/m^2 on days 1 and 8 every 3 weeks) or BSC alone till disease progression. The primary endpoint was a comparison of overall survival (OS) between two arms, and the secondary endpoint was progression-free survival (PFS). **Results:** Exactly 134 patients were enrolled (median age: 50 years, males 76.8%, Stage IV disease 50.7%, Eastern Cooperative Oncology Group performance status 0/1: 67.9%). Following 6 cycles of initial therapy, the Response Rate (RR) was 35.1% (Complete Response (CR) 3%, Partial Response (PR) 32.1%), and 38.8% had stable disease. Ninety-nine nonprogressors were randomized to receive Gem (n = 50) or BSC (n = 49). The median OS for Gem was 10 months (95% confidence interval [CI]: 9.2–10.7) and 8 months (95% CI: 6.7–9.2) for BSC, with a hazard ratio (HR) 0.64 (95% CI: 0.51–0.77, P = 0.002). The median PFS was 9 months (95% CI: 8.1–9.9) for G versus 7 months (95% CI: 6.3–7.7) for BSC, with a HR 0.67 (95% CI: 0.50–0.84, P = 0.009). Maintenance therapy was tolerated well despite a higher incidence of grade 3/4 toxicity (anemia 12% vs. 8.1%; neutropenia 18% vs. 4.1%; thrombocytopenia 14% vs. 2%; and fatigue 8% vs. 2%). **Conclusion:** Switch maintenance therapy with gemcitabine, following initial platinum-based doublet chemotherapy in advanced NSCLC can produce significantly longer PFS and OS compared to BSC alone at the cost of higher grade 3/4 hematological toxicities.

Key words: Best supportive care, gemcitabine, nonsmall cell lung cancer, switch maintenance

INTRODUCTION

Lung cancer is the leading cause of death worldwide. Approximately two-thirds of all patients with newly diagnosed nonsmall cell lung cancer (NSCLC) have advanced disease (Stage IIIB or IV).[1] Improving survival in lung cancer is a major challenge for modern oncology. Four to six cycles of platinum-based chemotherapy is currently recommended as the frontline treatment of advanced NSCLC.[2] Several studies have now demonstrated some benefit in patients treated beyond induction chemotherapy

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Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.182056

Cite this article as: Satyanarayan, Beniwal S, Kapoor A, Mittal A, Jakhar SL, Sharma N, *et al*. Maintenance gemcitabine versus best supportive care following platinum-paclitaxel chemotherapy for patients with advanced nonsmall cell lung cancer. Clin Cancer Investig J 2016;5:236-9.

to improve disease control, in terms of progression-free survival (PFS), overall survival (OS) with minimal toxicity and improvement of the quality of life.

The maintenance therapy can be given in the form of either continuous or switch maintenance. Switch maintenance is the treatment with an agent with a distinct mechanism of action after completion of induction chemotherapy in patients with nonprogressive disease. Switch maintenance therapy aims to hit clonal variants resistant to the first-line therapy before they had time to increase in number.[3] Based on this, we conducted a randomized Phase III study to compare gemcitabine (Gem) versus best supportive care (BSC) as maintenance therapy for patients with advanced NSCLC. The primary goal of the study is to evaluate the survival outcome, and a secondary goal of the study is to assess the toxicity during switch maintenance.

METHODS

Eligible patients had a histologic diagnosis of advanced NSCLC (Stage III B disease or Stage IV disease) not amenable to curative treatment. Patients who have not been previously treated with chemotherapy. Other selection criteria included (1) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; (2) age between 18 and 70 years; (3) life expectancy of ≥3 months; (4) adequate liver and renal function; (5) adequate bone marrow reserve (White blood cell >3.0 × 109/L, and hemoglobin >10g/dl, Platelet count >1.0 Lac). Exclusion criteria were: The presence of symptomatic central nervous system metastases, inadequate liver function (total bilirubin >1.5 times upper normal limit [UNL] and serum glutamate-pyruvate transaminase and serum glutamic oxaloacetic transaminase >3.0 or up to 5.0 UNL in the presence of hepatic metastases), inadequate renal function (serum creatinine >1.25 times UNL), active infection, serious concomitant systemic disorder not consistent with the study, and second primary malignancy. Pretreatment screening consisted of general physical examination, routine blood count, biochemical tests, echocardiogram, chest X-ray, computed tomography (CT) scans of the chest including adrenal glands and liver, brain CT scan or magnetic resonance imaging, and bone scan.

Between July 2011 and January 2012, chemo-naive patients with Stage IIIB/IV NSCLC were initially treated with six cycles of cisplatin (40 mg/m^2 day 1, 2) and paclitaxel (175 mg/m^2 day 1) every 3 weekly. Subsequently, nonprogressors were randomized 1:1 to receive maintenance Gem (1000 mg/m^2 on days 1 and 8 every 3 weekly) or BSC till disease progression. The primary endpoint was the comparison of OS, PFS between the two arms and the secondary endpoint was to evaluate toxicity. The survival analyses were performed using Kaplan–Meier survival analysis SPSS version 20.0 (IBM, Armonk, NY, United States of America).

RESULTS

A total of 134 patients were enrolled in the study, the median age of the patients was 50 years (range: 38–65 years). The male:female ratio was 4.6:1 (105:29). The ECOG PS was 0/1 score in 67.9% and 32.1% in score 2. The stage wise distribution was 50.7% Stage IV disease and Stage III disease by 49.7%. Following 6 cycles of initial therapy, the response rate was 35.1% (CR-3%, PR-32.1%), and 38.8% had stable disease (SD). Ninety-nine nonprogressors were randomized to receive Gem (n = 50) or BSC (n = 49). Seven patients have the left treatment in between; rest of patients have completed the treatment and were available for follow-up.

Survival

The median PFS was 9 months (95% confidence interval [CI]: 8.1–9.9) for Gem versus 7 months (95% CI: 6.3–7.7) for BSC, with an hazard ratio (HR) 0.67 (95% CI: 0.50–0.84, P = 0.009). The median OS for Gem was 10 months (95% CI: 9.2–10.7) and 8 months (95% CI: 6.7–9.2) for BSC, with a HR 0.64 (95% CI: 0.51–0.77, P = 0.002).

Safety

Safety was analyzed in 92 treated patients. Gem maintenance therapy was tolerated well despite a higher incidence of grade 3/4 toxicity (anemia 12% vs. 8.1%; neutropenia 18% vs. 4.1%; and thrombocytopenia 14% vs. 2%). The gastrointestinal toxicities and fatigue were also present in the chemotherapy arm frequently. Grade 3–4 toxicities includes (fatigue 8% vs. 2%), nausea and vomiting (6% vs. 2%). Furthermore, abdominal pain was more common in Gem arm.

DISCUSSION

The maintenance therapy includes continuing the initial doublet chemotherapy regimen, continuing only single agent (continuation maintenance) or introducing a new agent ("switch" maintenance therapy). The platinum-based doublet therapy is responsible for the majority of serious treatment-related complications. For this reason, most patients cannot tolerate further administration of platinum-based doublet chemotherapy. This is not true for third-generation single-agent treatment, a finding frequently demonstrated in the trials of second-line therapy in advanced NSCLC, in which few patients received up to 28 cycles of single-agent chemotherapy.[4,5] As these drugs are well tolerated , a current strategy has been to investigate the value of continued treatment of responding and stable patients with the nonplatinum component of their induction

regimen, "continuation maintenance" therapy. Various clinical trials have evaluated maintenance strategies using a variety of therapies for patients with NSCLC. Brodowicz *et al*. in his study showed that significant difference in median time to progression (TTP) in patients with advanced NSCLC treated with single-agent Gem maintenance therapy versus BSC following Gem plus cisplatin initial first line therapy.[6] TTP throughout the study period was 6.6 months and 5 months for Gem and BSC arms, respectively, while values for maintenance period were 3.6 and 2.0 months (for $P < 0.001$ for both). Median OS throughout the study was 13.0 months for Gem and 11.0 months for BSC arms ($P = 0.195$). The toxicity was mild, with neutropenia being most common Grade 3/4 toxicities. In our study, the median PFS was 9 months (95% CI: 8.1–9.9) for Gem versus 7 months (95% CI: 6.3–7.7) for BSC, with an HR 0.67 (95% CI: 0.50–0.84, $P = 0.009$). The median OS for Gem was 10 months (95% CI: 9.2–10.7) and 8 months (95% CI: 6.7–9.2), with a HR 0.64 (95% CI: 0.51–0.77, $P = 0.002$). Another study by Belani *et al*. with a similar study design failed to show a difference in PFS or OS between the Gem and the BSC group.[7]

Table 1: Summary of the patients characteristics and treatment response

Characteristic	Category	*n*=134	Percentage
Sex	Male	105	78.3
	Female	29	21.7
Median age (range) (year)	38-65	50	
Performance status (ECOG)	0-1	91	67.9
	2	43	32.1
Smoking history	Smoker	89	66.4
	Nonsmoker	45	33.6
Stage of disease	III	66	49.2
	IV	68	51.8
Site of metastasis	Lung	32	23.8
	Liver	25	18.6
	Bone	21	15.6
	Adrenals	8	5.9
	Skin	2	1.5
Treatment response (after initial therapy) (%)	Nonprogressors (35.1 [CR: 3+PR: 32.1], SD: 38.8)	99	73.8
	Progressors	35	26.2
		n=99	
Randomization Nonprogressors	Gemcitabine arm	50	50.5
	BCS arm	49	49.5

ECOG: Eastern Cooperative Oncology Group, SD: Standard deviation, BCS: Best supportive care, PR: Partial response, CR: Complete response

Petrol *et al*. compared Gem and erlotinib to BSC. In this study, 464 patients were randomized to receive erlotinib (switch maintenance), Gem (continuous maintenance), or no further treatment (BSC).[8] Primary endpoint found that PFS was significantly improved for both maintenance arms, Gem and erlotinib compared to the BCS (3.7 vs. 2.8 months vs. 2.1 months, respectively). OS data of this have not yet been reported. Regarding erlotinib, the Committee for Medicinal Products for Human Use adopted a new indication as a single agent for maintenance treatment in patients with locally advanced or metastatic NSCLC with SD after four cycles of standard platinum-based first line chemotherapy. When prescribing erlotinib, factors associated with prolonged survival should be taken into account.

The ECOG 4599 study found that the addition of bevacizumab to paclitaxel plus carboplatin followed by bevacizumab maintenance therapy significantly improved OS compared to paclitaxel plus carboplatin alone (12.3 vs. 10.3 months, HR 0.79, $P = 0.003$).[9] AVAiL trial (Avastin in Lung Study), demonstrated that cisplatin plus Gem with either bevacizumab, at 7.5 or 15 mg/kg, or placebo (each administered concurrently with chemotherapy and as a maintenance treatment until disease progression) [Table 1].[10] Patients treated with bevacizumab had a significant improvement in PFS compared with chemotherapy plus placebo, for either the 7.5 or 15 mg/kg bevacizumab regimens (13.6 and 13.4 vs. 13.1 months, HR 0.93 and HR 1.03, $P = 0.420$ and $P = 0.761$, respectively). However, OS was not different between both treatment arms. To demonstrate if targeted agents are effective as maintenance therapy, alternative study designs are needed.

Randomized Phase III studies have recently met their primary endpoints and OS was significantly improved in the maintenance arms investigated for pemetrexed and erlotinib as "switch" maintenance therapy. Based on this conclusive data, these two compounds have now been indicted for "maintenance therapy." A recently presented study has reveled as survival benefit for pemetrexed in a "continuation" maintenance therapy. Thus, pemetrexed could be a new option for both switches as well as continued maintenance regimen.

European Medicines Agency indicated pemetrexed as a single agent for the maintenance therapy of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed following platinum-based chemotherapy. First-line treatment should be a platinum-based doublet with gemcitabine, paclitaxel, or docetaxel. Bevacizumab and cetuximab, a monoclonal antibody against vascular endothelial growth factor and epidermal growth factor receptor receptors, respectively, have demonstrated clinical benefit for patients, when added to first line chemotherapy and continued until disease progression in advanced NSCLC.[11] A meta-analysis by Zhang *et al*. suggests, that OS and PFS are clearly in favor of maintenance therapy for both, switch and continuation strategy.[12] However, to give a clear recommendation for the future, other aspects such as cost effectiveness and toxicity must be taken into consideration.

CONCLUSION

Switch maintenance therapy with Gem, following initial platinum-based doublet chemotherapy in advanced NSCLC, has a significantly higher PFS and OS compared to BSC alone at the cost of higher grade 3/4 hematological toxicities.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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