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SWITCH MAINTENANCE WITH ORAL VINORELBINE: A PROMISING APPROACH FOR EGFR WILD-TYPE ADENOCARCINOMA?

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Abstract:
This study was performed to evaluate the efficacy and safety of switch maintenance therapy with oral vinorelbine in advanced non-small cell lung cancer (NSCLC) with adenocarcinoma limited to epidermal growth factor receptor (EGFR) wild type. Materials and Methods: In this single randomized trial, patients with advanced stage (IIIB and IV) NSCLC with adenocarcinoma EGFR wild-type status, treated with 6 cycles of platinum-based chemotherapy. Patients did not show progression after first-line chemotherapy were randomly assigned to receive switch maintenance with vinorelbine (80 mg/m2, day 1, 8) (group I) or the best supportive care until disease progression (group II). Results: The median progression free survival (PFS) was 9.7 months for group I versus 5.7 months for group II with statistically significant difference between both groups [HR = 1.15; 95% CI 1.19 to 1.49; P value = 0.002], while the median overall survival (OS) was 13.2 months for group I versus 11.9 months for group II with no statistically significant differences between both groups [HR = 1.24; 95% CI 1.05 to 1.46; P value = 0. 3]. The patients who received oral vinorelbine had tolerable toxicity profile. Conclusion: Switch maintenance therapy with oral vinorelbine, though improve PFS, did not improve OS in patients with NSCLC with adenocarcinoma EGFR wild type.

Keywords: Lung Cancer, Maintenance Chemotherapy, Vinorelbine, EGFR-Wild Type

1. Introduction

Lung cancer is the most common cause of cancer death worldwide, with an estimated 1.6 million deaths each year [1]. Nearly, 85% of newly diagnosed lung cancers have non-small cell lung cancer (NSCLC) pathology [2].

Over the past decade, the treatment of NSCLC has evolved. While early diagnosis and surgical treatment results in optimal patient outcomes, the majority of patients are diagnosed at later, largely incurable stages [3].

Wild-type epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) non-rearranged patients have to be treated with combination chemotherapy which usually includes cisplatin or carboplatin, gemcitabine, taxanes, vinorelbine, pemetrexed and antiangiogenic agents such as bevacizumab [1]. With combination platinum-based chemotherapy regimens, the median of overall survival (OS) and median progression free survival (PFS) are 8 - 11 and 4 months, respectively [4].

Maintenance strategies, which are defined as opportunities for extending the duration of first-line treatment (continuing one or all the drugs previously administered as first-line) or switching to a different and non-cross-resistant agent, are introduced immediately after completion of first-line treatment [5]. They have received great attention, especially in patients who benefit from the initial treatment, in order to prolong the duration of disease control [6].

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In the search of improving the outcome of patients with advanced NSCLC, switch maintenance therapy is an option which provides a different agent that was not included as part of the first-line regimen. In this setting, Vinorelbine is a chemotherapy agent which has shown activity and tolerability in lung cancer, and its oral formulation achieved promising results and good safety profile also in elderly patients [7] [8].

The aim of this study was to evaluate the efficacy and safety of a switch maintenance treatment consisting of oral vinorelbine in advanced NSCLC in the patients with wild-type EGFR after induction chemotherapy with gemcitabine plus cisplatin as Primary objective and evaluation of survival as a secondary objective.

1. Patients and Methods

This is prospective randomized study done at south Egypt cancer Institute in the period from 2015 to 2019. Patients involved in this study were histologically or cytologically confirmed NSCLC with adenocarcinoma type EGFR wild-type status which unresectable (stage IIIB) or metastatic (stage IV). All Patients involved in this study were stable disease after received induction chemotherapy by six cycles of platinum based chemotherapy as first line therapy. Other inclusion criteria included performance status (PS) ≤ 2; adequate liver and renal function; adequate bone marrow reserve; at least one measurable lesion (RECIST criteria) according to WHO recommendation (5) and written informed consent obtained from all patients before enrolled in study, which approved by ethical committee of South Egypt Cancer Institute.

Exclusion criteria were active infection, presence of symptomatic central nervous system metastases, inadequate liver or renal function, and serious concomitant systemic disorder incompatible with the study.

The patients were divided into two groups. Eighty two patients received oral vinorelbine 80 mg/m^2, day 1, 8 every three weeks (group I) until disease progression or grade 4 toxicity and seventy eight patients observed closely till disease progression (group II). Randomization with a 1:1 allocation ratio was stratified.

The primary endpoint was PFS. Secondary endpoints were OS and safety.

All patients were evaluated during the first 7 - 10 days after starting vinorelbine and then monthly thereafter. Each follow-up visit included a complete blood count and liver and kidney function tests. All patients were followed by computed tomography to determine tumor response every 3 months in 1 year and every 4 - 6 months thereafter.

Statistical analysis

All analysis was conducted using SPSS software version 23. Univariate factors were analyzed using the chi-square test for categorical variables. Difference was considered statistically significant at $P < 0.05$., the disease free survival was calculated according to Kaplan Meier method and was compared with the log-rank test.

2. Results

A total of 160 patients with stage IIIb/IV NSCLC adenocarcinoma with EGFR wild type were enrolled in this study. These patients received 6 cycles of platinum based chemotherapy with no progression and were divided into two groups. Eighty two patients received oral vinorelbine 80 mg/m^2, day 1, 8 every three weeks (group I) and seventy eight patients observed closely (group II).

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The mean age of the patients in group I was 55.24 ± 15.3 years. M/F: 50/32; stage IIIb/IV: 56/26; PS 1-2: 62/20 while in group II, the mean age of the patients was 57 ± 16.74 years. M/F: 49/29; stage IIIb/IV: 43/55; PS 1-2: 57/21 whish show no significance difference between both groups as shown in Table 1.

The median PFS was 9.8 months for group I versus 5.7 months for group II with statistically significant difference between both groups [HR = 1.15; 95% CI 1.19 to 1.49; P value = 0.002], while the median OS was 13.2 months for group I versus 11.9 months for group II with no statistically significant differences between both groups [HR = 1.24; 95% CI 1.05 to 1.46; P value = 0. 3]. Figure 1 compares the PFS and OS between the two groups.

Table 1. Patients characteristic in both groups.

	Group 1 (n 82)	Group 2 (n 78)	P value
Age	55.24 ± 15.3	57 ± 16.74	0.32
SEX (male/female)	50/32	49/29	0.871
Response to first line CTR (SD/PR)	52/30	58/20	0.172
Performance status	62/20	57/21	0.727
Stage (III/VI)	56/26	43/35	0.104

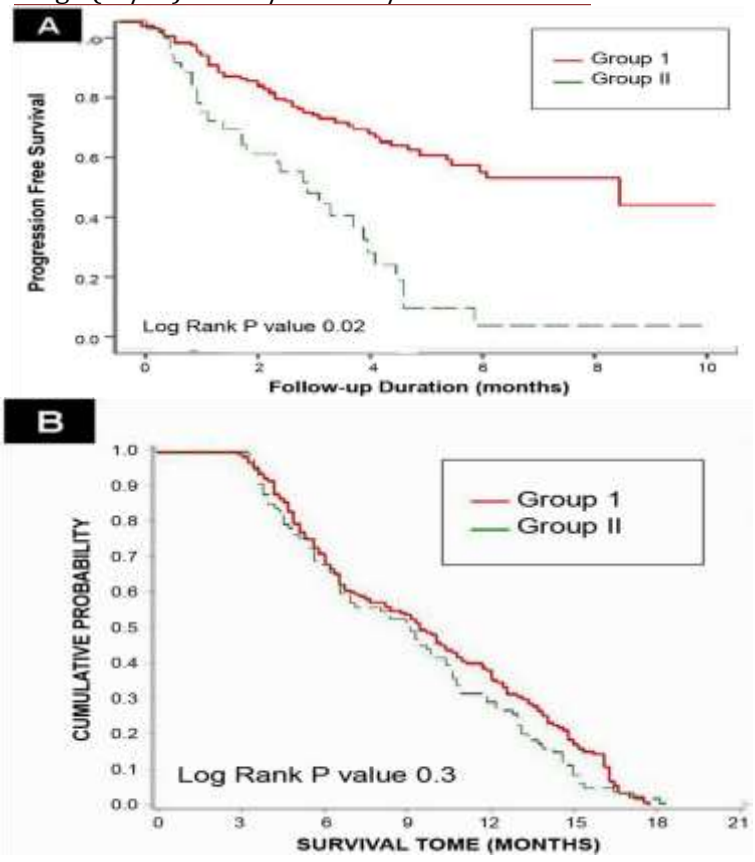

Figure 1. (A) progression free survival of both study group * oral vinorelbine versus best

best supportive care as switch maintenance therapy advanced adenocarcinoma Non-Small Cell Lung Cancer EGFR wild type*; (B) overall survival of both study group * oral vinorelbine versus best best supportive care as switch maintenance therapy advanced adenocarcinoma Non-Small Cell Lung Cancer EGFR wild type*.

In the patients received oral vinorelbine, overall toxicity was mild. The most common grade 3 - 4 toxicity were nausea and vomiting (13%), anemia (7%) and febrile neutropenia (5%). Toxicities for the two groups are reported in Table 2.

3. Discussion

According to National Comprehensive Cancer Network guidelines, the first-line treatment in patients with advanced NSCLC without a driver mutation, such as EGFR mutation or ALK rearrangement is 4 - 6 cycles of platinum-based doublet chemotherapy [9].

Table 2. Comparison of toxicity profile in both groups.

Toxicity	Group 1 (n 82)	Group 2 (n 78)	P value
Anemia	7	1	0.064
FN	5	1	0.21
GIT	13	2	0.0051
CVA	3	2	0.978

Maintenance therapy is one strategy that has been investigated extensively in recent years as a way of improving outcomes in patients with NSCLC. The challenges that lie in interpreting the literature come from the heterogeneity of studies of maintenance chemotherapy and the lack of consensus with respect to what constitutes maintenance treatment. This heterogeneity has become even more complex with the introduction of molecularly targeted therapy for NSCLC [10].

Vinorelbine could have multiple sites and mechanisms of action including the antiangiogenic properties and more recently an impact on the tumor microenvironment has been proposed as a potential effect involving the immune system [11]. A large quantity of studies demonstrated that doublet chemotherapy as second-line therapy is more toxic and does not improve overall survival compared to single-agent [12].

Our data suggest safety profile of switch maintenance of oral vinorelbine in advanced NSCLC with EGFR wild type. The mean PFS observed in our patients suggests that vinorelbine is effective in such subgroups of patients.

Results from this study showed no improvement in OS in patients received switch maintenance of oral vinorelbine compared by best supportive care. However, In contrast to many studies done before, the findings in our study revealed improvement in PFS in patients received switch maintenance of oral vinorelbine. The PFS was 9.8 months for patients received maintenance of oral vinorelbine versus 5.7 months for observation with statistically significant difference between both groups [HR = 1.15; 95% CI 1.19 to 1.49; P value = 0.002].

Previously report showed, vinorelbine 25 mg/m^2 was evaluated as a maintenance therapy given weekly for 6 month until disease progression compared with observation alone in stage IIIB/IV NSCLC patients after induction with MIC treatment (mitomycin 6 mg/m^2, ifosfamide 1.5 mg/m^2, cisplatin 30 mg/m^2 given every four wk × 2 - 4 cycles ± radiotherapy). A total of 91 patients were randomized to vinorelbine maintenance therapy. Median PFS for vinorelbine was 5 mo vs. 3 months with observation, but the difference was not statistically significant. Median OS for both groups was the same at 12.3 mo and evaluation of molecular subtypes was not performed [13].

Also, in contrary to our results, a study done in 100 patients with advanced stage NSCLC (IIIB and IV), of whom 34 had a non-progressive response to first-line chemotherapy of gemcitabine 1250 mg/m^2 (day 1 and 8) plus carboplatin AUC 5 (day 1) every 3 weeks and randomly received maintenance vinorelbine (n = 19) or best supportive care (n = 15). The hazard ratio of PFS in the vinorelbine group relative to the best supportive care group was 1.097 (95% confidence interval = 0.479 - 2.510; P-value = 0.827). There was no significant difference between the overall survival for the two groups (P = 0.068) [5] but no evaluation of molecular subtypes.

Even when oral vinorelbine used as continuation maintenance, there was no improvement in PFS or OS. This approved by a retrospective study published in 2018 by C Carriles Fernández et al., to analyse OS and PFS of maintenance therapy with oral vinorelbine after induction therapy with platinum plus vinorelbine in patients with advanced or metastatic NSCLC, they found that maintenance therapy with oral vinorelbine does not seem to provide advantages in PFS or OS compared to results found in the placebo [14].

The discrepancy between our results and other studies may be explained by the fact that we selected subgroup of patients with advanced stage (IIIB and IV) NSCLC with adenocarcinoma EGFR wild-type status which makes the comparison not relevant. This group may have additional benefits in the form of PFS from switch maintenance therapy with oral vinorelbine.

Switch maintenance therapy with oral vinorelbine had tolerable toxicity with the most common grade 3 - 4 toxicity were nausea and vomiting (13%), anemia (7%) and febrile neutropenia (5%). These findings were consistent with those of many studies [5] [13] [14] without interruption of treatment or delay.

4. Conclusion

Switch maintenance therapy with oral vinorelbine had tolerable toxicity and improve PFS in subgroup of patients with NSCLC. However, our results should stimulate further investigations to prove this fact.

Compliance with Ethical Standards

Author Amen Zaky declares that he has no conflict of interest. Author Ahmed Refaat declares that he has no conflict of interest. Author Ola Nabih declares that she has no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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