Original Research

THE RESULT OF ADJUVANT VINORELBINE PLUS CISPLATIN IN COMPLETELY RESECTED STAGE IB-IIIA NON-SMALL CELL LUNG CANCER AT HANOI MEDICAL UNIVERSITY HOSPITAL

Le Huy Trinh[1,2*], Dinh Anh Tran[2]

DOI: 10.38103/jcmhch.2021.72.5

ABSTRACT

Background: *Assess clinical, subclinical characteristics of stage IB-IIIA non - small cell lung cancer patients (NSCLC). Evaluating the result of adjuvant vinorelbine plus cisplatin in completely resected stage IB - IIIA NSCLC.*

Methods: *Descriptive study of 70 patients completely resected stage IB - IIIA non - small cell lung cancer were received adjuvant vinorelbine plus cisplatin chemotherapy at Hanoi Medical University Hospital from 01/2016 to 6/2020.*

Results: *The mean age of 56.94 years old, male: female ratio was 2.9:1. 23 (32.8%) patients had postoperative stage IB disease, 24 (34.3%) had stage IIA disease, 13 (18.6%) had stage IIB disease and 10 (14.3%) had stage IIIA disease. The major histological type was adenocarcinoma (78.6%). Median disease free survival was 29.10 ± 1.63 months, and 3 - year survival was 41%. Chemotherapy caused hematologic side effects in 66.67% of patients including neutropenia in 61.4% and grade 3/4 neutropenia in 28.1%. Non - hematologic toxic effects of chemotherapy were reported at low rates and almost mild (grade 1/2).*

Conclusions: *The vinorelbine - cisplatin regimen is an effective regimen in the adjuvant treatment of non - small cell lung cancer, the study showed that the results in disease - free survival and overall survival were comparable to those of other studies in the world. The most common side effect was neutropenia, the other side effects were reported at low rate and usually mild.*

Keywords: *Non - small cell lung cancer, vinorelbine, cisplatin, adjuvant chemotherapy NSCLC.*

I. INTRODUCTION

Lung cancer is one of the leading causes of cancer death in Vietnam. GLOBOCAN 2021 reported 26262 new cases of lung cancer and 23797 cases of cancer death due to lung cancer in 2021 [1]. Approximately 85% of lung cancers are of the non - small - cell lung cancer (NSCLC) type, and for patients who present with early stage NSCLC (approximately 30%), surgery is the initial treatment of choice [2].

Adjuvant chemotherapy is indicated for patients with stage IB - IIIA after radical surgery. Cisplatin - based adjuvant chemotherapy has been shown by many studies to be effective in prolonging overall survival and reducing recurrence rates [3].

Vinorelbine is a new semi - synthetic Vinca alkaloid, which has been shown to be effective in adjuvant treatment of NSCLC in clinical studies when used alone or in combination [4].

[1]Department of Oncology, Hanoi Medical University, Hanoi
[2]Department of Oncology and Palliative care, Hanoi Medical University Hospital, Hanoi

- **Received:** 05/9/2021; **Revised:** 03/10/2021;
- **Accepted:** 10/10/2021
- **Corresponding author:** Trinh Le Huy
- **Email:** trinhlehuy@hmu.edu.vn; **Phone:** 037 9576782

In randomized trials comparing the Vinorelbine plus Cisplatin regimen with previous regimens such as Cisplatin alone or Cisplatin in combination with Etoposide or another Vinca alkaloid, the dual Vinorelbine - Cisplatin regimen was superior. Phase III trials have demonstrated the advantages of a combination regimen of Vinorelbine with cisplatin in adjuvant therapy in patients with NSCLC that have shown to prolong disease-free survival as well as overall survival [5 - 7]. Due to its effectiveness and superiority, Vinorelbine - Cisplatin regimen has become an accepted regimen in the world and in Vietnam in adjuvant treatment of NSCLC.

Currently, there have been veryfew Vietnamese studies evaluating the effectiveness and safety of this regimen. Therefore, we conducted thisto evaluate the treatment result of adjuvant vinorelbine plus cisplatin in completely resected stage IB - IIIA NSCLC.

II. PATIENTS AND METHODS

2.1. Patients

70 stage IB - IIIA non-small cell lung cancer patients were treated with adjuvant vinorelbine - cisplatin at Hanoi Medical University Hospital from January 2016 to April 2021.

Inclusion criteria:

- Patients diagnosed with stage IB - IIIA NSCLC (AJCC 8th)
- Histopathology was non-small cell carcinoma.
- Performance status (PS) 0-1.
- Patients received initial curative surgery.
- Patients were treated with 4 cycles of vinorelbine - cisplatin regimen (cisplatin 80mg/m^2 day 1 and vinorelbine 30mg/m^2 day 1.8, every 3 weeks).

Exclusion criteria:

- Patients had any another cancer at the same time.
- Patients had any contraindication of chemotherapy (severe acute liver failure, acute renal failure, heart attack, stroke…)
- Insufficient medical record information.

2.2. Methods

- Methods: Descriptive, retrospective study
- Sample size: Convenient sample
- Variables:

+ Clinicophathological characteristics: age, sex, smoking status, presenting symptoms, tumor site, pathology, lymph status, grade and stage of tumor. (AJCC 8th was used in this study).

+ Disease - free survival (DFS), overal survival (OS), DFS by stages.

+ Heamatologic side effects: anemia, neutropenia, thrombocytopenia

+ Non - heamatologic side effects: nausea/ vomiting, diarrhea, hepatitis, renal failure, peripheral neuropathy

2.3. Data analyses

- Statistical analyses were carried out using SPSS ver 20.0 software.

2.4. Ethics

The study has been approved by the ethics committee of Hanoi Medical University.

III. RESULTS

Table 1 showsthe baseline characteristics. Overall, 52 (74.3%) patients were male and the male: female ratio was 2.9:1. The mean of tumor's size was 3.88cm (the max value was 9cm). In 70 patients, 49 (70%) had N0 status, 16 (22.9%) had N1 status and 5 (7.1%) had N2 status. In case of histopathology, Adenocarcinoma made up the majority (78.6%), SCC and large - cell carcinoma accounted for 11.4% and 5.7% respectively, there were 2 cases of mixed adenosquamous carcinoma and 1 case of intestinal type carcinoma.

In terms of stage of disease, 23 (32.8%) patients had postoperative stage IB disease, 24 (34.3%) had stage IIA disease, 13 (18.6%) had stage IIB disease and 10 (14.3%) had stage IIIA disease.

The median disease free survival was 29.10 ± 1.63 month (Figure 1) and the median disease-free survival of stage IB - II group was higher than that

of stage III group, the difference was statistically significant **(Figure 2)**.

Table1: Patient's baseline characteristics

Baseline characteristics	No.	%
Sex		
Male	52	74.3
Female	18	25.7
Age (years)		
< 40	1	1.4
40 - 49	7	10.0
50 - 59	38	54.3
≥ 60	24	34.3
Lymph status		
N0	49	70.0
N1	16	22.9
N2	5	7.1
Histopathology		
Adenocarcinoma	55	78.6
Squamous cell carcinoma	8	11.4
Large cell carcinoma	4	5.7
Other	3	4.3
Tumor Size		
< 3cm	15	21.4
3 - 5cm	36	51.4
5 - 7cm	15	21.4
≥ 7cm	4	57.1
Stage of disease		
IB	23	32.8
IIA	24	34.3
IIB	13	18.6
IIIA	10	14.3
	70	100

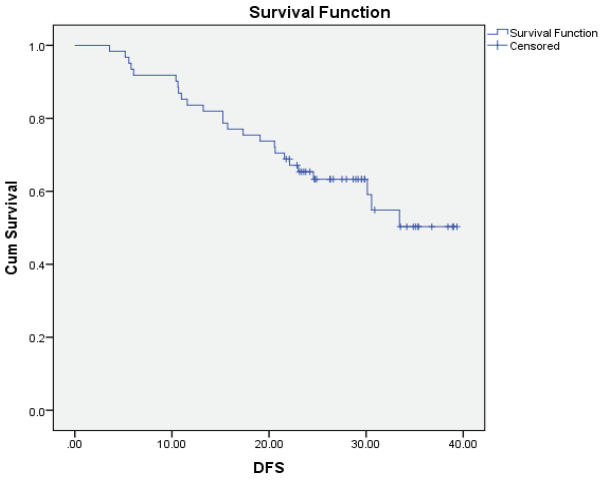

Figure 1: Disease - free survival (DFS)

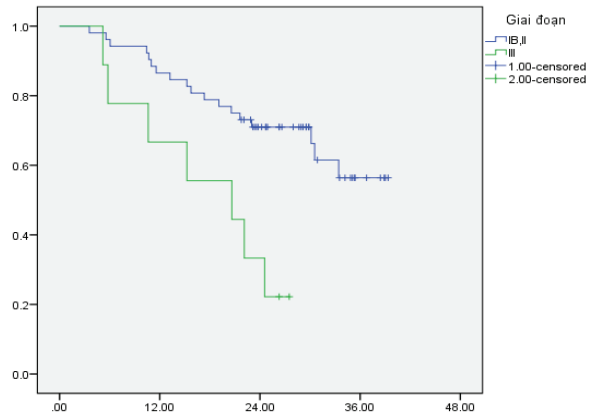

Figure 2: Disease - free survival (DFS) by stage group

The survival rates of patients in our study at the time of 1 - year, 2 - year and 3 - year were 80.0%, 61.4% and 41.4%, respectively **(Table 2)**. The most common side effects of the regimen were neutropenia (61.4%), nausea,vomiting (78.6%) and anemia (45.7%). Grade III/IV neutropenia accounted for 28.1%. The frequency of hepatic and renal toxicity was low and almost at mild grade (I/II) **(Table 3)**.

Table 2: Overall survival estimates

	No.	%
1 - year survival	56	80.0
2 - year survival	43	61.4
3 - year survival	29	41.4
	70	100

Table 3: Sumary of Vinorelbine - cisplatin regimen's toxicity

Toxicity	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%	No.	%
Nausea, vomiting	15	21.4	21	30.0	18	25.7	12	17.1	4	5.7
Diarrhea	64	91.4	3	4.3	3	4.3	0	0.0	0	0.0
Hepatic toxicity	55	78.6	7	10.0	5	7.1	2	2.9	1	1.4
Renal failure	64	91.4	2	2.9	1	1.4	3	4.3	0	0.0
Peripheral Neuropathy	66	94.3	4	5.7	0	0.0	0	0.0	0	0.0
Anemia	45	64.3	23	32.9	2	2.8	0	0.0	0	0.0
Neutropenia	27	38.6	10	14.2	13	18.6	13	18.6	7	10.0
Thrombocytopenia	70	100	0	0.0	0	0.0	0	0.0	0	0.0

IV. DISCUSSION

The most common age group was 50 - 59 years old accounting for 34.5%. The mean age was 56.94 years old, the youngest was 36 years old and the oldest was 69 years old. Male patients accounted for 74.3% primarily (52/70), accounting for 25.7% of female patients (18/70); the male:female ratio was 2.9:1. The age and sex characteristics of our study population were quite similar to other trials in the world such as the JBR.10 trial (2007), ANITA trial (2006), IALT trial (2008) or the LACE (2010) (Lung Adjuvant Cisplatin Evaluation) meta - analysis [5 - 8].

In terms of postoperative histopathology, adenocarcinoma accounted for the highest rate (78.6%), our result did not differ from studies of Shukuya (2009) and Winton (2005) [9,10]. In contrast, in ANITA trial (2006) and LACE meta - analysis (2010), the majority of histopathological types was squamous cell carcinoma (58% and 49% respectively) [5,8]. However, according to the conclusions of many studies, histopathology is not an independent prognostic factor.

Patients with stage IB accounted for 33.3%, stage II accounted for 53%, stage IIIA accounted for 13.6%. The group of patients in stage IIIA also accounted for the lowest rate as studied by Shukuya [9].

* Disease free survival and overall survival

The median disease-free survival (DFS) was 29.10 ± 1.63 months. This result was lower than that reported in the ANITA trial (2006), with disease - free survival in the ANITA trial (2006) in the adjuvant chemotherapy group reaching 36.3 months (for the control group, 20.7 months) [5]. The JBR.10 trial (2007) concluded that adjuvant chemotherapy significantly prolonged survival without recurrence compared with no treatment. The median survival without recurrence of the group following only after surgery was 46.7 months; for the adjuvant chemotherapy group, at the end of the study, the median survival had not been reached [6]. Thus, the disease - free survival time of patients treated with vinorelbine - cisplatin in the JBR.10 trial (2007) was much higher than that in our study. Part of this difference was due to the fact that the patients enrolled in the JBR.10 trial (2007) were only in stage I and II, different from the ANITA trial and our study (including stage III patients) [5, 6]. According to LACE meta - analysis (2010), adjuvant vinorelbine - cisplatin significantly prolonged disease - free survival (DFS) for patients with stage II, III lung cancer; although it did not provide a statistically significant benefit for stage I disease [8]. Also in the other arms of the LACE trial (2010) for other adjuvant regimens (LACE - other), there was a statistically significant difference on DFS in stage

IB patients in the adjuvant chemotherapy group compared with postoperative follow - up alone [8].

We also analyzed the relationship between disease - free survival time and some other factors such as disease stage, lymph node metastasis, tumor size.... The results showed a statistically significant difference in disease - free survival (DFS) by disease stage, with p = 0.003. This result was similar to that of the ANITA trial (2006), in which, the group of patients with stage I, II had a higher disease - free survival time than the group of patients with stage III, with p = 0.001 [5]. The disease - free survival time was lower in the groups of patients with tumor size ≥ 3cm, with lymph node metastasis in absolute value, however, the difference was not statistically significant.

The survival rates of patients in our study at the time of 1 - year, 2 - year and 3 - year were 80.0%, 61.4% and 41.4%, respectively. The 1 - year and 3 - year survival rate of patients our study was much higher than that of Hobbins S. (2016) - a retrospective study of 162.959 NSCLC patients through UTP data in the UK (2008 - 2013): overall survival rates at 1 - year and 3 - year was 36.2% and 15.6% (all stages) [11]. This difference came from the reason that Hobbins's study selected both advanced and metastatic patients (43%), which resulted in a lower survival outcome compared to our study. However, our overall survival results were similar to the results of other studies **(Table 4)** [5], [8], [12], [13].

Table 4: OS rate of NSCLC in different studies

Study		OS (%)			
		1 - year	2 - year	3 - year	5 - year
Nguyễn Thị Lê (2012) [12]	PT đơn thuần	87,5	8,4		
	PT + HT bổ trợ	90,6	17,8		
	HT đơn thuần	59,4	0		
Nguyễn Khắc Kiểm (2016) [13]		89,0	73,0	67,0	
ANITA trial (2006) [5]		79,0	61,0		46,0
LACE - Vinorelbine (2010) [8]				64,3	55,1
Our study (2021)		80,0	61,4	41,4	

In comparison with the results of the ANIA trial (2006) on the efficacy of vinorelbine - cisplatin regimens in patients with stage IB - IIIA, which was similar to our study design, overall survival rates at 1 - year and 2 - year were 79.0% and 61.0%, respectively, not significantly different from our study results [5].

* Toxicity

Neutropenia was reported at rate of 61.4%, and drade III/IV neutropenia accounted for 28.1%. According to the result of the JBR.10 trial (2007), the rate of neutropenia at all levels was up to 88%, of which grade 3 and 4 neutropenia accounted for 73% [6]. Similarly, the rates of all levels neutropenia and grade 3,4 neutropenia in the ANITA trial (2006) were 92% and 85%, respectively, in the adjuvant chemotherapy group; much higher than the results of our study [5]. In our study, the regimen was used with a dose of cisplatin 80mg/m2 day 1 and vinorelbine 30mg/m2 day 1,8 every 3 weeks; all patients received the full dose (95 - 100%). A retrospective review of the study designs of these two trials showed that, trial ANITA (2006) was designed with a dose of cisplatin 100mg/m2 on day 1 and vinorelbine 30mg/m2 on days 1, 8, 15, 22 for a 28 - day cycle (cisplatin dose was higher than our study). The JBR.10 trial (2007) used a dose of cisplatin 50

mg/m^2 on day 1,8 and vinorelbine 30 mg/m^2 on days 1, 8, 15, 22 for a 28 - day cycle. Differences in the doses and combinations of vinorelbine - cisplatin may in part lead to different rates of toxicity among studies [6]

The other toxicity was reported at the low rate and primarily mild (grade 1/2). This results did not differ from the findings of other studies.

V. CONCLUSION

The vinorelbine - cisplatin regimen is an effective regimen in the adjuvant treatment of non - small cell lung cancer, the study showed that the results in disease - free survival and overall survival were comparable to those of other studies in the world. The most common side effect was neutropenia, the other side effects were reported at low rate and usually mild.

REFERENCES

1. Sung, H., Ferlay, J., Siegel, R. L. et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians.2021; 71(3): 209-249.
2. Trần Văn Thuấn. Non - small cell lung cancer. Guidelines for the diagnosis and treatment of common cancers. Medical Publishing House, Hanoi, 2019; 92-105.
3. Nguyễn Bá Đức, Trần Văn Thuấn, Nguyễn Tuyết Mai. Lung cancer. Medical treatment of cancer. Medical Publishing House, Hanoi, 2010; 81-98.
4. Lê Văn Quảng, Trịnh Lê Huy. Chemotherapy for Cancer, Medical Publishing House, Hanoi, 2021; 207-221.
5. Douillard J.-Y., Rosell R., De Lena M. et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB - IIIA non - small - cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol. 2006; 7(9): 719-727.
6. Pepe C., Hasan B., Winton T.L. et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR. 10. J Clin Oncol. 2007; 25(12): 1553-1561.
7. Winton T., Livingston R., Johnson D. et al. Vinorelbine plus cisplatin vs. observation in resected non - small - cell lung cancer. N Engl J Med. 2005; 352(25): 2589-2597.
8. Douillard J.-Y., Tribodet H., Aubert D. et al. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol. 2010; 5(2): 220-228.
9. Shukuya T., Takahashi T., Tamiya A. et al. Evaluation of the safety and compliance of 3 - week cycles of vinorelbine on days 1 and 8 and cisplatin on day 1 as adjuvant chemotherapy in Japanese patients with completely resected pathological stage IB to IIIA non-small cell lung cancer: a retrospective study. Jpn J Clin Oncol. 2009; 39(3): 158-162.
10. Winton T., Livingston R., Johnson D. et al. Vinorelbine plus cisplatin vs. observation in resected non - small - cell lung cancer. N Engl J Med. 2005;352(25): 2589 - 2597.
11. Hobbins S., West D., Peake M. et al. Patient characteristics, treatment and survival in pulmonary carcinoid tumours: an analysis from the UK National Lung Cancer Audit. BMJ Open. 2016; 6(9): e012530.
12. Nguyễn Thị Lê, Evaluation of the results of non - small cell lung cancer treatment with surgery and chemotherapy at the Central Lung Hospital, Master Thesis, Hanoi Medical University. 2012
13. Nguyễn Khắc Kiểm. Research of lymphadenectomy based on map in surgery treating non - small cell lung cancer in stage I,II,IIIA, PhD Thesis, Hanoi Medical University. 2016.
14. Phan Lê Thắng. Study on treatment results of non - small cell lung cancer patients at stages II, IIIA with combination of radical surgery and post - operative complementary chemo - radiotherapy, PhD Thesis, Hanoi Medical University. 2017.