

Experience of treatment of lung cancer patients using paclitaxel and carboplatin

Anwar Jusuf *, Sutji Astuti Mariono**, Karmel L. Tambunan*, A. Harryanto Reksodiputro*, Noorwati Soetandyo*, Ronald Hukom*, Eddy Suratman*, A. Mulawarman Jayusman*

Abstrak

Sembilan belas pasien kanker paru jenis karsinoma bukan set kecil stage J11 & J14 mendapat kemoterapi dengan paduan paklitaksel dan karboplatin di Rumah Sakit Kanker Dharmais dan Rumah Sakit Pusat Pertamina Jakarta, terdiri dari 14 laki-laki dan 5 perempuan. Diagnosis histologis ialah adenokarsinoma pada 13 pasien, karsinoma skuamosa pada 4 pasien dan karsinoma adenoskuamosa pada 1 pasien. Empat belas pasien termasuk stage J14, stage IIIB terlihat pada 4 pasien dan stage IIIA pada 1 pasien. Paduan obat terdiri dari paklitaksel, dengan dosis 135-200 mg/m² dan karboplatin 300 mg/m² atau AUC 6 mg/ml.min, diberikan melalui infus setiap 3 minggu, paling sedikit 3 siklus. Pasien diikuti secara teratur sampai meninggal. Respon objektif berupa respon parsial (partial response) terlihat pada 12 pasien (63%), 2 pasien tidak menunjukkan perubahan (stable disease) dan perburukan terlihat pada 5 orang (26%). Dua pasien masih hidup masing-masing 22 dan 23 bulan setelah kemoterapi dimulai. Masa tahan hidup 1 tahun adalah 58% dan masa tengah tahan hidup ialah 14 bulan.

Abstract

Nineteen patients with stage III & IV non-small cell lung cancer were treated with regimen containing paclitaxel and carboplatin at Dharmais National Cancer Center Hospital and Pertamina General Hospital, Jakarta - Indonesia. There were 14 males and 5 females, the histologic diagnosis being adenocarcinoma in 13 patients, squamous carcinoma in 4 patients and adenosquamous carcinoma in 1 patient. Fourteen patients were in stage IV, 4 had stage III/B, one had stage III/A disease. The regimen contains paclitaxel 135-200 mg/m², combined with carboplatin 300 mg/m² or AUC 6 mg/ml. min, given every 3 weeks. Those who underwent at least 3 cycles of chemotherapy were followed up until death. Objective improvement (partial response) was seen in 12 patients or 63%; 2 had stable disease (11%) and 5 had progressive disease (26%). Two patients are still alive at 22 months and 23 months after starting chemotherapy. The one year survival rate was 58% and median survival time was 14 months.

Keywords: non-small cell carcinoma, chemotherapy, paclitaxel, carboplatin

The treatment of lung cancer has been a problem in Indonesia. In Dharmais National Cancer Center Hospital, 541 lung cancer patients were hospitalized during 1993-1997, 344 of them were non-small cell lung cancer in stage III & IV. Chemotherapy should have been indicated for them, but mainly due to financial reason only 54 of them could be so treated. In spite of such a situation, a small number of them were able to provide cytostatic drugs for themselves.

Paclitaxel in combination with carboplatin were among of the regimens that were chosen for these patients. In

Pertamina Hospital, 40-50 non-small lung cancer patients were seen annually. The majority of the patients were the employees of Pertamina, for whom the cytostatic drugs were provided by the company.

This combination was relatively new, introduced in Jakarta in 1993, but it was not until 1994 that we began to use this combination for the treatment of lung cancer in Dharmais Hospital and since 1996 in Pertamina Hospital. According to literature^{1,2,3} this combination is quite effective for non-small cell lung cancer with tolerable side effects. To evaluate the usefulness of this combination for our patients, we studied retrospectively the outcome of treatment using this combination on lung cancer patients in both hospital.

* Dharmais National Cancer Center Hospital, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia

** Pertamina Central General Hospital, Jakarta, Indonesia

MATERIAL AND METHODS

This is a retrospective study on nonsmall cell lung cancer patients that were treated during 1994-1998 at Dharmais National Cancer Center Hospital and Pertamina Hospital. The inclusion criterias were :

- confirmed histologic diagnosis of nonsmall cell carcinoma
- nonsmall normal blood counts, normal CCT stage IIIA, IIIB and IV, with measurable disease, performance status >/ 70 (Kamofsky)
- chemotherapy regimen, containing paclitaxel 135 mg/m2 - 200 mg/m2 and carboplatin 200 mg/m2 or AUC 6 mg/ml.mm given every 3 - 4 weeks, for 6 cycles.
- at least 3 cycles must be administered
- follow up was done every month up to 3 months and then every 3-4 months or whenever the patients had complaints, until death
- objective responses were be recorded, according to UICC criteria (complete response, partial response, stable disease and progressi ve disease) by physical examination and chest X-ray examination
- all side effects were recorded according to WHO Classification
- dates of death were recorded in the patient's journal, survival time was calculated from the date of the beginning of chemotherapy. A special call was given on December 31si, 1998 to check which patients were surviving

The details of treatment were as follows :

- hydration with saline solution before the administration of cytostatic
- premedication with dexamethason, ondansetron and diphenhydramine
- paclitaxel was given over 3 hrs infusion, the dose being 135 mg/m2 at the beginning of the study, later being 175 mg/m2 or 200 mg/m2.

carboplatin was given 300 mg/m2 intravenousl y, later dosed to a targeted AUC 6 hematologic examination (Hb, granulocytes, trombocyte count) was performed every week during treatment

RESULTS

Nineteen patients were recruited for evaluation. There were 12 males and females, the age ranged between 42 years and 73 years (median : 57 yrs). Fourteen of them were stage IV disease, 4 stage IIIB disease and one had stage IIIA disease. Histologic diagnoses were squamous carcinoma in 4 patients, adenocarcinoma in 14 patients and adenosquamous carcinoma in 1 patient. Seventeen patients completed 6 cycles of chemotherapy, one had only 3 cycles and one had 4 cycles. The shortest follow up period was 4 months and the longest was 35 months after the start of chemotherapy. Two patients are still alive at 22 and 23 months after the start of chemotherapy. Objective response was seen in 12 out of 19 patients 63%. No patients had complete response, twel ve had partial response. Two patients (10,5%) showed stable disease and progression was seen in 5 patients (26,3%), as seen in Table 1.

Table 1. Objective Response in 16 Lung Cancer Patients Treated with Paclitaxel & Carboplatin (n = 19)

Response	No	%
- Complete response	0	0
- Partial response	12	63
- Stable disease	2	11
- Progressi ve disease	5	26

Eleven patients live one year after chemotherapy, giving the one year survival rate of 58. The median survival time was 15 months as shown in Figure 1.

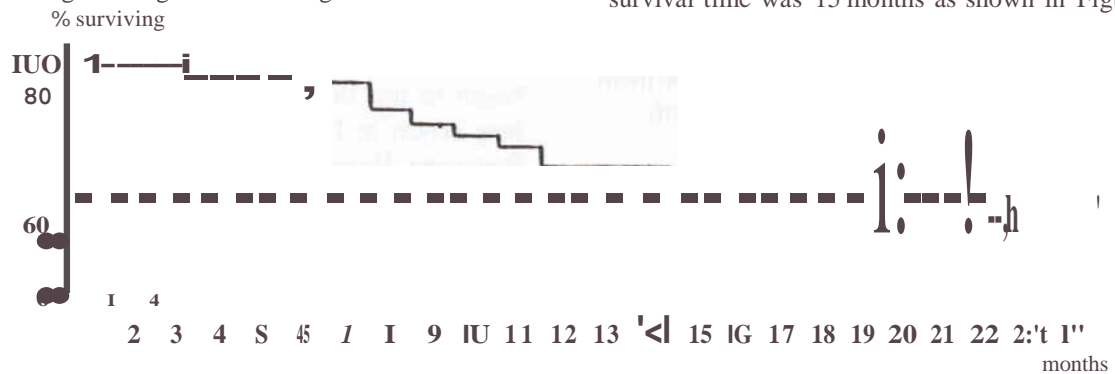


Figure J. The Survival Curve of Lung Cancer Patients Receiving a Combination of Paclitaxel and Carboplatin Calculated from the Beginning of Chemotherapy (n = 19)

Fourteen patients had stage IV disease. Among this group, 4 patients had radiotherapy for metastasis to the weight bearing bones or the primary tumor. The results are shown in Table 2 and Figure 2. Complete response was not seen, partial response in 10/14 (71%) and progressive disease in 4/14 (29%), as seen in Table 2. Among these patients, one year survival rate was 6 out of 14 patients (43%); the median survival time was 14 months (see Figure 2).

Table 2. Objective Response in Stage IV Disease Treated with Paclitaxel & Carboplatin (n = 14)

Response	No	%
- Complete response	0	0
- Partial response	10	71
- Stable disease		
- Progressive disease	4	29

All patients had nausea and vomiting grade 1-2, none had grade 3-4. Alopecia was seen in all patients. No renal or cardiac toxicity was found. Neurotoxicity such as peripheral neuropathy was not well recorded, but were seen in some patients, none of them had grade 3 or 4. Serious side effects, namely grade 3 thrombocytopenia were seen in 5 patients (26%), 1 patient (5%) and 2 patients (11%), respectively (Table 3).

Table 3. Side Effects of Paclitaxel & Carboplatin Combination

Toxicity Parameter	WHO Grade (%)	
	3	4
Neutropenia	5 (31.3%)	I (6.3 %)
Thrombocytopenia	2 (12.5 %)	
Nausea/vomiting		
Neurotoxicity		
Renal		
Cardiac		

DISCUSSION

Paclitaxel and carboplatin combination has been studied by many investigators with various results, as seen in Table 4 and 5. Using similar dose of paclitaxel and carboplatin, Johnson et al, Giaccone et al and Bunn et al⁴ had seen response rates of less than 50% or more. Other investigators like Belani et al, Schutte et al, and Rowinsky et al⁴ used combinations of paclitaxel with carboplatin dosed to different targeted AUC-s, also had PR of over 50%. Our result which was surprisingly high, may be due to more selected patients; as this is a retrospective report of patients after completing the treatment and follow up.

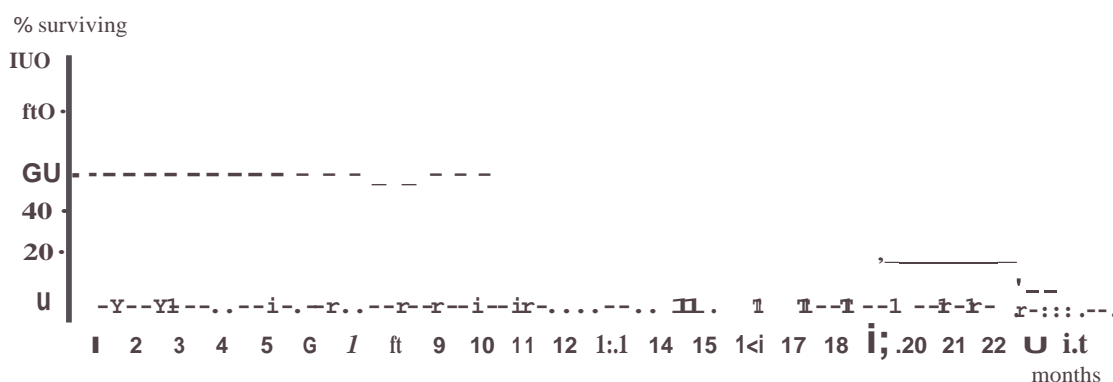


Figure 2. The Survival Curve of Patients with Stage IV Lung Cancer Receiving a Combination of Paclitaxel and Carboplatin Calculated after the Beginning of Chemotherapy (n = 14)

Fourteen patients had stage IV disease. Among this group, 4 patients had radiotherapy for metastasis to the weight bearing bones or the primary tumor. The results are shown in Table 2 and Figure 2. Complete response was not seen, partial response in 10/14 (71%) and progressive disease in 4/14 (29%), as seen in Table 2. Among these patients, one year survival rate was 6 out of 14 patients (43%); the median survival time was 14 months (see Figure 2).

Table 2. Objective Response in Stage IV Disease Treated with Paclitaxel & Carboplatin (n = 14)

Response	No	%
- Complete response	0	0
- Partial response	10	71
- Stable disease		
- Progressive disease	4	29

All patients had nausea and vomiting grade 1-2, none had grade 3-4. Alopecia was seen in all patients. No renal or cardiac toxicity was found. Neurotoxicity such as peripheral neuropathy was not well recorded, but were seen in some patients, none of them had grade 3 or 4. Serious side effects, namely grade 3 thrombocytopenia were seen in 5 patients (26%), 1 patient (5%) and 2 patients (11%), respectively (Table 3).

Table 3. Side Effects of Paclitaxel & Carboplatin Combination

Toxicity Parameter	WHO Grade (%)	
	3	4
Neutropenia	5 (31.3%)	1 (6.3 %)
Thrombocytopenia	2 (12.5 %)	
Nausea/vomiting		
Neurotoxicity		
Renal		
Cardiac		

DISCUSSION

Paclitaxel and carboplatin combination has been studied by many investigators with various results, as seen in Table 4 and 5. Using similar dose of paclitaxel and carboplatin, Johnson et al, Giaccone et al and Bunn et al⁴ had seen response rates of less than 50% or more. Other investigators like Belani et al, Schutte et al, and Rowinsky et al⁴ used combinations of paclitaxel with carboplatin dosed to different targeted AUC-s, also had PR of over 50%. Our result which was surprisingly high, may be due to more selected patients; as this is a retrospective report of patients after completing the treatment and follow up.

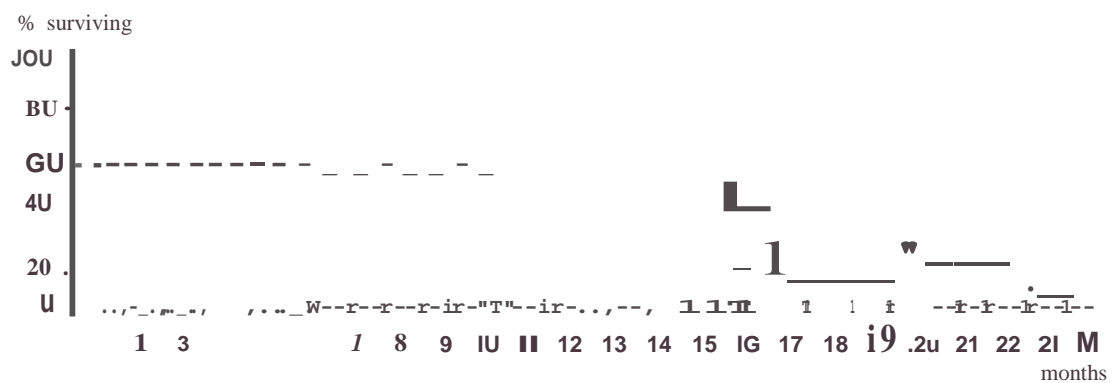


Figure 2. The Survival Curve of Patients with Stage IV Lung Cancer Receiving a Combination of Paclitaxel and Carboplatin. Calculated after the Beginning of Chemotherapy (n = 14)

table 6 reviews the side effects seen in our serie and in other studies. Neutropenia grade 3 and grade 4 seen in 10% - 70% cases, depending on the doses of drugs and that of the other modality. Thrombocytopenia grade 3 was found in 11% - 20% of patients, none had

grade IV trombocytopenia. Other side effects like gastrointestinal symptoms, myalgia, neurotoxicity, fatigue, renal toxicity, cardiac toxicity, hipersensitivity and other symptom/signs were seen, but otherwise quite tolerable to the patient.

Table 6. Side Effects of Paclitaxel and Carboplatin Combination in Various Regimens. Including Multimodality

Side Effects (grade 3 & 4)	Jusuf et al	Hainsowarth et al	Schute et al	Langer et al	Belani et al
- Neutropenia	37%	10%	16%	70%	22%
- Neutropenia + fever	NR	14%	NR	2%	(-)
- Thrombopenia	11%			20%	(-)
- Nausea & vomiting				20%	6%
- Esophagitis & mucositis					3%
- Myalgia	NR		48%		
- Neurotoxicity	NR	18%			
- Fatigue					6%
- Renal toxicity					
- Cardiac toxicity					
- Hypersensitivity		2%			
- Death		2%			9%
- Dose of Drugs & other modality	P. 135, 175, 200 mg/m2 C. 200 mg/m2 or AUC 6	P. 225 mg/m2 (1 h) C. AUC 7.5	P. 200 mg/m2 C. AUC 5	P. 175 mg/m2-280 mg/m2 C. AUC 7.5 Prior radiotherapy in 25%	P. 45 mg/m2 C. 100 mg/m2 Radiotherapy (standard dose)

CONCLUSION

1. Paclitaxel in combination with Carboplatin is quite effective for stage III & IV nonsmall cell lung cancer, with 63% response rate (PR), one year survival rate of 58% and median survival time 14.2 months.
2. Major side effects are gastrointestinal symptoms (nausea and vomiting), alopecia and bone marrow depression, which are quite tolerable.

Acknowledgement

The authors wish to thank the Oncology Team, Bristol Meyer Squibb Indonesia for their support in carrying out this study and Dr. I. Sita Laksrni Andarini and Wahyu Anidwiyangsih, Miss Anggriani, SKM and Mr. Apang Sulaiman for preparing the report.

REFERENCES

1. Hainsworth JD, Thomson DS, Urban WJ, et al. One Hour Paclitaxel plus Carboplatin in Advanced Nonsmall Cell Lung Cancer (NSCLC). Preliminary Results of a Multinstitutional Phase II Study, Scientific Proceedings, 32nd Annual Meeting, American Thoracic Society of Clinical Oncology, 1996 : 125.
2. Langer C, Kaplan R, Rosvold E, et al. Paclitaxel (P) by 1 hr Infusion Combination with Carboplatin (C) in Advanced Nonsmall Cell Lung Carcinoma (NSCLC) : A Phase II Study J. Clin Oncology 1995, 13: 1860-70.
3. Schutte W, Bork I, Sucker S. Phase II Trial of Paclitaxel and Carboplatin as First Line Treatment in Advanced Nonsmall Cell Lung Cancer, Scientific Proceedings, 32nd Annual Meeting, American Thoracic Society of Clinical Oncology, 1996 : 137.
4. Belani CP. Paclitaxel/Carboplatin in the Treatment of Nonsmall Cell Lung Cancer. Oncology (Suppl), 1998, 12: 74-9.
5. Pisters KMW, Ginsberg RJ. Phase II Trial of Induction Paclitaxel & Carboplatin (PC) in Early Stage (T2NO, T1-2N1 & Selected T3NO-I), Nonsmall Cell Carcinoma,

- Scientific Proceedings, 34th Annual Meeting, American Thoracic Society, 1998:129.
6. Langer C. Kaplan R. Rosvold E. Milleson M. Smith MR. Johnson C, et al. Paclitaxel (P) by 1 hr Infusion Combination with Carboplatin (C) in Advanced Nonsmall Cell Lung Carcinoma (NSCLC) : A Phase II Study, Scientific Proceedings, 32nd Annual Meeting, American Thoracic Society of Clinical Oncology, 1996:135.
 7. N, Triaspolitica. "Yang Perlu Anda Ketahui Tentang Penyakit Kanker Paru Paru, Gejala Umum, Penyebab, Serta Pengobatan." *Mau Nanya Dong Dok*. N.p, 29 June 2017. Web. 29 June 2017. <<https://nanyadongdok.blogspot.com/2017/06/yang-perlu-anda-ketahui-tentang.html>>.