Lung Cancer 133 (2019) 38–44

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Prognostic impact of blood transfusion in patients with metastatic non-small cell lung cancer receiving chemotherapy

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ARTICLE INFO

Keywords:
Non-small cell lung adenocarcinoma
Chemotherapy
Allogeneic blood transfusion
Survival
Prognosis
Lung cancer

ABSTRACT

Purpose: To investigate the prognostic effects of Allogeneic Blood Transfusion (ABT) in patients with metastatic Non-Small Cell Lung Cancer (NSCLC) receiving Chemotherapy (CT) in the first-line treatment, comparing untransfused patients to those receiving blood transfusion during treatment period or before treatment period.
Methods: This was a retrospective study of 433 patients with metastatic NSCLC receiving CT in the first-line treatment. Patients were categorized into 3 groups according to the transfusion strategy as follows; group-U (Untransfused patients, n = 303), group-B(patients receiving transfusion Before treatment period, n = 43), and group-D(patients receiving transfusion During treatment period, n = 87).
Results: There were 433 patients in the analysis, consisting of 388 (89.6%) males, with a median age of 60 years (range, 21–92). The median Overall Survival(mOS) according to the ABT was 14 months for group-U, 9 months for group-B, and 7 months for group-D ($p < 0.001$). In subgroup analysis, patients with squamous cell carcinoma subtype, mOS was 11 months for group-U, 12 months for group-B, and 9 month for group-D ($p = 0.074$) The corresponding mOS durations for adenocarcinoma subtype were 21 months, 7 months, and 6 months ($p < 0.001$). Performing ABT during treatment period was found to be a negative independent factor related to OS (HR 1.50 for progression-free survival, 95% CI 1.15–1.97, HR 1.36 for OS, 95% CI 1.04–1.80).
Conclusion: Our results demonstrated that ABT was significantly associated with earlier progression and shorter survival in patients with metastatic NSCLC, especially in adenocarcinoma histology, hence suggesting that transfusion strategy in this group should remain limited, and its benefit should outweigh the risk of progression.

1. Introduction

Lung Cancer (LC) is the most common cancer worldwide and the most common cause of cancer-related deaths. In 2012, approximately 1.8 million patients had LC worldwide, with 1.6 million deaths occurring in the same year. Due to recent innovations and developments in LC treatment, mortality has started to decrease in both men and women, but even so prognosis is still poor, with a 5-year survival rate being less than 15%. Non-Small Cell Lung Cancer (NSCLC) accounts for 85% of all LC cases [1,2]. Stage I, II, and III patients are treated with surgery, chemotherapy (CT), radiotherapy, or combined-modality approach. In contrast, patients with stage IV disease are managed with palliative systemic treatment [2].

Allogeneic Blood Transfusion (ABT) may cause various immune system dysfunctions [3]. In renal transplant patients, ABT is known to be beneficial, possibly due to its immunosuppressive effects [4,5]. However, since immunosuppression is detrimental for cancer patients, the hypothesis that blood transfusions may be harmful due to possible immunosuppression effect has been investigated in various cancer types. ABT has been shown to adversely affect disease prognosis in a diverse range of cancer types such as early stage LC, stomach cancer, colorectal cancer, bladder cancer, and prostate cancer [6–10].

In this current study, we aimed to investigate the prognostic impact of ABT in patients with NSCLC receiving CT, comparing untransfused patients to those receiving blood transfusion during treatment period or before treatment period.

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https://doi.org/10.1016/j.lungcan.2019.05.007
Received 19 March 2019; Received in revised form 3 May 2019; Accepted 5 May 2019

Table 1
Patients' data.

		All patients (n = 433)		Group U (n = 303)		Group B (n = 43)		Group D (n = 87)		
		n	%	n	%	n	%	n	%	p
Gender	Female	45	10.4	32	10.6	7	16.3	6	6.9	0.247
	Male	388	89.6	271	89.4	36	83.7	81	93.1	
Age (Years)	Median (min-max)	60 (21-92)		60 (21-92)		58 (37-77)		60 (36-90)		0.520
Smoking status	No	27	6.2	19	6.3	3	7.0	5	5.7	0.639
	Former	68	15.7	49	16.2	9	20.9	10	11.5	
	Yes	338	78.1	235	77.6	31	72.1	72	82.8	
ECOG PS	0-1	241	55.7	199	65.7	16	37.2	26	29.9	< 0.001
	2	131	30.3	64	21.1	20	46.5	47	54.0	
	3	61	14.1	40	13.2	7	16.3	14	16.1	
Tumor histology	Undetermined subtype	106	24.5	68	22.4	10	23.3	28	32.2	0.629
	Squamous cell carcinoma	168	38.8	121	39.9	15	34.9	32	36.8	
	Adenocarcinoma	148	34.2	106	35.0	17	39.5	25	28.7	
	Others	11	2.5	8	2.6	1	2.3	2	2.3	
Site of metastasis at diagnosis	Brain	96	22.2	69	22.8	11	25.6	16	18.4	0.571
	Contralateral lung	80	18.5	61	20.1	6	14.0	13	14.9	0.377
	Liver	64	14.8	42	13.9	11	25.6	11	12.6	0.111
	Surrenal	88	20.4	58	19.1	9	21.4	21	24.1	0.596
	Bone	131	30.3	83	27.4	16	37.2	32	36.8	0.141
	Pleura	105	24.2	59	19.5	17	39.5	29	33.3	0.002
	Distant lymph node	35	8.1	30	9.9	3	7.0	2	2.3	0.056
	Other	36	8.3	16	5.3	5	11.6	15	17.2	0.002
Metastasectomy	Brain	11	84.6	11	84.6					
	Surrenal	2	15.4	2	15.4					
First-line treatment	Platine-based combination	389	89.8	272	89.8	40	93.0	77	88.5	0.858
	Single-agent CT	44	10.2	31	10.2	3	7.0	10	11.5	
First-line CT regimens	Platine + pemetrexed	24	5.5	23	7.6	1	2.3	0	0.0	0.400
	Platine + gemcitabine	145	33.5	100	33.0	14	32.6	31	35.6	
	Platine + docetaxel	90	20.8	58	19.1	11	25.6	21	24.1	
	Platine + vinorelbine	35	8.1	25	8.3	3	7.0	7	8.0	
	Platine + paclitaxel	95	21.9	66	21.8	11	25.6	18	20.7	
	Vinorelbine	22	5.1	16	5.3	2	4.7	4	4.6	
	Gemcitabine	22	5.1	15	5.0	1	2.3	6	6.9	
Second-line CT		81	18.7	77	25.4	4	9.3	0	0	< 0.001
Last status	Alive	62	14.3	60	19.8	2	4.7	0	0.0	< 0.001
	Dead	371	85.7	243	80.2	41	95.3	87	100.0	

Abbreviations: **CT**, Chemotherapy; **ECOG PS,** Eastern Cooperative Oncology Group Performance status; **Group B**, Transfused before treatment period; **group D**, transfused during treatment period; **Group U**.

2. Materials and methods

2.1. Patients

Medical records of 433 metastatic NSCLC patients treated with CT in an oncology clinic between 2012 and 2018 were retrospectively analyzed. The staging procedure of the patients was performed according to the imaging outcomes of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography, computed tomography, and brain magnetic resonance. The following parameters were defined as the inclusion criteria; age < 18 years, patients with a second primary malignancy, those with benign or malign hematological disorder, patients without evidence of metastasis at diagnosis, prior exposure to tyrosine kinase inhibitors or immunotherapy, and those with incomplete data. The patients were divided into three groups according to whether or not they received transfusion and timing of transfusion as follows: group U (Untransfused patients, n = 303), group B (patients receiving transfusion Before treatment period, n = 43), and group D (patients receiving transfusion During treatment period, n = 87). In the study, both groups (patients receiving transfusion before treatment period and patients receiving transfusion during treatment period) were included in group D.

2.2. Data collection

Demographic and disease characteristics such as age, gender, smoking status, Eastern Cooperative Oncology Group Performance status (ECOG-PS), tumor histology (undetermined subtype, Squamous Cell Carcinoma [SCC], Adenocarcinoma [AC], and others), sites of metastasis at diagnosis (brain, contralateral lung, liver, surrenal glands, bone, pleura, Distant Lymph Nodes [DLN], and others), history of metastasectomy or site of metastasectomy, first-line treatment (single-agent CT or platinum-based regimens), regimens used in the first-line setting (platinum + pemetrexed, platinum + gemcitabine, platinum + docetaxel, platinum + vinorelbine, platinum + paclitaxel), second-line treatment, and the final status (dead or alive) were carefully obtained from patients' archive files.

2.3. Ethical approval

The study was performed in accordance with the declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University of Health Sciences, Okmeydani Training and Research Hospital (26.2.2018). Patients were not required to give informed consent to the study since the analysis used anonymous clinical data that were obtained after each patient made an agreement to treatment by a written consent.

2.4. Statistical analysis

Statistical Package for the Social Sciences 22.0 for Windows software (Armonk NY, IBM Corp. 2013) was used for the statistical analysis. Descriptive statistics were presented as the mean, standard deviation, minimum, and maximum values for numerical variables; and as number and percentage for categorical variables. Numerical variable between two independent groups were analyzed with student *t*-test in

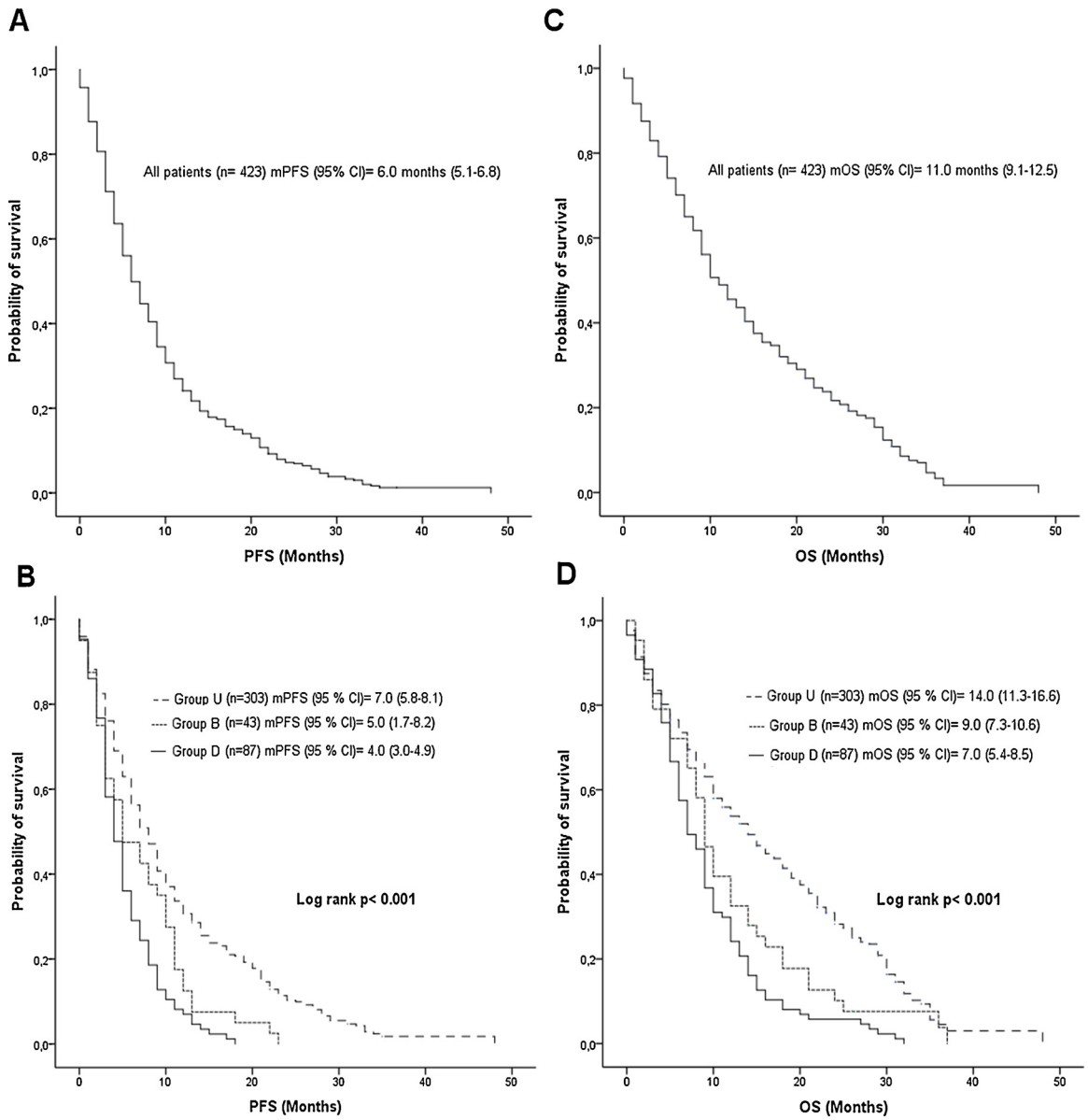

Fig. 1. PFS and OS according to allogenic blood transfusion status in all patients.
Abbreviations: **Group B**, Transfused before treatment period; **group D**, transfused during treatment period; **Group U**, Untransfused; **PFS**, Progression-free survival; **OS**, Overall survival.

case of normal distribution and with Mann Whitney U test if else. The comparison of the rates between the groups was performed by chi-square analysis. Monte Carlo simulation was applied if conditions could not be met. Survival analyses were performed with Kaplan-Meier Analysis. Determinant factors were examined with cox regression. Backward stepwise model was used with parameters having a p-value below 0.100. An overall 5% alpha error level was used to infer statistical significance. Progression-Free survival (PFS) was defined as the time from the initiation of first-line treatment to the date of progression. Overall Survival (OS) was calculated as time from the diagnosis to the date of last follow-up or death.

3. Results

The study included 433 metastatic NSCLC patients, consisting of 388 (89.6%) males and 45 (10.4%) females. The median age was 60 years (range, 21–92). Twenty-seven (6.2%) patients had no history of smoking. Of the 433 patients, 192 (44.3%) had ECOG-PS $\geq$ 2. The most common sites of metastasis at diagnosis were as follows; brain (22.2%), contralateral lung (18.5%), liver (14.8%), surrenal glands (20.4%), bone (30.3%), pleura (24.2%), DLN (8.1%), and other (8.3%). At the time of diagnosis, metastasectomy could be carried out in 13 patients. In the first-line treatment, 389 (89.8%) patients received platinum-based combination CT and 44 (10.2%) received single-agent CT. During the median follow-up time of 10.0 months (range, 1–48) 371 (85.7%) patients died (Table 1).

There was no statistically significant difference between the groups in terms of gender, age, smoking status, tumor histology, first-line treatment, treatment regimens, and the rates of metastasis to brain, contralateral lung, liver, surrenal glands, bone, and DLN. The number of patients with ECOG-PS 0–1 was significantly higher in the group U ($p < 0.001$). Pleural and other regional metastasis were significantly at low rates in the group U ($p = 0.002$, $p = 0.002$). In the group U, statistically significant more second-line CT could be given ($p < 0.001$) (Table 1).

Median PFS was 6.0 months (95% CI 5.1–6.8) in all patients. In

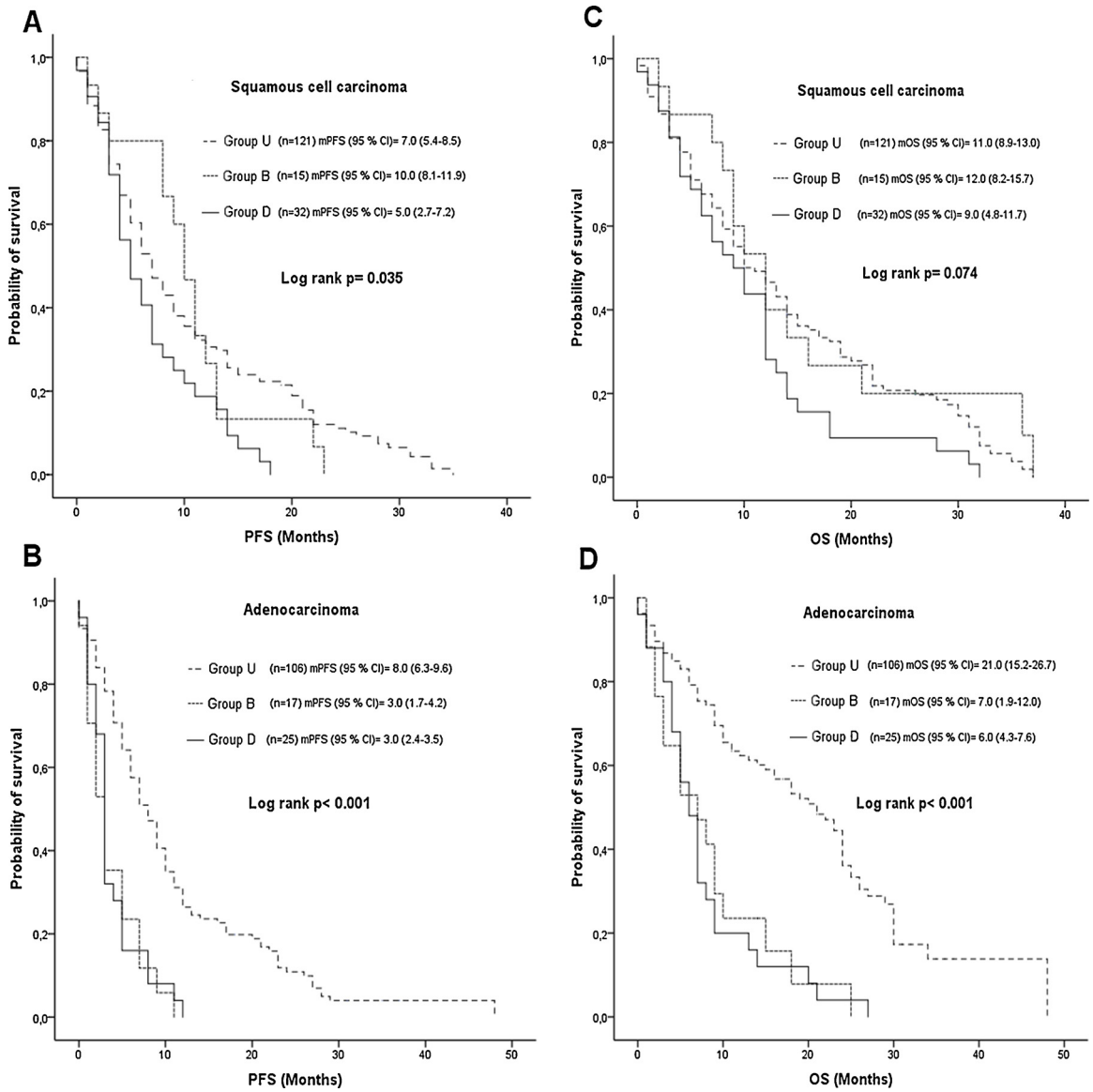

Fig. 2. PFS and OS according to allogenic blood transfusion status in histologic subtypes.
Abbreviations: **Group B**, Transfused before treatment period; **group D**, transfused during treatment period; **Group U**, Untransfused; **PFS**, Progression-free survival; **OS**, Overall survival.

subgroup analysis, median PFS in group U was 7.0 months (95% CI 5.8–8.1), whereas it was 5 months for group B (95% CI 1.7–8.2) and 4.0 months for group D (% 95 CI 3.0–4.9), indicating a statistically significant difference between the groups (Log rank $p < 0.001$). The median OS was 11.0 months (95% CI 9.1–12.5) in all patients. The median OS according to ABT status was 14.0 months (95% CI 11.3–16.6) for group U, 9.0 months (95% CI 7.3–10.6) for group B, and 7.0 months (CI 5.4–8.5) for group D, with a statistically significant difference between the groups (Log rank $p < 0.001$) (Fig. 1).

In subgroup analysis, patients with SCC subtypes; group U, group B, and group D had median PFS of 7.0 months (95% CI 5.4–8.5), 10.0 months (95% CI 8.1–11.9), and 5.0 months (95% CI 2.7–7.2), respectively ($p = 0.035$). The corresponding OS durations were 11.0 months (95% CI 8.9–13.0), 12.0 months (95% CI 8.2–15.7), and 9.0 months (95% CI 4.8–11.7), respectively (Log rank $p = 0.074$). In patients with AC subtypes; group U, group B, and group D had median PFS of 8.0 months (%95 CI 6.3–9.6), 3.0 months (%95 CI 1.7–4.2), and 3.0 months (%95 CI 2.4–3.5), respectively ($p < 0.001$). The corresponding OS durations were 21.0 months (%95 CI 15.2–26.7), 7.0 months (%95 CI 1.9–12.0), and 6.0 months (%95 CI 4.3–7.6), respectively (Log rank $p < 0.001$) (Fig. 2).

In the univariate analysis for PFS, performing ABT, ECOG-PS, histological subtype, bone metastasis, and pleural metastasis were the negative factors affecting PFS, whereas undergoing metastasectomy and receiving combination CT in the first-line setting were the factors associated with favorable PFS ($p < 0.001$, $p < 0.001$, $p = 0.024$, $p = 0.004$, $p < 0.001$, $p = 0.002$, and $p < 0.001$, respectively). Likewise, in the multivariate analysis for PFS, performing ABT, ECOG-PS, histological subtype, bone metastasis, and pleural metastasis were the negative predictor of PFS, whereas undergoing metastasectomy and receiving first-line platinum-based therapy were the factors associated with favorable PFS (0.010, $p < 0.001$, $p = 0.001$, $p = 0.011$, $p = 0.001$, $p = 0.037$ and $p = 0.004$, respectively) (Table 2).

Univariate analysis for OS revealed that performing ABT, ECOG-PS, metastasis to brain, bone, and pleura were the negative predictors of OS, whereas undergoing metastasectomy and receiving combination CT were the positive factors associated with OS ($p = 0 < 001$, $p < 0.001$, $p = 0.045$, $p < 0.001$, $p < 0.001$, $p = 0.001$ and $p < 0.001$, respectively). In multivariate analysis, performing ABT during treatment period, ECOG-PS, metastasis to bone and pleura were negative factors

Table 2
Factors affecting PFS.

		Univariate analysis for PFS			Multivariate analysis for PFS		
		HR	95% CI	p	HR	95% CI	p
Blood transfusion status	Group U			< **0.001**			0.010
	Group B	1.587	1.147-2.195	0.005	1.226	0.878-1.709	0.231
	Group D	2.044	1.591-2.626	< 0.001	1.506	1.151-1.970	0.003
Gender	Male vs. Female	0.897	0.657-1.222	0.490			
Age	Years	1.002	0.992-1.012	0.682			
Smoking status	No			0.449			
	Former	1.034	0.661-1.616	0.884			
	Yes	0.884	0.596-1.310	0.539			
ECOG-PS	0-1			< 0.001			< 0.001
	2	2.437	1.938-3.064	< 0.001	1.994	1.554-2.558	< 0.001
	3	3.103	2.321-4.147	< 0.001	2.960	2.187-4.006	< 0.001
Tumor histology	Undetermined subtype			0.024			0.001
	Squamous cell carcinoma	0.940	0.733-1.203	0.620	1.032	0.804-1.324	0.802
	Adenocarcinoma	1.042	0.808-1.343	0.752	1.318	1.012-1.716	0.040
	Others	2.452	1.309-4.590	0.005	3.137	1.663-5.914	< 0.001
Brain metastasis	Yes vs. No	0.843	0.669-1.062	0.147			
Contralateral lung metastasis	Yes vs. No	1.013	0.790-1.297	0.921			
Liver metastasis	Yes vs. No	1.170	0.895-1.531	0.250			
Surrenal metastasis	Yes vs. No	1.026	0.809-1.301	0.830			
Bone metastasis	Yes vs. No	1.360	1.103-1.675	0.004	1.327	1.066-1.651	0.011
Pleura metastasis	Yes vs. No	1.683	1.344-2.106	< 0.001	1.498	1.177-1.906	0.001
Distant lymph node metastasis	Yes vs. No	0.919	0.646-1.306	0.637			
Other metastasis	Yes vs. No	1.332	0.941-1.886	0.106			
Metastasectomy	Yes vs. No	2.736	1.457-5.135	0.002	0.505	0.265-0.960	0.037
First-line treatment	Single-agent CT vs. Platine-based combination	1.902	1.387-2.606	< 0.001	1.618	1.168-2.240	0.004

Abbreviations: see Table1.

Table 3
Factors affecting OS.

		Univariate analysis for OS			Multivariate analysis for OS		
		HR	95% CI	p	HR	95% CI	p
Blood transfusion status	Group U			< 0.001			0.080
	Group B	1.520	1.089-2.122	0.014	1.095	0.777-1.544	0.602
	Group D	2.148	1.670-2.762	< 0.001	1.369	1.041-1.800	0.025
Gender	Male vs. Female	1.045	0.746-1.463	0.799			
Age	Years	1.010	0.999-1.020	0.064			
Smoking status	No			0.574			
	Former	1.252	0.759-2.065	0.378			
	Yes	1.269	0.814-1.978	0.292			
ECOG-PS	0-1			< 0.001			< 0.001
	2	3.143	2.469-4.002	< 0.001	2.527	1.938-3.297	< 0.001
	3	4.482	3.311-6.066	< 0.001	4.052	2.960-5.546	< 0.001
Tumor histology	Undetermined subtype			0.281			
	Squamous cell carcinoma	1.028	0.796-1.327	0.834			
	Adenocarcinoma	0.817	0.622-1.072	0.145			
	Others	1.047	0.508-2.154	0.902			
Brain metastasis	Yes vs. No	0.773	0.601-0.994	0.045			
Contralateral lung metastasis	Yes vs. No	1.040	0.801-1.352	0.767			
Liver metastasis	Yes vs. No	1.191	0.896-1.585	0.229			
Surrenal metastasis	Yes vs. No	1.002	0.776-1.295	0.986			
Bone metastasis	Yes vs. No	1.519	1.218-1.894	< 0.001	1.555	1.237-1.956	< 0.001
Pleura metastasis	Yes vs. No	1.608	1.274-2.029	< 0.001	1.298	1.016-1.658	0.037
Distant lymph node	Yes vs. No	0.720	0.472-1.099	0.128			
Other metastasis	Yes vs. No	1.333	0.936-1.898	0.111			
Metastasectomy	Yes vs. No	0.265	0.118-0.595	0.001	0.440	0.194-0.997	0.049
First-line treatment	single-agent CT vs. Platine-based combination CT	2.090	1.521-2.870	< 0.001	1.478	1.068-2.045	0.018

Abbreviations: see Table1.

affecting OS, whereas undergoing metastasectomy and receiving platinum-based combination therapy in the first-line setting were found to be positive predictor of OS ($p = 0.025$, $p < 0.001$, $p < 0.001$, $p = 0.037$, $p = 0.049$ and $p = 0.018$, respectively) (Table 3).

4. Discussion

In this study, the prognostic effects of ABT in patients with advanced-stage NSCLC at diagnosis, who were treated with CT in the first-line setting, were investigated, comparing untransfused patients to those receiving blood transfusion during treatment period or before treatment period. It was demonstrated that performing ABT during treatment period had a significant negative effect on survival, with the greatest negative effect being in AC subtype.

In cancer patients, anemia may develop due to treatment effects as well as the tumor itself [11]. Although ABT may improve anemia

symptoms in oncology patients, there are some disadvantages associated with blood transfusion, such as contagious infections, hemolytic reactions, transfusion-related lung injury, and Transfusion-Related Immunomodulation (TRI) [12]. In a variety of malignancies, it has been proposed that TRI including allo-immunization, tolerance, or immunosuppression may elucidate the relationship between perioperative ABT and survival [7,10,13–15]. Kim et al. reported that ABT was associated with shorter survival in prostatic cancer [10]. Likewise, Liu et al. also demonstrated that preoperative ABT was found to be an independent risk factor on survival in gastric cancer [7].

Tartter et al. first reported that perioperative ABT increases the risk of recurrence in LC [16]. Many studies showed that perioperative ABT had a negative effect on recurrence and survival in LC. Several subsequent studies also reported that perioperative ABT in LC had a negative effect on disease recurrence and patients' survival [6,17–21]; however, this relation could not be shown in some other studies [22–27]. Wan et al., who conducted a meta-analysis including 23 studies and 6474 patients, showed that ABT was significantly associated with earlier recurrence and worse survival in patients with resected LC [28]. In our study, performing ABT during the treatment period was shown to increase the risk of progression and mortality by 1.5 times and 1.3 times, respectively, compared with the untransfused patients. In subgroup analysis, ABT significantly shortened PFS and OS, particularly in AC subtype.

The mechanisms that induce TRI are still unclarified. Most experimental studies have shown that transferred leukocytes mediate to damaging in the immune system [29]. However, a meta-analysis by Vamvakas reported that there was no significant difference in survival between patients receiving ABT with or without leukocytes [30]. In contrast, Ng et al. demonstrated that leukocyte-depleted blood transfusion was associated with worse DFS and OS in patients with resected LC [21], suggesting a hypothesis that any other mechanism may be involved in this process. The most commonly reported mechanisms for TRI are as follows; the decrease in natural killer cell function, reduction in the rate of T-helper lymphocytes, decrease in the efficacy of antigen presentation, and suppression of tolerance/hematopoiesis induced by specific antigens [31,32]. Alternatively, Procter et al. reported that the depletion of serum arginine, which is an essential amino acid for normal body immunity, may be the mechanism of immunosuppression [33].

The cytotoxic immune response to tumor cell requires a complex and rapidly-developing interaction among a variety of immune cell types in the adaptive and natural immune system. Several therapeutic approaches are now being investigated in order to release the immune system and control malignancy, such as cytokines, T-cells, manipulation of T-cells, oncolytic viruses, treatments intended for other cell types, and vaccines [34–36]. In recent years, Programmed Cell Death-1 (PD-1) and PD-Ligand-L1 (PD-L1) inhibitors, which are used in the treatment of advanced NSCLC, have significantly prolonged survival in LC patients [37]. But, it is not known how ABT affects the treatment outcomes in patients treated with immunotherapy, thus further studies are needed on this issue.

So far, studies on this area have remained limited and included only early-stage operated patients [6,17,18,21–28]. Unlike other studies, our study included metastatic NSCLC patients at diagnosis, but even so our study had some limitations as follows; 1- It had retrospective nature, 2- We could not reach the data regarding the number of transfusions performed before treatment period or during treatment period, thus we do not know how this condition affects survival, 3- We don't exactly know after which cycle we performed transfusion.

In conclusion, our results indicated that ABT was significantly associated with earlier progression and shorter survival in patients with metastatic NSCLC, particularly in AC subtype. There is insufficient evidence to establish a direct causal link between ABT and worse outcomes in patients with metastatic NSCLC. Based upon these findings demonstrated in our study, we suggest that the transfusion strategy in LC, particularly in lung AC subtype, should remain limited unless physicians absolutely have to. Further prospective studies including larger sample size treated with immunotherapy are needed in order to clarify and confirm these outcomes.

Conflict of interest

All authors declare that there is no conflict of interest related to this article.

Funding source

None.

Author contributions

Concept – AS, SC; Design – SA, AS, SS; Supervision – SC, AS, NY; Resources – NY, CG, CD; Materials – AS, NY, CD; Data Collection and/or Processing – AS, NY, CG; Analysis and/or Interpretation – SC, AS; Literature Search – CD, SS; Writing Manuscript – AS, SS; Critical Review – SC, CD; Other – CG, NY

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