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Blood Parameters Demonstrating a Significant Survival Impact in Patients With Locally Advanced NSCLC Undergoing Definitive Chemoradiotherapy

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Abstract. *Aim: We investigated blood parameters in patients with inoperable stage III non-small cell lung cancer (NSCLC) to predict individual outcomes after definitive chemo-radiotherapy (CRT). Patients and Methods: Blood parameters of consecutive patients undergoing definitive CRT between 2010 and 2016 for inoperable stage III NSCLC before multimodal treatment and at first follow-up were measured and analyzed. Results: Blood parameters from 99 patients were evaluated. Histologically, about 50% of patients had an adenocarcinoma. All patients received platinum-based sequential or concurrent CRT. The median total dose to the primary tumor was 60 (range=48-70) Gy. On multivariate analysis after adjustment for all co-founders, median overall survival for pre-treatment cutoffs were: lactate dehydrogenase (LDH) >250 U/l was 17 vs. 27 months [hazard ratio (HR)=2.05, 95% confidence intervaI (CI)=1.15-3.66; p=0.015], thrombocytosis >400×10^6/l: 11 vs. 23 months (HR=2.75, 95% CI=1.1-6.88; p=0.03), hypoalbuminemia <3.5 g/dl: 12 vs. 24 months (HR=2.42, 95% CI=1.21-4.84; p=0.013) and post-treatment neutrophilia >7×10^6/l: 12 vs. 27 months (HR=2.5, 95% CI=1.21-5.17; p=0.013). Conclusion: Pre-treatment elevated LDH, thrombocytosis, hypoalbuminemia and post-treatment neutrophilia were associated with significantly worse overall survival in patients with inoperable stage III NSCLC treated with CRT. Patients with both pre-therapeutic elevated LDH and hypoalbuminemia demonstrated a dismal prognosis despite completion of multimodal treatment.*

Lung cancer is the most common cause of cancer-related deaths worldwide (1). At diagnosis, about 25% of patients with non-small cell lung cancer (NSCLC) present with inoperable stage III disease. Historically, median overall survival following chemoradiotherapy (CRT) has ranged between 15 and 30 months (2). Currently, the best reported survival rates including progression-free survival and overall survival overall survival were achieved with tri-modality treatment consisting of chemotherapy, radiotherapy and immunotherapy (3). Several studies in locally advanced lung cancer have already described blood parameters as prognostic factors, such as neutrophilia (4), the neutrophil-to-lymphocyte ratio (NLR) (5), thrombocytosis (6), lactate dehydrogenase (LDH) (7) and serum albumin levels (8) in patients with lung cancer.

The aim of the present study was to find the prognostic value of different blood parameters measured before and at first follow-up after completion of platinum-based CRT in patients with inoperable stage III NSCLC.

Patients and Methods

Study population. The medical charts of 99 consecutive patients with locally advanced stage III NSCLC [according to the seventh edition of the Union for International Cancer Control classification (9)] that were treated with curative-intent mainly platinum-based CRT to a median total dose of 60 Gy (range=45-70 Gy) at our Department between 2010 and 2016 were assessed. Patient and

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treatment characteristics are summarized in Table I. The Institutional Research Ethical Review Board approved the study (approval number: 17-230).

Complete blood count analysis. We retrospectively assessed the blood parameters of all patients and focused on the examination and comparison of the lymphocyte count, neutrophil count, serum hemoglobin, thrombocyte count, NLR, platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index, and LDH and serum albumin levels.

For the analysis, we chose the latest blood values before initiation of (up to 1 week before treatment start) and the earliest upon completion of CRT (last day of treatment, up to 1 week after treatment). As optimal cut-off values remain a controversial topic, we chose cut-off points that have been recognized as standard pathological definitions. We defined thrombocytosis and neutrophilia as $>400\times10^6$/l and $>7\times10^6$/l respectively. To evaluate anemia, we chose different cut-off values 10, 11 and 12 g/dl as described in the literature (10). High LDH and hypoalbuminemia were defined as >250 U/l and ≤3.5 g/dl, respectively. For indices, we chose values in the literature; as the NLR cut-off we chose ≤3.5 *vs*. >3.5 (11) and for PLR ≤150 *vs*. >150 (12).

Statistical analysis. Statistical analyses were performed using SPSS statistics 25 (IBM, New York, United States) and R version 3.5.3. Subgroups were compared using the log-rank test. All significant variables in univariate analysis were included in a multivariate Cox regression analysis. The proportional hazard assumption of the Cox regression analysis was tested. Overall survival was defined as the time between the diagnosis and death. Event-free survival was defined as the time between diagnosis and the occurrence of either disease recurrence or death. For all statistical analyses, a significance level of $\alpha=0.05$ was defined.

Results

In the univariate analysis, elevated LDH (>250 U/l), high NLR (>3.53), thrombocytosis ($>400\times10^6$/I), neutrophilia ($>7\times10^6$/l) and hypoalbuminemia (≤3.5 g/dl) demonstrated a significant negative impact on overall survival (Table II).

On multivariate analysis after adjustment for all co-founders, elevated LDH [hazard ratio (HR)=2.05, 95% confidence intervaI (CI)=1.15-3.66; $p=0.015$], thrombocytosis (HR=2.75, 95% CI=1.1-6.88; $p=0.03$) and hypoalbuminemia (HR=2.42, 95% CI=1.21-4.84; $p=0.013$) were associated with significantly worse patient outcome (Table II).

In the univariate analysis, only neutrophilia and hypoalbuminemia were associated with significantly worse median overall survival. On multivariate analysis after adjustment for all co-founders, only neutrophilia remained significant (HR=2.5, 95% CI=1.21-5.17; $p=0.013$).

Based on the analyzed data set, a most prominent overall survival difference was found between patients with pre-therapeutic elevated LDH (median=20.8 months, 95% CI=12.6-29 months) and the combination of pre-therapeutic elevated LDH and hypoalbuminemia (median=11.1 months, 95% CI=2-20 months) ($p=0.001$).

Table I. *Patient characteristics*.

Characteristic		
Age, years	Median	68
	Min.	43
	Max.	88
Ever-smoker, n (%)	Yes	90 (91%)
	No	9 (9%)
Gender, n (%)	Male	62 (63%)
	Female	37 (27%)
cT stage, n (%)	cT1	11 (11%)
	cT2	17 (17%)
	cT3	30 (30%)
	cT4	41 (41%)
cN stage, n (%)	cN0	11 (11%)
	cN1	9 (9%)
	cN2	36 (36%)
	cN3	44 (44%)
Chemotherapy, n (%)	Platinum	67 (68%)
	Non-platinum	28 (28%)
	Missing	4 (4%)

Discussion

Upon diagnosis of locally advanced NSCLC, physicians tend to base the patient's prognosis primarily on the performance status and age. In the present study, we revealed that several blood parameters are also associated with patient outcome. In our study, pre- and post-treatment elevated LDH (>250 U/l) was associated with a worse median overall survival on univariate analysis. However, on multivariate analysis, only elevated pre-treatment LDH remained significant. Forty-four of our patients (44%) exhibited an elevated LDH level before treatment start. Our finding was among others confirmed by a large meta-analysis including over 4,000 patients (13). Typical cancer-induced LDH elevation is caused by increased anaerobic glycolytic metabolism, which typically occurs in an intra-tumoral environment and therefore indirectly reflects the extent of a tumor (7). Preclinical attempts to lower LDH and thereby improve the outcome of patients with NSCLC already exist (14).

Thrombocytosis ($>400\times10^6$/l) is a prognostic factor associated with worse overall survival. Eleven of our patients (11%) exhibited thrombocytosis before treatment start, with this having a significant negative impact on survival in multivariate analysis. Other studies have also confirmed thrombocytosis as a paraneoplastic syndrome (15, 16).

Pre- and post-treatment hypoalbuminemia (<3.5 g/dl) was associated with reduced overall survival on univariate analysis, and on multivariate analysis, only a low pre-treatment albumin level remained significant. In our study, 17% of patients showed hypoalbuminemia before treatment start. A worse prognosis associated with hypoalbuminemia

Table II. *Significant factors before and after treatment regarding overall survival (OS). Results of multivariate analysis include all significant covariates of univariate analysis.*

	Parameter		Median OS (95% CI), months	Univariate		Multivariate	
				HR (95% CI)	*p*-Value	HR (95%-CI)	*p*-Value
Before CRT	LDH	≤250 U/l	27 (18-40)	1 (Reference)	0.016	1 (Reference)	0.015
		>250 U/l	17 (14-25)	1.74 (1.11-2.74)		2.05 (1.15-3.66)	
	NLR	≤3.53	29 (22-40)	1 (Reference)	0.03	1 (Reference)	0.192
		>3.53	17 (12-28)	1.69 (1.02-2.8)		1.52 (0.81-2.85)	
	Platelet count	≤400×10^6/l	23 (19-30)	1 (Reference)	<0.001	1 (Reference)	0.031
		>400×10^6/l	11 (8-NA)	3.32 (1.64-6.69)		2.75 (1.10-6.88)	
	NeutrophiIs	≤7×10^6/l	27 (21-37)	1 (Reference)	0.008	1 (Reference)	0.805
		>7×10^6/l	12 (8-NA)	2.31 (1.25-4.29)		1.11 (0.49-2.53)	
	Albumin	>3.5 g/dl	24 (19-31)	1 (Reference)	<0.001	1 (Reference)	0.013
		≤3.5 g/dl	12 (6-22)	2.85 (1.61-5.05)		2.42 (1.21-4.84)	
After CRT	NeutrophiIs	≤7×106/l	24 (18-31)	1 (Reference)	0.003	1 (Reference)	0.013
		>7×10^6/l	13 (10-NA)	2.89 (1.44-5.81)		2.50 (1.21-5.17)	
	Albumin	>3.5 g/dl	23 (19-37)	1 (Reference)	0.019	1 (Reference)	0.267
		≤3.5 g/dl	12 (8-29)	1.77 (1.1-2.84)		1.38 (0.78-2.43)	

CI: Confidence interval; CRT: chemoradiotherapy; HR: hazard ratio; LDH: lactate dehydrogenase; NLR: neutrophil-to-lymphocyte ratio.

seems logical as it is related to cancer cachexia and malnutrition, and patients showing these symptoms are clinically less fit to receive aggressive multimodal treatment. Ikeda *et al*. also found that hypoalbuminemia was associated with worse overall survival and early termination of chemotherapy in elderly patients with NSCLC and suggested that the decision between best-supportive care and chemotherapy in patient group should be based on the performance status and the serum albumin level (17).

Post-treatment neutrophilia (>7×10^6/l) was associated with reduced overall survival. Eleven percent of our patients showed neutrophilia after treatment. After excluding obvious causes for neutrophilic leukocytosis such as infection, injury, inflammatory disorder and certain drugs, one may assume that neutrophilia in patients with cancer is derived from hematopoietic colony-stimulating factors and inflammatory cytokines direct from solid tumors compromising granulocyte colony-stimulating factor (4). Another point is a potential role of neutrophils in the metastatic process.

It was surprising that the hemoglobin count, an established prognostic factor (10), did not show any prognostic value in our study. This may partly be due to the relatively small sample size in our study. Additionally, only one patient in our study had a grade III anemia, which also plays a significant role when discussing the results.

Furthermore, NLR, an established prognostic marker had no impact on our patients' prognosis. Similarly as described by Bernhardt *et al*. (18), there are no defined cutoff values for NLR, making it difficult to compare different studies. Even by using different cutoff values as suggested by Bernhardt *et al*., the NLR failed to be a significant prognostic marker for our cohort. As described by Contreras *et al*., there are even additional co-founders for the absolute neutrophil and lymphocyte counts. Specifically, these values are influenced by the radiation treatment plan, especially by the percentage of heart receiving ≥50 Gy (V50), thereby further complicating the comparability of studies with patients undergoing CRT (19).

The present study has shown that using routinely accessible laboratory values may further help physicians to individualize available treatment options and predict patient prognosis. Limitations of this study include the small number of patients and the retrospective nature; further prospective research will be necessary. One may consider correlating blood values and their dynamic changes with tumor response upon completion of CRT or after initiation of consolidation treatment with immune check-point inhibitors.

In summary, pre-treatment elevated LDH, thrombocytosis, hypoalbuminemia and post-treatment neutrophilia were associated with a significantly shorter median survival in patients with inoperable stage III NSCLC undergoing definitive CRT. This study emphasizes a role of blood parameters and their dynamic changes to further infer patient prognosis and individualize multimodal treatment.

Conflicts of Interest

All Authors have declared that there are no conflicts of interest with regard to this work.

Authors' Contributions

M.H., D.R., L.K., J.T., C.E., O.R., M.K., C.B. and F.M. contributed to the design and implementation of the research, M.H. and D.R. to the analysis of the results and M.H., D.R. L.K., C.E. and F.M. to the writing of the article.

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