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Role of Peripheral Blood Markers for Detecting Response and Predicting Prognosis in Patients with Non-small-cell Lung Cancer Undergoing Neoadjuvant Therapy and Surgery

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Abstract

Introduction To date**,** no validated predictors of response before neoadjuvant therapy (NAD) are currently available in locally advanced non-small-cell lung cancer (NSCLC). In this study, different peripheral blood markers were investigated before NAD (pre-NAD) and after NAD/before surgery (post-NAD) to evaluate their influence on the treatment outcomes.

Methods Patients affected by locally advanced NSCLC (cT1-T4/N0-2/M0) who underwent NAD followed by surgery from January 1996 to December 2019 were considered for this retrospective analysis. The impact of peripheral blood markers on downstaging post-NAD and on overall survival (OS) was evaluated using multivariate logistic and Cox regression models. Time to event analysis was performed by means of Kaplan–Meier survival curves and Log Rank tests at 5 years from surgery.

Results Two hundred and seventy-two consecutive patients were included. Most of the patients had Stage III NSCLC (83.5%). N2 disease was reported in 188 (69.1%) patients. Surgical resection was performed in patients with stable disease or downstaging post-NAD. Nodal downstaging was observed in 80% of clinical N2 (cN2) patients. The median follow-up of the total series was 74 months (range 6–302). Five-year OS in the overall population and in N2 population was 74.6% and 73.5%, respectively. The pre-surgery platelets level (PLT) ($p = 0.019$) and the variation (pre-NAD/post-NAD) of the neutrophil/lymphocyte ratio ($p = 0.024$) were identified as independent prognostic factors of OS.
The preoperative PLT value (p value $= 0.031$) was confirmed as the only predictor of NAD response.

Conclusions The clinical role of peripheral blood markers in locally advanced NSCLC needs to be further investigated. Based on these preliminary results, these factors may be used as auxiliary markers for the prediction of response to neoadjuvant treatment and as prognostic factors for stratification in multimodal approaches.

Keywords Biomarkers · Neutrophils · Blood markers · NSCLC · Induction therapy · Surgery

Introduction

Despite the numerous recent progresses in the treatment of lung cancer, the strategy of care for locally advanced non-small-cell lung cancer (NSCLC) (mostly N2 disease) has not been adequately standardized and survival outcomes are still disappointing with no remarkable improvements in the last decades [1]. The choice of local treatment modality can indeed vary across countries and centres, and is usually more prone to local policies and personal opinions than those suggested by standardized protocols. Surgery is generally the most accepted treatment after neoadjuvant therapy (post-NAD) in the subsets of locally advanced NSCLC patients

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experiencing complete or partial response to NAD itself or those with stable disease and evidence of technical feasibility of resection with radical intent [2–4].

Literature data suggest indeed that downstaging post-NAD is directly associated with an improvement of the disease-free survival (DFS) and lower distant recurrence rates [5, 6].

However, the preoperative identification of the best candidates for surgery post-NAD is a very complex process and current decisional factors to predict the NAD response and/or prognosis (mainly represented by restaging imaging findings at CT or PET/CT scan) are still not completely validated [7, 8].

Therefore, the identification of biomarkers in this setting remains a crucial issue to tailor the best therapeutic interventions by identifying a priori the best candidates for such a challenging strategy of care.

Besides imaging data, hematological parameters may play a significant role in terms of response prediction and patients stratification. As an example, inflammation status is well known to correlate with cancer growth and long-term patient outcome [9]. Several inflammation markers including red cell distribution width (RDW) [10], neutrophil to lymphocyte ratio (NLR) [11] and platelet to lymphocyte ratio (PLR) [12] have been reported as useful prognostic factors for patients with NSCLC who undergo lung resection and their promising performance justifies the possibility to further investigate their role in other disease settings, such as response to NAD prediction.

Aims of this study are

- To evaluate the role of different peripheral blood markers before neoadjuvant treatment (pre-NAD) and post-NAD to predict pathological response;
- To evaluate the prognostic role in terms of OS prediction of different peripheral blood markers pre-NAD and post-NAD.

Materials and Methods

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board (N. 0012949/22 del 13.04.22).

A retrospective review of a prospective institutional lung cancer database was conducted to select the clinical records of locally advanced NSCLC (cT1-T4/N0-2/M0) who underwent NAD followed by surgery at Catholic University of the Sacred Heart–Fondazione Policlinico Universitario "A. Gemelli" IRCCS of Rome (Italy).

From January 1996 to December 2019, 272 consecutive patients were included (median age of 63 years; range 26–81). We excluded those patients with incomplete crucial data, those who did not complete the NAD-protocol or those excluded from surgery for functional or oncological reasons.

Information based on the available clinical records, such as demographics and clinical features, were collected and taken into consideration for statistical analysis.

Follow-up data were retrieved from our database. However, in a situation where data were absent or corrupted, records from direct phone interviews with patients or legal family representatives (next of kin) as in the case of death were used. All privacy-related issues were covered by the original comprehensive informed consent. At the time of the analysis, all patients had a follow-up period of at least 6 months.

The 8th edition of the American Joint Committee on Cancer's tumour (T), node (N) and metastasis (M) system of staging was adopted and extended to all the considered cohorts [13]. Inclusion criteria for the multimodal treatment were previously reported [5]. Clinical staging was based on radiological (CT scan and MRI) and nuclear medicine (18^F-FDG PET/CT, in NSCLC cases treated after 2008) results.

Moreover, in the case of suspected N-disease at diagnosis, the mediastinal involvement was always pathologically proven, usually by mini-invasive (trans-bronchial/trans-oesophageal biopsy) or surgical procedures (mediastinoscopy/mediastinotomy/thoracoscopy) prior to the start of NAD. Pathological complete response was defined as the absence of tumour cells in all surgical specimens (ypT0N0).

Induction Therapy, Restaging and Surgery

Procedures and schedules regarding the NAD protocols were extensively described in previous publications by our group [1, 5]. To explain briefly, uniformly platinum-based compounds (CBDCA, CDDP) plus 5 fluorouracil (5FU) were previously used until the introduction of Gemcitabine (GEM) which was used to substitute 5FU.

Over the years, there has been an evolution of the irradiation technique from 2- to 3-dimensional conformal radiotherapy (CRT) to intensity-modulated radiation therapy (IMRT) and more recently, the volumetric modulated arc therapy (VMAT).

The total administered radiotherapy (RT) dose was 50.4 Gy in all cases, with the classical (1.8 Gy per fraction) or hyper-fractionated schedule (640 cGy at 40 cGy fractions bis in die 1–8 q14 followed by 50.4 Gy at 1.8 Gy per fraction).

A complete clinical and radiological restaging usually consisting of a chest CT scan and 18^F-FDG PET/CT (which was used for cases treated after 2008) was performed 4–6 weeks at the end of NAD. Re-mediastinoscopy was never performed in the present series, whereas EBUS/EUS approach was performed for cases treated after 2012.

All NSCLC patients with no progression at restaging and with resectable disease were addressed to surgery after careful cardio-pulmonary evaluation.

Surgery was usually performed 16 days (mean; range from 10 to 21 days) after disease restaging. Considering the initial locally advanced disease stage, a parenchymal resection to an extent lesser than a lobectomy was referred to as oncological inappropriate and therefore never performed. Systematic mediastinal lymph node dissection was performed following the principles reported in the ESTS guidelines [14].

Adjuvant therapy was performed only in persistent N2 disease (including RT, if not performed before surgery).

Peripheral Blood Biomarkers Evaluation

The evaluation of the peripheral blood biomarkers consisted in the following parameters (RDW, Hb, platelets, neutrophils, lymphocytes).

We also evaluated 3 derived parameters according to recent literature data [11, 12]

- Derived neutrophils/(leucocytes) ratio (NLR),
- Platelet to lymphocyte ratio (PLR)
- (Platelet × neutrophils)/leucocytes (PNL)

Blood samples were collected within 15 days pre-NAD and extracted from institutional electronic medical records. A further evaluation analysing the same parameters was performed within 15 days before surgery and not more than 15 days post-NAD.

Variation values were calculated for each parameter, taking into account the values obtained pre-NAD and post-NAD, as reported in this formula: (Δ = post-NAD − Pre-NAD/Pre-NAD × 100%).

Statistical Analysis

Descriptive statistics were used to summarize pertinent study information.

The impact of peripheral blood markers on downstaging post-NAD and OS was evaluated using the logistic regression and Cox regression models, respectively. The Odds ratio (OR), hazard ratio (HR) and the 95% Confidence interval (95% CI) were calculated using the logistic regression model. At univariable analysis, baseline demographic and clinical characteristics were evaluated: Age, Sex, cT stage, type of NAD, histology, Hb, platelets count, neutrophils count, Lymphocytes count, PLR, NLR, PNL and Pre-NAD and post-NAD values of RDW.

A multivariate logistic regression and proportional hazard model were developed using stepwise regression (forward selection, enter limit and remove limit, $p = 0.10$ and $p = 0.15$, respectively), to identify independent predictors of outcomes, considering the significant variables at univariate analysis. The assessment of interactions between significant investigational variables was taken into account when developing the multivariate model.

Overall Survival (OS) was estimated by the Kaplan–Meier product limit method from the date of surgery until death due to cancer or death for any cause.

The SPSS (version 21.0; SPSS, Inc., Chicago, IL) a licensed statistical programme was used for all analyses.

Results

A Total of 272 consecutive patients were included (median age of 63 years; range 26–81). Adenocarcinoma was the most common histology (Table 1).

The majority of the enrolled patients were diagnosed with locally advanced NSCLC, with Stage III accounting for 83.5% of the cases. Involvement of mediastinal lymph node (cN2-disease) was reported in 188 (69.1%). NAD consisted of a combined approach of radio-chemotherapy in about 2/3 of the patients, and chemotherapy alone which was administered in the remaining cases. Surgical resection was performed in patients with stable disease or downstaging and most commonly consisted of lobectomy (237 cases, 87%) and radical resection (258 R0-resections, 95%). At pathological staging, about 70% of patients had stage I-II with 66.5% of pN0-patients.

Blood Biomarkers Predicting Response to Neoadjuvant Therapy

Considering only NSCLC patients with cN2 at diagnosis (188), we detected N-downstaging in 80% of them. We observed at the regression analysis that only the platelet level evaluated in the preoperative setting (p value = 0.031) was a predictor of NAD response (OR 0.0994, 95% CI 0.988–0.999), while a positive trend was observed for the pre-surgery (post-NAD) platelet/lymphocyte ratio (p value = 0.080).

There was no difference when comparing the association between blood biomarkers and response according to age, histology and type of NAD-protocol (Table 2).

Blood Biomarkers Predicting Long-term Survival

The median follow-up of the total cohort was 74 months (range 6–302). Five-years OS in the overall population and in cN2-population were 74.6% and 73.5%, respectively (Figs. 1 and 2).

Considering the entire cohort at univariable analysis, early cT stage (1–2 vs 3–4, $p = 0.012$), pre-surgery platelets

Table 1 Clinical findings, pathological features and surgical notes of the study population

Variables	Total $N=272$ (%)	Variables	Total $N=272$ (%)
Gender	209 (76.8)	*Neoadjuvant treatment*	
Male	63 (23.1)	Chemotherapy (CT)	82 (30.1)
Female		Radiotherapy (RT)	3 (1.1)
Age		CT + RT	187 (68.8)
< 63	140 (51.4)	*Downstaging LNF (only N2 population N = 188)*	
> 63	132(48.5)	Yes	149 (79.2)
Histological type		No	39 (20.7)
Adenocarcinoma	133 (48.8)	*Surgery (R0 = 258)*	
Squamous cell carcinoma	111 (40.8)	Pneumonectomy	38 (14.7)
Others	28 (10.2)	Lobectomy	220 (85.3)
cT stage		*pTstage*	
T1	24 (8.8)	T0	50 (18.4)
T2	73 (26.9)	T1	97 (35.7)
T3	92 (33.8)	T2	65 (23.9)
T4	83 (30.5)	T3	36 (13.2)
cN stage		T4	24 (8.8)
N0	38 (14.0)	*pN stage*	
N1	68 (25.1)	N0	181 (66.5)
N2	188 (69.1)	N1	44 (16.2)
N3	16 (5.8)	N2	47 (17.3)
cTNM stage		*pTNM stage*	
I + II	31 (11.4)	I + II	191 (70.2)
III	227 (83.5)	III	69 (25.3)
IV	14 (5.1)	IV	12 (4.4)

value ($p=0.016$) and the variation (pre-NAD/post-NAD) of the neutrophil/lymphocyte ratio (p value = 0.024) were shown to be significantly associated with OS (Table 3). The post-NAD platelets value (p value = 0.019) and the variation (pre-NAD/post-NAD) of the neutrophil/lymphocyte ratio (p value = 0.024) (Table 2) were independent prognostic factors of OS in the whole population (Table 4).

Regarding cN2 patients only, ΔNLR ($p=0.013$) and ΔPNL significantly correlated with OS at univariable analysis, while at multivariable analysis, the ΔNLR ($p=0.012$) was confirmed as independent prognostic factor (Table 2).

Discussion

Despite the fact that no other studies have been performed on the role of peripheral biomarkers in this specific subset, several evidences have been reported in NSCLC patients [15–21].

We analysed the ability to predict the response to NAD and prognosis of peripheral blood markers in a specific subset of patients with locally advanced NSCLC who underwent NAD followed by surgical resection.

The use of peripheral blood biomarkers is encouraged for several reasons, such as their well-established standardization, reproducibility, limited costs and the possibility to easily store them in terms of format and archiving space. Their use in the framework of artificial composite biomarkers together with other omics-derived predictors (i.e. radiomics, genomics, metabolomics, lifestyle) will probably disclose information that we currently still do not fully understand about the hallmarks of NSCLC, its biological behaviour and response to therapy patterns [22].

Recent literature suggests that cancer-related inflammation plays a key part in tumour progression mechanisms [15–17]. Platelets and blood neutrophils are involved in the systemic inflammatory response and can participate in tumorigenesis, cancer proliferation and chemotherapy or immunotherapy resistance induction [18–24].

Among other factors (i.e. combination of RT and chemotherapy), we observed that the preoperative platelet level may have a role in predicting response post-NAD (defined as N2-dowstaging in N2 population only) (p value = 0.031).

The post-NAD platelet/lymphocyte ratio was also associated with response to NAD, showing a trend of correlation (p value = 0.080) that suggests a possible role and deserves further analysis.

Table 2 Univariable analysis exploring factors predicting response to neoadjuvant therapy (cN2-population only)

Variables Univariate analysis	(p value)
Pre- neoadjuvant treatment (Pre-NAD)	
AGE	0.366
SEX	0.068
CT I-II vs III-IV	0.105
TYPE OF NAD	
CT	0.734
RT	0.066
HISTOLOGY	
Adenocarcinoma	0.463
Squamous cell carcinoma	0.801
RDW	0.309
Hb	0.977
PLATELETS	0.951
NEUTROPHILS	0.911
LYMPHOCYTES	0.333
PLR	0.216
NLR	0.257
PNL	0.196
Post-NAD	
RDW	0.130
Hb	0.660
PLATELETS	**0.031**
NEUTROPHILS	0.950
LYMPHOCYTES	0.470
PLR	0.080
NLR	0.519
PNL	0.222
Δ (Post-NAD − Pre-NAD/Pre-NAD × 100%)	
VAR_RDW	0.274
VAR_Hb	0.423
VAR_PLATELETS	0.608
VAR_NEUTHOPHILS	0.950
VAR_LYMPHOCYTES	0.737
VAR_PLR	0.791
VAR_NLR	0.892
VAR_PNL	0.981

Bold value indicates significant variables

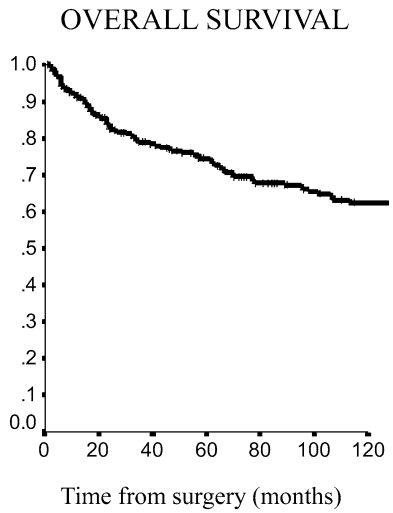

Fig. 1 Overall Survival (OS) in the entire cohort of patients underwent neoadjuvant treatment

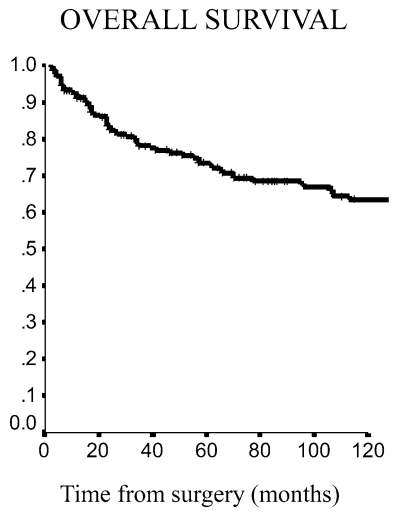

Fig. 2 Overall Survival in the cN2 patients underwent neoadjuvant treatment

Interestingly, peripheral blood biomarkers were also considered for their potential role as survival predictors and prognostic profilers. We found that the platelet count observed in the preoperative window (p value = 0.019) and the variation of the NLR (pre-NAD/post-NAD) (p value = 0.024) are independent prognostic factors of OS.

Besides the aforementioned peripheral blood indices, we decided not to include other potential inflammatory biomarkers, whose prognostic values are more debated, such as the lymphocyte-to-monocyte ratio (LMR) or other biomarkers, such as nutritional ones such as serum albumin concentration and C-reactive protein level. We chose not to include too many variables in order to avoid an increased risk of a type I error when making multiple statistical tests.

In the present analysis, we observed that the variation of NLR pre-NAD and post-NAD represents a significant prognostic factor in NSCLC patients.

Neutrophils produce cytokines which inhibit lymphocyte-mediated immune activity comprised of natural killer T cells or activated T cells [25, 26].

As we know, an increase in NLR depends on both a growth of neutrophils and a decrease in lymphocytes, an

Table 3 Univariable analysis for survival in the entire cohort and in cN2 patients only

Variables	*p* value Entire cohort Pre- neoadjuvant treatment (Pre-NAD)	*p* value cN2 patients Pre- neoadjuvant treatment (Pre-NAD)
AGE	0.177	0.192
SEX	0.139	0.437
CT I-II vs III-IV	**0.012**	0.069
TYPE OF NAD		0.786
CT	0.345	0.488
RT	0.949	0.975
HISTOLOGY	0.200	
Adenocarcinoma	0.313	0.500
Squamous cell carcinoma	0.107	0.331
RDW	0.358	0.424
Hb	0.907	0.423
PLATELETS	0.987	0.140
NEUTROPHILS	0.930	0.386
LYMPHOCYTES	0.324	0.247
PLR	0.454	0.522
NLR	0.628	0.859
PNL	0.652	0.926
	Post NAD	Post NAD
RDW	0.235	0.253
Hb	0.179	0.291
PLATELETS	0.016	0.456
NEUTROPHILS	0.834	0.646
LYMPHOCYTES	0.254	0.463
PLR	0.737	0.702
NLR	0.238	0.459
PNL	0.816	0.962
	Δ (Post-NAD − Pre-NAD/Pre-NAD × 100%)	Δ (Post NAD − Pre-NAD/Pre-NAD × 100%)
VAR_RDW	0.293	0.322
VAR_Hb	0.396	0.974
VAR_PLATELETS	0.168	0.286
VAR_NEUTHOPHILS	0.420	0.231
VAR_LYMPHOCYTES	0.339	0.479
VAR_PLR	0.235	0.325
VAR_NLR	**0.003**	**0.013**
VAR_PNL	**0.020**	**0.041**

Bold values indicate significant variables

event that may both occur very often during the multimodal therapies for lung cancer. Previous meta-analysis findings revealed that an increase in NLR is correlated with poorer prognosis in NSCLC patients [27, 28], with similar results reported in cases of surgically resected NSCLC [29].

This investigation suggests that this observation is valid even in a different cohort of patients with locally advanced NSCLC undergoing multimodal approaches including surgical resection post-NAD.

Table 4 Multivariate analysis for overall survival

Variable	*p* value	HR (95%CI)
Long-term survival entire cohort		
Post NAD platelets	0.019	0.9957 (0.99211–99929)
VAR_NLR	0.024	1.0003 (1.00004–1.00061)
Long-term survival in cN2 patients		
VAR_NLR	0.012	1.0001 (1.0000–1.0020)

The impact of the proposed biomarkers on therapy-related toxicities and early post-operative outcomes is another topic of great interest; we did not explore it in the present study as we aim to address it in a more focussed analysis.

Limitations and Strengths

There are several limitations of this study. Firstly, it is a retrospective study over a long period of time (more than 25 years) and a lot has evolved within the clinical path, such as diagnostic methods, surgical techniques, chemotherapeutic agents and radiotherapy techniques (as reported in "methods"). Therefore, lots of concerns exist about whether the initial clinical stage and restaging are properly accurate or not. Moreover, this is a super-selected cohort of patients with several selection biases; in this framework, we may explain the high response rate to NAD-protocol (also due to high RT dose administered) and OS. Therefore, in light of all limitations reported above, readers should interpret our results with caution, as multiple biases exist.

On the other hand, this study was focussed on a specific population of NSCLC cases, collecting a large monocentric dataset, which is the main point of strength. In addition, for the first time, we have identified peripheral blood markers as predictive factors for NAD response and prognosis in this specific subset of patients. However, future prospective trials will give more appropriate information on this topic.

Conclusions

The results obtained from this study suggest a potential clinical role of peripheral blood markers in locally advanced NSCLC. Based on this preliminary evidence, these factors could be used as auxiliary markers for the composite prediction of response to NAD treatment and as prognostic profilers in multimodal approaches.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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