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Research Article

Predictive biomarkers of febrile neutropenia resolution in cancer patients. Are platelets the new rising stars of the immune system?

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Abstract. Objective. Febrile neutropenia (FN) is a major chemotherapy toxicity with implications both on the short and long-term prognosis of the oncological patient, but also on the global costs that affect the healthcare system. Our study aims to identify affordable and easily accessible biomarkers that could predict neutropenia resolution and therefore, limit unnecessary hospitalization or shorten its duration. Material and Method. This prospective study included chemotherapy-treated cancer patients that developed FN. All patients received adequate hematological support with G-CSF, empirical or targeted anti-infective agents depending on the microbiology results and other supportive and symptomatic care. Blood samples were drawn daily throughout the FN period, until resolution. Results. 96 patients with FN hospitalized in a tertiary cancer center were included between 2015 and 2018. The neutropenia duration was significantly longer in patients with higher levels of total bilirubin and granulocyte count in the preceding chemotherapy cycle and higher C reactive protein and procalcitonin measured at the onset of FN. The neutropenia duration was significantly shorter with higher values of platelet counts. There were no significant associations between the platelet evolution and the number of days of neutropenia, nor with the number of days until neutropenia resolution after the first decrease of platelets. A directly proportional relationship was found between the amount of G-CSF used for FN resolution and the value of D-index and D-index percent of area, respectively. Conclusion. Our study showed the great potential of some usual blood tests (leukocytes, platelets, creatinine, total bilirubin, neutrophils, CRP and procalcitonin) as predictive markers for the febrile neutropenia resolution in cancer patients.

Key Words: febrile neutropenia, chemotherapy, platelets, biomarkers

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Introduction

Febrile neutropenia (FN) is one of the most frequent and serious complications of cancer chemotherapy. It is defined by an oral temperature above 38.3 º C or above 38.0 º C on at least two consecutive readings for 2 hours, together with a grade 4 neutropenia (polymorphonuclear neutrophils <0.5 x 10 9/L) (Klastersky et al 2016). The overall burden of FN consists of life-threatening infections and sepsis, delayed and/or dose-limiting chemotherapy and altered treatment outcomes, decreased quality of life, lowered life expectancy and increased direct and indirect treatment costs (Dinan et al 2015). It also represents a potential cause of mortality in cancer patients. Among hospitalized patients with FN, there is a 10% rate of mortality (Klastersky et al 2016). Although they were not shown to significantly reduce mortality, the use of G-CSF in neutropenia proved to shorten the duration of hospitalization and associated health-care costs.

A thorough and adequate stratification of FN patients in terms of potential life-threatening complications is of utmost importance. Hence, up to date several systems have been proposed, such as the MASCC score (Klastersky et al 2000) which identifies patients at low risk for developing complications and the CISNE score (Carmona-Bayonas et al 2015), designed to predict complications in patients with high-risk features. Management of FN can be extremely challenging, as it depends both on the available logistical resources (radiology department, bacteriology, intensive care unit, access to a trained specialist in infectious diseases) and also, on the patient's health education (ability to recognize the first potential symptoms of febrile neutropenia, the time until the first hospital visit related to the onset of symptoms).

The discovery and use of granulocyte-stimulating factors (G-CSFs) in the prevention and treatment of grade 4 neutropenia in patients undergoing systemic chemotherapy represents an important step forward in the oncological field (Klastersky et al 2016, Căinap et al 2021). From a structural point of view, G-CSFs are glycoproteins that stimulate the production of granulocytes and stem cells from the bone marrow and release into the bloodstream. Their main action is manifested on neutrophils, having a role both in stimulating their hematopoietic precursors and in the survival of mature neutrophils (Bendall et al 2014, Rankin et al 2010). Together with anti-infective agents and supportive care, they are part of the therapeutical strategy in FN.
As previous studies show, low-risk patients can be managed on an outpatient basis, carrying the same efficacy and safety as for the hospitalized patients, but significantly reduces the financial burden by almost half the costs (Elting et al 2008).
The objective of the current study was to identify available, inexpensive, predictive biomarkers for FN resolution in the standard blood tests. If validated by further clinical studies, these biomarkers could be used to stratify patients into risk categories that would allow them to be treated in an in/outpatient basis, as appropriate and therefore, limit the associated healthcare costs. This study is part of a wider research protocol which also aimed to identify means to shorten the duration of FN, results that have already been published elsewhere (Căinap et al 2021).

Materials and methods

This was a prospective study conducted in a tertiary cancer center, within the "Prof. Dr. Ion Chiricuță" Institute of Oncology, Cluj-Napoca, Romania. The study was approved by the Institutional Ethics Committee, respecting the principles and recommendations of the Declaration of Helsinki. All patients expressed written and signed informed consent regarding the administration of the oncological and supportive treatment and the blood sampling. This study complied with General Data Protection Regulations, all patient data being anonymized. The main inclusion and exclusion criteria were as follows (already presented in our published article (Căinap et al 2021):
Main inclusion criteria:
•Age ≥18 years;
•Histologically-confirmed malignancy- solid or hematological tumor;
•Patients treated with chemotherapy, regardless of the treatment-line or cycle;
•Patients who were prescribed treatment with G-CSF as adjunctive therapy for established neutropenia (prior prophylaxis with G-CSFs was allowed);
•Treatment as an inpatient, with anti-infective agents and other supportive drugs as per institutional protocols
•Grade 4 febrile neutropenia (granulocyte count < 500/mm3) induced by curative or palliative chemotherapy regimens, without other identified cause of bone marrow supression;
Main exclusion criteria:
•Patients with shock (whatever the etiology) (systolic blood pressure less than 90mmHg, less responsive to treatment peripheral perfusion), coma or altered mental status;
•Patients subject to a bone marrow transplantation procedure;
•Patients with severe renal failure (creatinine clearance rate < 15mL/min/1.73 m2 surface body);
•Patients with abnormal liver function (transaminases elevated more than five times the upper limit of normal and/or total bilirubin more than 3 mg/dL);
•Patients allergic to any of the ingredients in the G-CSF product;
•Patients presenting with a myelodysplastic syndrome;
•Patients not treated with chemotherapy;
•Patients that were included and excluded from a clinical trial less than 90 days from the current study.
•Pregnancy or breastfeeding
Fever was defined as per institutional protocol by an oral or axillary temperature above 38°C, with a presumed infectious etiology (even non-documented by positive bacteriological cultures) in the absence of paraneoplastic or other documented, non-infectious causes (e.g., blood transfusion, etc)
The study objectives were:
1.Shortening the recovery time from febrile neutropenia (the results were previously published)
2.Correlation between blood samples values and FN time recovery, identification of new predictive biomarkers for FN resolution.
96 patients were included in this prospective study, between 2015 and 2018. All patients included were hospitalized during the FN period, blood samples were taken according to the institutional and international protocols and clinical evolution. The medical records were available to be analyzed: demographic data, personal history, co-morbidities, associated medication, blood works (one cycle prior to the FN, starting date of neutropenia, daily lab samples until FN resolution), type and stage of the tumor, cancer treatments, type of the current chemotherapy administered, the length of FN duration. The duration of the FN was calculated in minutes taking into account the timepoint of the initial blood sample and the resolution of the FN (registration date of the samples were available in the computed system of the laboratory).

Results

From the initial 96 patients enrolled, 95 patients recovered from grade 4 neutropenia with only one death event in a patient with initially severe neutropenia (<100/mm3) which was improved to grade 3 under adequate treatment. Table 1 describes the main characteristics of the enrolled population.

Associations with the number of days of neutropenia
The neutropenia duration was significantly longer with higher values of leukocytes, granulocytes, creatinine, total bilirubin measured in the cycle before FN, C reactive protein and procalcitonin measured at the onset of FN (Table 2, Supplementary figure 1-6). For most of these, the correlation coefficient values were relatively small, the most important correlations being those with the total bilirubin, and the C reactive protein, followed by procalcitonin and granulocytes' count.
The neutropenia duration was significantly shorter with higher values of platelet counts measured in the cycle at the onset of FN, but the correlation was relatively small (Supplementary figure 7-9).

Associations with platelets' evolution
We identified for each patient when the platelets count decreased for the first time compared to a previous day count, and the difference between the two-platelet count was named

Table 1. Main characteristics of the enrolled patients

Characteristics		N (%) (n = 96)
Age, mean (SD)		58.79
Gender	**Male**	47 (48.96)
	Female	49 (51.04)
BMI, median (IQR)		24.05 (21.68–28.1)
Prophylactic G-CSF before FN episode		19/94 (20.21)
Type of cancer	**colon/rectum**	21 (21.87)
	gastric	13 (13.54)
	ovarian	10 (10.42)
	lung	10 (10.42)
	head and neck	11 (11.46)
	germinal tumors	5 (5.20)
	other	26 (27.09)
TNM initial stage of FN	**1**	5 (7.14)
	2	15 (21.42)
	3	21 (30)
	4	29 (41.42)
Chemotherapy with FN episode	**Line**	2
	Cycle	3.6
Chemotherapy regimen		
	platinum -based	48 (50)
	taxane-based	17 (17.70)
	antracycline	25 (26.04)
	other	6(6.25)
Disease status	**controlled**	2 (2.08)
	evolutive	94 (97.92)

the first absolute decrease of platelets from a previous day after the onset. Furthermore, the difference between the platelet counts in the prior cycle (before the chemotherapy cycle that induced the neutropenia) and the platelets count at their first decrease in the cycle associated with neutropenia (see above, Figure 1), was named the first absolute decrease of platelets from the onset. There were no statistically significant associations between these measures of platelets evolutions and the number of days of neutropenia, nor with the number of days until neutropenia resolution after the first decrease of platelets (Table 2, Supplementary figure 7-9).

Associations with the D-index

D-index values were significantly higher with higher values of G-CSF amounts, with moderate values for the correlation coefficient (Table 2, Supplementary figure 12-13). We computed what percentage D-Index represents compared to the neutropenia period and it was statistically significant correlated to G-CSF amount too.

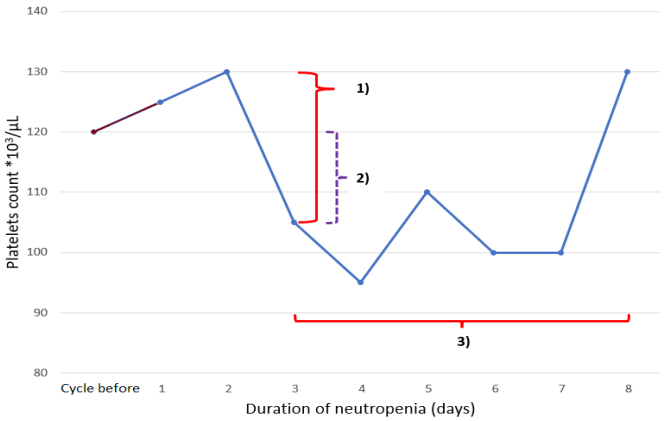

Figure 1. Explanation of platelet-derived parameters. 1) First absolute decrease of platelets from a previous day after the onset (here the first decrease is in day three, and the difference in platelets counts between the previous day – two and day three is: 130 – 105 = 25); 2) First absolute decrease of platelets day from the onset (here the first decrease is in day three, and the difference in platelets counts between the day in the cycle before entering neutropenia and day three is: 120 – 105 = 15); 3) Days till neutropenia resolution after the first decrease of platelets (here the first decrease is in day three, and the difference the last day of neutropenia and the first decrease is: 8 – 3 = 5 days).

Discussion

The current armamentarium of systemic treatments in cancer patients consists of chemotherapy, targeted treatments, immunotherapy, hormonal treatments. Due to the lack of specificity for the tumor cell, chemotherapy can be associated with a wide range of adverse events. Grade 4 bone marrow toxicity with leuco-neutropenia represents one of the most impairing and life-threatening side effects and its occurrence depends on the particularities of the patients, the type and aggressiveness of the chemotherapy protocol, the intent of treatment (curative vs palliative), the treatment line.

The mortality associated with febrile neutropenia varies from 5-20%, and can reach up to 50% if septic shock occurs (Long et al 2019). The results of our study showed some statistically significant associations between the number of FN days until resolution and certain blood parameters taken at various timepoints related to the FN onset (on the day of administration of the cycle before entering the FN, at the beginning of the FN or during the FN period).

Due to the important role in the elimination of certain drugs, high values of creatinine and total bilirubin in the cycle before the FN-causing cycle may increase the toxicity of the drugs administered so that the duration of FN days increases.

Higher CRP and procalcitonin values at the onset of FN are statistically significantly associated with a longer duration of FN. PCR and procalcitonin being markers of bacterial infections in the body, high values at the onset of FN, may cause a favorable delayed response in FN resolution. The importance of CRP and procalcitonin as markers of bacterial infections was previously mentioned in the literature (Giamarellos-Bourboulis et al 2001, Shilpakar et al 2019).

A possible explanation for the correlation found between high levels of leukocytes and neutrophils values at the cycles before the onset of FN could be that they indicate the beginning of an

Table 2. Spearman correlation coefficient between febrile neutropenia characteristics

Characteristic 1	Characteristic 2	Correlation coefficient (95% CI)	P-value
Number of days of neutropenia	**Leukocytes (*10^3/uL)** #	0.29 (0.12 - 0.56)	0.004
	Granulocytes (*10^3/uL) #	0.39 (95% CI 0.18 - 0.59)	<0.001
	Creatinine (mg/dL) #	0.28 (0.18 - 0.67)	0.018
	Total bilirubin #	0.59 (0.02 - 0.41)	<0.001
	Platelets (10^3/uL) *	-0.34 (-0.46 - 0.13)	<0.001
	First absolute decrease of platelets from a previous day after the onset (10^3/uL)	0.04 (-0.74 - 0.29)	0.807
	First day when platelets decreased after the onset of neutropenia	-0.10 $	0.563
	C reactive protein (mg/dL) *	0.51(0.24 - 0.62)	<0.001
	Procalcitonin (ng/mL) *	0.4 (0.03 - 0.51)	<0.001
First absolute decrease of platelets from a previous day after the onset (10^3/uL)	**Days till neutropenia resolution after the first decrease of platelets**	0.06 (-0.72 - 0.31)	0.755
First absolute decrease of platelets day from the onset (10^3/uL)	**Days till neutropenia resolution after the first decrease of platelets**	0.05 (-0.75 - 0.35)	0.804
D-index	**G-CSF amount**	0.5 (0.14 - 0.76)	<0.001
D-index percentage of area	**G-CSF amount**	0.42 (0 - 0.69)	<0.001

CI = confidence interval; # = cycle before FN; * = cycle at the onset of FN $ = CI could not be computed; G-CSF = granulocyte-colony-stimulating factors

infection, so that at the next cycle, the one causing FN, the return from FN will be difficult.

An interesting observation is made regarding the platelet counts. Higher values at the onset of FN are significantly associated with a shorter duration of FN. In clinical practice, a relationship was observed between platelet counts and the number of days until FN resolution. In the last decade, special attention has been paid to the role of platelets in the immune system, as they are the second most abundant blood cells. More research places them as important factors in the innate and acquired immune response and the inflammatory response. Platelets act as important circulating sentinels, through their ability to release a wide variety of immunomodulatory cytokines, chemokines and other mediators and express a wide range of functional immunoreceptors (Jenne et al 2013, Ali et al 2015). Platelets may intervene against various types of threats (bacteria, viruses and parasites). Due to their rudimentary antibacterial and phagocytic activity, when interacting with bacteria, platelet activation occurs and secretion of antimicrobial peptides. Platelets express some important receptors such as Toll-like receptors, glycoprotein (GP) IIb–IIIa, GPIbα, FcγRIIa complement receptors. Due to the interaction with TLR-4, TLR-2 and TLR-7 on platelets with neutrophils, complexes with role in the immune defense are formed. One of them is neutrophil extracellular traps (NETs), where pathogens are captured and neutralized (either viral or bacterial infections). Some studies showed that platelets play an important role in the plasmodium parasite infection. It seems that they can kill the parasite inside the red blood cells by releasing platelet granule components (Cox et al 2011, Koupenova et al 2019, Conglei et al 2012). The mode of action of platelets as key factors and reliable soldiers of the immune system is detailed in various articles. All these, corroborated with the results of our study, place platelets as molecules with an important protective role during FN and as potential biomarkers for predicting FN resolution. The significant correlations found in our study can be explained by their potentially active role in the fight with infections. Moon and collaborators studied the role of platelet count, CRP and pulmonary infiltration on chest radiographs at initial presentation for febrile neutropenia in predicting complicated neutropenic fever in the emergency department. They included 192 episodes of FN and identified 38 episodes of complicated FN in which low platelet count (less than 50 x 103 / mm3) together with elevated PCR and pulmonary infiltrates were independently associated with a complicated course of FN and worse prognosis (Moon et al, 2009).

Another interesting result was the analysis of the D-index used to reflect both the intensity and duration of neutropenia, also investigated by other teams. The D-index is based on the evolution of the absolute neutrophil counts during an episode of FN (the area over the neutrophil curve). Kimura and collaborators (2010) showed that the D-index, together with the days of neutropenia and profound neutropenia, respectively, had a nearly significant impact on the occurrence of blood and lung infections. Later on, in another research (Kimura et al, 2020) it was showed that the D-index and cumulative D-index were important predictive biomarkers for the development of invasive fungal disease in neutropenic patients. We found a significant correlation between the value of the D-index or D-index percentage of the area and the amount of G-CSF used for the FN resolution. A directly proportional relationship was found between the amount of G-CSF used for FN resolution and the value of D-index and D-index percent of area, respectively.

Conclusions

The results of our study show the great potential of the usual blood tests as predictive biomarkers for FN resolution. In the light of the already published research papers, our study draws

the attention on the value of leukocytes, PMNs, total bilirubin and platelets, CRP, procalcitonin and creatinine values as possible predictive biomarkers in chemotherapy-induced FN in cancer patients.

Among the most important limitations of our study, we mention the limited number of patients, which highlights the need of prospective, multicentric clinical trials to validate these results.

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