Evaluation of mean platelet volume as a predictive marker for cancer-associated venous thromboembolism during chemotherapy

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ABSTRACT

Mean platelet volume has been proposed as a predictor for venous thromboembolism in cancer. We, therefore, investigated the effects of different anti-cancer drugs on mean platelet volume in order to assess its possible value in the risk prediction of a first thromboembolic episode in cancer outpatients during treatment. Pre-treatment mean platelet volumes were retrospectively evaluated in 589 ambulatory patients at the beginning of a new chemotherapy regimen. Moreover, serial changes were evaluated at baseline and before each chemotherapy cycle on 385 of the 589 patients who consented to have additional blood withdrawals during treatment. Cox proportional hazards survival analysis demonstrated a 2.7 hazard ratio (P=0.01) of developing a first venous thromboembolic episode during chemotherapy for patients with baseline mean platelet volumes below the 10th percentile (<7.3 fL). This index significantly declined during the first three months of chemotherapy (-6%; P<0.0001) reverting to baseline at the end of treatment. Multivariate regression analysis showed that normal baseline volumes (P=0.012) and platinum-based regimens (P=0.017) were both independent predictors of mean platelet volume decline during chemotherapy which, in turn, was associated with a 2.4 hazard ratio (P=0.044) of venous thromboembolism. In conclusion, low pre-chemotherapy mean platelet volume might be regarded as a predictor of increased venous thromboembolism risk in cancer patients and chemotherapy further decreases platelet volumes, possibly due to drug-induced platelet activation and destruction. Changes in mean platelet volumes during chemotherapy might provide additional information on thromboembolic risk of patients treated with anti-cancer drugs, particularly platinum compounds.

Introduction

Mean platelet volume (MPV) is emerging as a novel index associated with thrombosis[1] as larger platelet size reflects increased platelet reactivity due to the presence of more adhesive receptors, granules and metabolically active mediators. Accordingly, increasing MPV value has been proposed as a predictor for venous thromboembolism (VTE), in particular that of unprovoked origin.[2] Unexpectedly, a recent report by the Vienna Cancer and Thrombosis Study (CATS) investigators demonstrated that MPV levels of 10.8 fL or over (i.e. the 75th percentile of all cancer patients included in their study) were associated with a significantly decreased risk of VTE,[3] indirectly confirming, in a large cohort of patients, preliminary data reporting a decreased MPV in cancer patients who developed VTE during follow up.[4]

VTE risk in cancer patients is approximately 4-fold higher than in the general population, being associated to various risk factors such as tumor site, stage, co-morbidities, or a variety of biological variables including platelet count.[5] Chemotherapy, for its part, may act as an additional trigger on this already fertile ground contributing to increased incidence of thrombotic events which ultimately impact on active treatment, quality of life and life expectancy.[6] There is little information available about the value of MPV on risk prediction and data on the effects of chemotherapy on this platelet index are contradictory. Indeed, MPV has been reported to increase after tamoxifen adjuvant therapy of breast cancer patients[7] which led some authors to solicit studies to assess the need and timing of anti-platelet drugs if elevated MPV is found in tamoxifen-treated patients.[8] On the other hand, MPV was significantly reduced by antiangiogenic treatment of metastatic colon cancer, a condition known to increase thromboembolic risk.[9]

Thus, there is still a long way to go before the role of MPV in VTE risk prediction in cancer patients undergoing chemotherapy is characterized. Therefore, in order to contribute to this debate, the aims of this study were to investigate the value of pre-treatment MPV in the risk prediction of a first VTE episode in cancer outpatients without previous history of VTE and to determine the effects of combination regimens including different anti-cancer drugs on MPV in the treatment of solid cancers.

Methods

A cohort of 589 consecutive patients with primary (n=381) or

 doi:10.3324/haematol.2014.109470
The online version of this article has a Supplementary Appendix.
Manuscript received on April 22, 2014. Manuscript accepted on July 15, 2014.
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relapsing/recurrent (n=208) solid cancers was enrolled. All patients had to be at the start of a new chemotherapy regimen (10% neoadjuvant, 35% adjuvant, 55% metastatic treatments); 3% of patients received concurrent radiotherapy. No patient received thromboprophylaxis. The study outcome was defined as the occurrence of a first symptomatic or asymptomatic VTE episode, either deep venous thrombosis (DVT) or pulmonary embolism (PE), during active treatment. Eligibility criteria were as previously reported.[6] Patients' characteristics are summarized in Table 1.

All patients were routinely screened with clinical and imaging procedures prior to chemotherapy to assess tumor burden and define the oncology strategy. Thereafter, they were regularly seen at scheduled chemotherapy visits or on the occurrence of clinically suspected VTE, and patient management was discussed by an interdisciplinary team. VTE risk was scored according to the model developed by Khorana *et al.*[5] taking into account: the site of cancer (2 points for very high-risk stomach, pancreas, or brain cancer; 1 point for high-risk lung or kidney cancer; 0 points for all other solid cancer sites), platelet count over 350 x 10^9/L, leukocyte count over 11 x 10^9/L, hemoglobin below 10 g/dL and/or use of erythropoiesis-stimulating agents, and body mass index over 35 kg/m^2 (1 point each). All patients were followed-up for a median

Table 1. Patients' characteristics.

		Overall population	Follow-up population
Age, years	Mean ± SD	62 ± 12	62 ± 12
	range	18 – 86	18 – 86
Sex	N (%)		
Males		289 (49%)	184 (48%)
Females		300 (51%)	201 (52%)
ECOG Performance status	N (%)		
0		481 (82%)	338 (88%)
1		98 (17%)	44 (11%)
2		9 (1%)	3 (1%)
Primary tumor	N (%)		
Gastrointestinal		237 (40%)	147 (38%)
Breast		124 (21%)	95 (25%)
Lung		120 (20%)	74 (19%)
Genitourinary		56 (10%)	32 (8%)
Prostate		25 (4%)	21 (6%)
Head-neck		27 (5%)	16 (4%)
Stage of disease	N (%)		
I		33 (7%)	28 (7%)
II		97 (17%)	66 (17%)
III		137 (22%)	85 (22%)
IV		114 (19%)	54 (14%)
Recurrent		7 (1%)	4 (1%)
Metastatic		201 (34%)	148 (39%)
Class of risk[a]	N (%)		
Low		264 (45%)	187 (48%)
Intermediate		289 (49%)	180 (47%)
High		36 (6%)	18 (5%)
Chemotherapy regimen:	N (%)		
Platinum compounds		322 (55%)	193 (50%)
Fluoropyrimidine		215 (37%)	148 (38%)
Anthracycline		115 (20%)	88 (23%)
Docetaxel		99 (17%)	80 (21%)
Bevacizumab		65 (11%)	54 (14%)
Irinotecan		77 (13%)	54 (14%)
Gemcitabine		79 (13%)	41 (11%)
Pemetrexed		44 (7%)	14 (4%)
Herceptin		22 (4%)	15 (4%)
Anti-tyrosine kinase inhibitors		10 (2%)	10 (3%)
Endocrine therapy		18 (3%)	13 (3%)
Supportive drugs	N (%)		
Erythropoietin stimulating agents		25 (4%)	13 (3%)
Prophylactic myeloid growth factors		40 (7%)	28 (7%)
Corticosteroids		155 (26%)	109 (28%)
Venous thromboembolism	N (%)	40 (7%)	25 (7%)
Platelet count, x10^9/L	Mean ± SD	250 ± 92	248 ± 87
Time-to-event, months	Median (IQR)	3.1 (1.3 – 5.5)	3.2 (1.6 – 5.7)

[a]*Class of risk was classified according to Khorana et al.*[5]

period of 8.5 months, during which outcomes were prospectively recorded.

Fasting blood samples were withdrawn from the antecubital vein using a 20 G needle after a rest period of at least 20 min and without stasis. Samples were obtained from 589 patients prior to chemotherapy start. In addition, serial samples were obtained before each chemotherapy cycle from 385 patients who consented to have additional blood withdrawals during treatment.

Complete and differential blood cell counts, including MPV measurement, were obtained within 30 min on EDTA anticoagulated whole blood using the same hematology analyzer (Coulter LH750; Beckman Coulter, Miami, FL, USA) in the same laboratory.

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by our Institutional Ethics Committees. All patients gave written informed consent.

Statistical analysis

Data are presented as percentages, mean±SD, or median and IQR. Differences between percentages were assessed by χ^2 test. Student's t-test, ANOVA test, and Pearson correlation analysis were used for normally distributed variables. Appropriate non-parametric tests (Mann-Whitney test, Kruskal-Wallis test, and Wilcoxon Matched Pairs test) were used for all other variables. Regression analyses were performed to quantify the relationship between clinical and biochemical variables. Survival curves were calculated by the Kaplan-Meier and log rank methods. Cox proportional hazards analysis was used to evaluate the association between clinical variables and time-to-event (TTE). TTE was calculated from the date of enrollment until the date of the event (any VTE, either DVT or PE) or the study end. For patients receiving neoadjuvant chemotherapy, follow up was stopped at completion of an entire antiblastic treatment and before surgery. Calculations were performed using Statistica v.8.0 software (StatSoft Inc., OK, USA) or free web-based applications (*http://statpages.org/*).

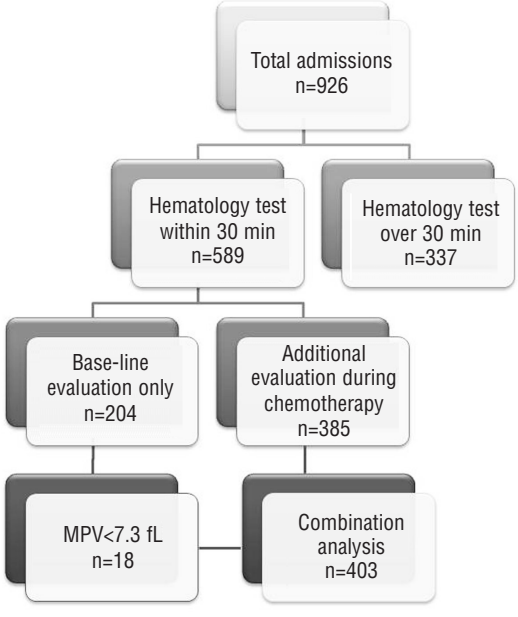

Figure 1. Recruitment data and patient distribution into analysis substudies.

Results

A total of 589 patients entered the study on the hypothesis that such a number would be able to detect a difference with a probability of more than 95%, at a 2-sided 5% significance level, if the true hazard ratio (HR) is 2. This was based on the assumption of an accrual period of at least two years, no more than 30 days between cycles, and a median TTE of 2.5 months. Information about patients' recruitment is shown in Figure 1.

All patients were prospectively followed-up for a median time of 8.5 months. During this period, 40 VTE events were recorded (6.8%, 11 PE and 29 DVT; median TTE: 3.1 months), 19 of whom (8 PE and 11 DVT) were incidentally diagnosed at time of CT-scan for re-staging. VTE occurred

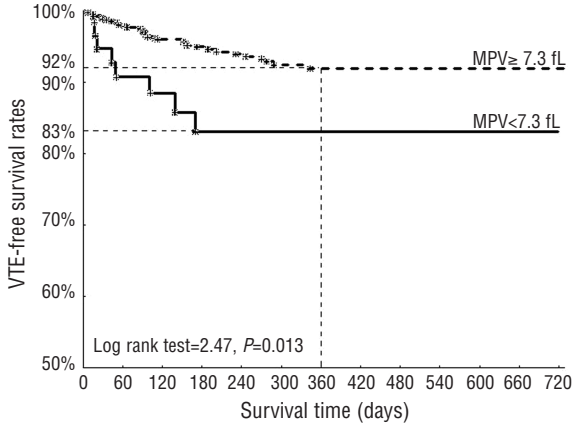

Figure 2. Kaplan-Meier analysis of venous thromboembolism (VTE) survival rates. Comparison of VTE-free survival time of cancer patients (n=589) categorized on the basis of mean platelet volume (MPV) prior to chemotherapy start. Dotted lines highlight the 1-year survival rates.

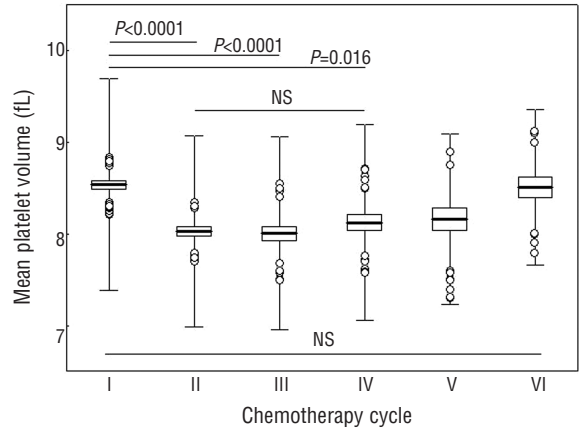

Figure 3. Sequential changes of mean platelet volume (MPV) in chemotherapy-treated cancer patients (n=385). Solid lines represent mean values, boxes represent standard errors, whiskers represent standard deviations. Anova test: F=15.6; *P*<0.0001. NS: not significant.

Table 2. Multivariate Cox proportional hazards survival analysis of the predictive value of clinical-pathological variables on venous thromboembolism occurrence in 589 cancer outpatients.

Variable	HR (95% C.I.)	P
Sex	1.15 (0.57–2.33)	0.699
Age	1.00 (0.97–1.02)	0.788
Site of tumor	1.07 (0.76–1.51)	0.696
Stage of tumor	1.15 (0.93–1.41)	0.189
ECOG PS	2.25 (1.18–4.27)	0.013
Mean platelet volume[a]	2.32 (1.03–5.23)	0.042
Class of risk[b]	1.15 (0.62–2.15)	0.651
Prophylactic G-CSF	0.97 (0.76–1.23)	0.810
Corticosteroids	0.98 (0.84–1.15)	0.823
Bevacizumab[b]	2.59 (0.84–7.97)	0.097
Platinum compounds	1.25 (0.53–2.95)	0.607
Fluoropyrimidine	0.89 (0.35–2.25)	0.807
Anthracycline	0.40 (0.08–1.95)	0.256
Docetaxel	0.92 (0.30–2.88)	0.888
Pemetrexed	0.75 (0.19–2.94)	0.683
Irinotecan	0.85 (0.25–2.897)	0.800
Gemcitabine	0.66 (0.23–1.90)	0.437
Herceptin	0.96 (0.11–8.11)	0.972
Anti-tyrosine kinase inhibitors	1.23 (0.13–11.5)	0.857
Endocrine therapy	0.78 (0.09–6.80)	0.822

ECOG-PS: Eastern Cooperative Oncology Group performance status. [a]Mean platelet volume was coded as 1/0 if ≤7.3 fL or >7.3 fL. [b]Class of risk was classified according to Khorana et al.[5]

Table 3. Multivariate Cox proportional hazards survival analysis of the predictive value of clinical-pathological variables on venous thromboembolism occurrence during chemotherapy treatment in 385 cancer out-patients.

Variable	HR (95% C.I.)	P
Sex	1.75 (0.66–4.66)	0.2608
Age	1.00 (0.96–1.04)	0.9749
Stage	1.18 (0.90–1.53)	0.2293
Bevacizumab[b]	2.98 (0.69–13.0)	0.1454
ECOG-PS	4.21 (1.74–10.2)	0.0015
MPV % change[a]	2.44 (1.02–5.81)	0.0443
Class of risk[b]	1.07 (0.52–2.21)	0.8548
Prophylactic G-CSF	1.04 (0.20–5.48)	0.9602
Corticosteroids	1.93 (0.77–4.83)	0.1591
Platinum compounds	0.83 (0.29–2.38)	0.7241
Fluoropyrimidine	0.97 (0.31–3.00)	0.9543
Anthracycline	0.43 (0.08–2.34)	0.3314
Docetaxel	0.50 (0.13–1.98)	0.3226
Pemetrexed	0.44 (0.08–2.43)	0.3433
Irinotecan	0.25 (0.04–1.44)	0.1205
Gemcitabine	0.31 (0.07–1.39)	0.1264
Herceptin	1.04 (0.12–9.05)	0.9733
Anti-tyrosine kinase inhibitors	0.75 (0.07–8.15)	0.8169
Endocrine therapy	0.00 (0.00–2.50)	0.9474

ECOG-PS: Eastern Cooperative Oncology Group performance status. [a]Mean platelet volume (MPV) percent change was coded as 1/0 if ≤5% or >5%. [b]Class of risk was classified according to Khorana et al.[5]

in 5%, 11% and 8% of the low, high and very high-risk tumor subset (*P*=0.063). No patient had surgery during follow up and none was admitted to the clinic for acute medical illness requiring thromboprophylaxis.

Mean platelet count in the entire cohort of patients was 250±92 (range 29-986 x 10^9/L). Overall, pre-chemotherapy MPV values were within the currently acknowledged reference range (mean±SD 8.6±1.1 fL, range 6.1-13.0 fL (10^{th}-90^{th} percentile boundaries: 7.3-10.1 fL)) and inversely correlated to platelet counts (R= -0.274; *P*<0.0001). Factorial ANOVA analysis of the association between MPV and clinical-pathological features showed that there was no correlation with tumor type or stage (*P*=0.41), although lower MPV values were observed in metastatic at-risk tumor types. As hypothesized, MPV values were lower in patients who developed VTE (8.2±1.1 fL) compared to those who did not (8.6±1.1 fL) (*P*=0.048) (*Online Supplementary Figure S1*). Thus, based on value distribution, patients were categorized using an arbitrary cut off set at the 10^{th} percentile of the overall population (7.3 fL). Eight (14%) of 57 patients with pre-chemotherapy MPV below 7.3 fL developed VTE compared to 32 (6%) of the 532 patients with MPV values of 7.3 fL or over (*P*=0.022). Cox proportional hazards survival analysis showed that pre-chemotherapy MPV values below 7.3 fL were able to significantly predict VTE with an HR of 2.3 (95%C.I.: 1.03-5.23; *P*=0.011) (Table 2). Kaplan-Meier survival curves are shown in Figure 2.

Among the 589 patients, 385 consented to have additional blood withdrawals during treatment. More than 90% of the patients received chemotherapy on a monthly basis. Hence, time between cycles was 28 days. Interestingly, mean MPV values significantly declined from 8.5±1.2 fL at baseline to 8.0±1.0 fL before the start of the 2^{nd} cycle and to 8.0±1.1 fL before the 3^{rd} (6% median change; *P*<0.0001), reverting almost to the initial level by the 6^{th} cycle (8.5±0.9 fL, -0.4% median change; *P*=0.999) (*P*<0.0001) (Figure 3). As observed in the overall population, a weak inverse correlation between MPV and platelet counts was confirmed in this subset of patients at baseline (R= 0.268; *P*<0.0001) but not during chemotherapy (R= 0.146; P=0.065 at 3 months).

To assess the possible determinants of the decline in MPV levels, a multiple regression analysis was performed in which change in MPV percentage at three months was used as the dependent variable and sex, age, tumor type and stage, ECOG performance status, body mass index, platelet and leukocyte counts, pre-chemotherapy MPV, pro-coagulant status, hemoglobin levels, use of supportive drugs and the type of anti-cancer drug were included as the predictor variables. Forward step-wise analysis showed that normal baseline MPV values (regression coefficient=0.190; *P*=0.012) or platinum-based regimens (regression coefficient=0.209; *P*=0.017) were the only independent predictors of MPV decline during chemotherapy in our patient population.

Over a median follow up of eight months, 25 VTE events (7%) were recorded in this subset of patients. Of interest, a MPV decline of more than 5% of the baseline value was capable of independently predicting VTE risk in a multivariate Cox proportional hazards survival analysis with an HR of 2.4 (95%C.I.: 1.02-5.81; *P*=0.044) (Table 3)

and a 1-year VTE-free survival time that was significantly shorter (87%) than that observed in patients with stable MPV (96%; *P*=0.05) (Figure 4).

Finally, to further asses the possible predictive value of MPV in VTE risk prediction, patients were categorized as "at-risk" if baseline MPV was below 7.3 fL or if during chemotherapy MPV decreased more than 5% of the initial value. A total of 403 patients entered this analysis (Figure 1). Of interest, 24 of 30 patients who developed VTE were correctly assigned to this category, with a sensitivity of 0.80, a negative predictive value of 0.96, but an accuracy of 0.46 due to a low specificity of 0.43 (OR=3.0; 95%C.I.: 1.15-8.51; *P*=0.013). In agreement with the finding of an independent role of platinum-based compounds in decreasing MPV during treatment, the VTE predictive value of MPV was mostly evident in patients treated with platinum analogs. Indeed, 16 (13%) of 123 patients receiving platinum-based regimens, who also had an impairment of MPV either at baseline or during treatment, developed VTE during chemotherapy compared to 7% (8 of 113) of patients with impaired MPV undergoing non-platinum-based regimens and 4% (6 of 167) of patients in whom MPV did not undergo substantial deviations from the normal ranges (HR=1.62; 95%CI: 1.12-2.36; *P*=0.012). Kaplan-Meier curves for patients categorized on this basis are reported in Figure 5.

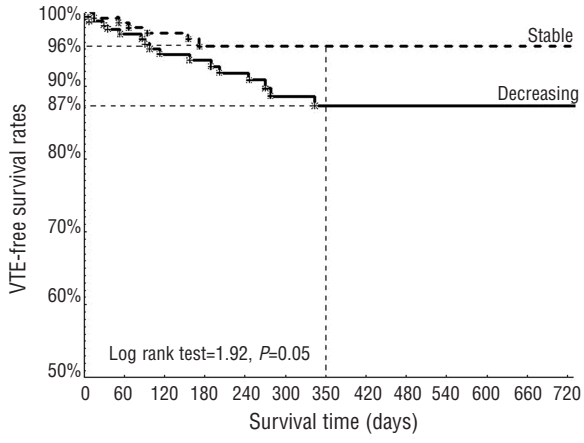

Figure 4. Kaplan-Meier analysis of venous thromboembolism (VTE) survival rates. Comparison of VTE-free survival time of cancer patients (n=385) categorized on the basis of mean platelet volume (MPV) percent changes during chemotherapy. Dotted lines highlight the 1-year survival rates.

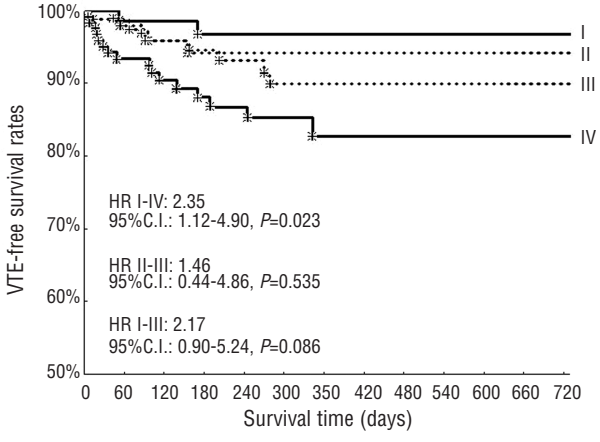

Figure 5. Kaplan-Meier analysis of venous thromboembolism (VTE) survival rates. Comparison of VTE-free survival time of cancer patients (n=404) categorized on the basis of mean platelet volume (MPV) impairment either before or during platinum-based or non-platinum-based regimens. I: normal MPV in platinum-based regimens; II: normal MPV in non-platinum-based regimens; III: impaired MPV in non-platinum-based regimens; IV: impaired MPV in platinum-based regimens.

Discussion

In the last decade, MPV has been regarded as an indicator of platelet activation[1] and a possible predictor of thromboembolic events, including VTE.[2-4] VTE is a threatening condition in the oncology setting, as it represents the first leading cause of death in ambulatory patients undergoing chemotherapy[10] and has been associated to decreased survival.[11] Hence, the need to recognize candidate biomarkers that may be used in VTE risk assessment and to identify patients at high risk. In this respect, MPV could be of clinical significance[3,4] but data have not been co-ordinated and little information is currently available about the effects of chemotherapy on this platelet index.

These considerations prompted us to carry out an in-depth investigation into the possible predictive role of MPV in cancer outpatients receiving chemotherapy. Overall, we found a significant association between low MPV prior to treatment start and a first VTE episode during chemotherapy, as evidenced by an approximately 2-fold higher risk in patients with pre-chemotherapy MPV below 7.3 fL (i.e. the 10th percentile of the whole population). These findings indirectly agree with those recently reported by Riedl *et al.*[3] who demonstrated that high MPV was associated with decreased VTE risk, and suggest that base-line MPV might be regarded as a predictive marker of VTE in cancer outpatients. On the other hand, both Riedl and our study are in disagreement with findings of Braekkan *et al.* which associated high MPV to increased VTE risk in a prospective, population-based study.[2] In the latter study, however, cancer represented the underlying cause only in approximately 23% of the VTE episodes, whereas unprovoked VTE was present in more than 40% of patients.[2] Looking in detail at the results reported by Braekkan *et al.*, it can be seen that the level of significance was fully satisfied only in unprovoked VTE (HR: 1.5; 95%CI: 1.0-2.3; *P*=0.04), whereas only a trend to significance was observed in the whole population (HR: 1.3; 95%CI: 1.1-1.7; *P*=0.09), despite the large number of individuals enrolled.[2] Unfortunately, no association analysis was reported by Braekkan *et al.* for cancer-related VTE.[2] On the other hand, our results are in agreement with the findings by Mutlu *et al.* in solid cancer patients undergoing chemotherapy who, rather than the theoretical increase expected in MPV, reported reduced values at the time of VTE diagnosis.[4]

A partial explanation to the issue raised above might come from the findings obtained in the second part of our study in which we analyzed, for the first time to our knowledge, the changes in MPV at various time points in the course of chemotherapy treatment. Of interest, we found a progressive decrease in this platelet index, which was max-

imal at the 3rd cycle and reverted to the initial level toward the end of chemotherapy. This decline in MPV value was not related to the different settings of cancer patients being treated (neoadjuvant *vs.* adjuvant *vs.* metastatic) but rather to the drug being administered, with platinum compounds showing the strongest association. Thus, in contrast to the conclusions drawn by Mutlu *et al.*,[4] we believe that the decline in MPV observed during treatment might be yet another sign of platelet activation triggered by chemotherapy. Consistent with this hypothesis is the finding, shown in Figure 5, that patients receiving platinum-based regimens, in whom MPV declined during treatment, had an approximately 2-fold higher risk of developing VTE compared to patients treated with non-platinum-based regimens, or in whom MPV remained stable.

The likelihood of platelet functional abnormalities following administration of cancer chemotherapy was first reported in 1969.[12] Since then, many studies have attempted to define the adverse circumstances leading to platelet modifications, both in terms of platelet count and size and platelet function, ultimately supporting the idea of an acquired platelet defect following administration of various anti-neoplastic drugs,[13-16] including platinum analogs.[16] Several mechanisms have been suggested to explain this hypothesis, including interference with protein kinase C signaling[12] or disturbance of the circumferential microtubule ring[15] which is responsible for platelet contraction, and centralization of the secretory granules and consequent degranulation. Beside these direct effects, other indirect effects might account for the decline in MPV values observed during chemotherapy. These include drug-related bone marrow hypoplasia that might be associated to decreased MPV[17] or the inflammatory status that accompanies cancer and its treatment. In this respect, an increase in tumor necrosis-alpha (TNF-α) has been demonstrated after the first two cycles of platinum-based chemotherapy.[18] TNF-α has been shown to trigger platelet activation[19] while other inflammatory cytokines may influence megakaryocytopoiesis and platelet volume.[20] Consistent with these findings, recent studies have reported the occurrence of decreased MPV values in inflammatory conditions other than cancer as a reflection of the role that blood platelets play in the inflammatory process.[21-23]

On the other hand, the possibility of chemotherapy-dependent platelet activation reopens the issue of the differences observed between the findings of Braekkan *et al.*[2] and those reported by Riedl *et al.*[3] or in the present study. Indeed, it could be argued that the finding of low MPV in pre-treatment samples might be related to the effects of previous lines of chemotherapy. However, the rates of MPV below 7.3 fL in patients undergoing second-line (8.8%, n=35) or third-line (7.0%, n=12) treatment were significantly lower (P=0.03) than those observed in the adjuvant setting (35.1%) or first-line chemotherapy (45.6%). Moreover, a 2-fold increased risk of developing VTE was retained for low MPV after exclusion of patients treated with second- or third-line treatment (*data not shown*), thus suggesting that the predictive value of MPV was related to the cancer itself and not to the effects of previous chemotherapy.

We must, of course, acknowledge that this study has some limitations. First of all, this study was a retrospective analysis, although all eligible consecutive patients within the designated timeframe were included and all measurements were taken while blinded to the patient outcome. Moreover, recruitment was performed in a single institution, which might have posed a further limitation because the primary and most obvious shortcoming of single-center studies is their potentially limited external validity. A final, most important, issue is represented by the use of EDTA anti-coagulated samples for MPV measurement.[17] Indeed, it is well known that EDTA may induce changes in platelets over time, usually related to a change in shape, resulting in a progressive increase in MPV using impedance technology.[17] This effect appears to be unpredictable and must be controlled either by the use of different anticoagulants or by standardizing the time between sampling and analysis.[17] In our study, samples were collected as part of a biobank project in which all samples were analyzed on the same instrument, and standard operating procedures, ICT tools and dedicated software were used to track the entire sample life, including time between blood withdrawal and processing.[24,25] This ensures a relative homogeneity among the samples used in a given study and minimizes the differences in analyses. Furthermore, the association between MPV and VTE was analyzed using percent change from baseline (after 3 months of treatment, i.e. a period corresponding to the median TTE) that should have prevented possible bias due to platelet activation occurring as a consequence, rather than a cause, of thrombotic disease. In spite of this, MPV reproducibility and standardization is still a major limitation for most of the analyses performed so far, and might at least partially explain some of the discrepancies found among the different studies in the literature.

In conclusion, low pre-chemotherapy MPV values might be regarded as a predictor of increased VTE risk in cancer patients and chemotherapy further decreases MPV values, possibly due to drug-induced platelet activation and destruction. Changes in MPV during the course of chemotherapy might provide additional information about VTE risk of patients treated with anti-cancer drugs, particularly platinum compounds. Standardization of MPV measurement is, however, necessary before MPV can be included in VTE risk stratification protocols.

Acknowledgments

The team expresses deep gratitude to all patients and their families for providing the opportunity to conduct the present research project. Authors also wish to thank the nursery staff of the Day Hospital of the Medical Oncology Unit, Tor Vergata Clinical Center who have contributed and supported the researchers towards the overall success of the project.

Funding

This work was partially supported by the Italian Ministry of Health Grant MERIT RBNE08NKH7.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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