Biomarkers, 2011; 16(1): 51–57

informa
healthcare

ORIGINAL ARTICLE

Discriminative value of platelet size indices for the identification of the mechanism of chemotherapy-induced thrombocytopenia

Maarten J. ten Berg[1,2], Albert Huisman[2], Patricia M.L.A. van den Bemt[1,3], Hanneke den Breeijen[1,4], Toine C.G. Egberts[1,4], and Wouter W. van Solinge[1,2]

[1]*Division of Pharmacoepidemiology and Pharmacotherapy, Department of Pharmaceutical Sciences, Faculty of Science, Utrecht University, The Netherlands,* [2]*Department of Clinical Chemistry and Haematology, University Medical Center Utrecht, The Netherlands,* [3]*Department of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, The Netherlands, and* [4]*Department of Clinical Pharmacy, University Medical Center Utrecht, The Netherlands*

Ethics: UPOD data acquisition and data management is in line with current Dutch regulations concerning privacy and ethics and it has been approved by the Medical Ethics Committee of the UMC Utrecht. The data that were used for this study were collected for patient-care purposes and were used retrospectively.

Abstract

Context: A biomarker for discriminating mechanisms of chemotherapy-induced thrombocytopenia (CIT) (i.e. increased platelet destruction and decreased platelet production) would be valuable in managing treatment.

Objective: We explored the discriminating value of platelet size indices for this purpose in a population of adult oncology patients.

Materials and methods: Mean platelet volume (MPV) and platelet distribution width (PDW) were compared between patients with (i) thrombocytopenia possibly due to increased platelet destruction; (ii) thrombocytopenia possibly due to decreased platelet destruction; and (iii) no thrombocytopenia.

Results and conclusions: We obtained negative results, suggesting that these indices are not useful for discriminating different CIT mechanisms.

Keywords: *Biomarker; mean platelet volume; platelet distribution width*

Introduction

Thrombocytopenia is a common and well-known adverse effect of cytostatic agents. Most frequently, chemotherapy-induced thrombocytopenia (CIT) is the consequence of bone marrow hypoplasia or aplasia due to toxic effect of the cytostatic agent on the megakaryocytic cell line in bone marrow (Jelic and Radulovic, 2006). Though far less frequently, cytostatic agents may also induce thrombocytopenia by causing increased consumption or destruction of platelets in the peripheral circulation involving immune antibodies (Jelic and Radulovic, 2006).When a patient develops severe hematotoxicity during cytostatic drug treatment, clinical oncologists evaluate whether treatment can be continued, whether treatment should be discontinued, or whether dose delay or dose reduction is warranted. Knowledge on the underlying mechanism of thrombocytopenia in patients treated with cytostatic drugs is relevant in making decisions in this situation. Renewed exposure to the suspected agent should be avoided in case of immune-mediated thrombocytopenia, whereas in case of bone marrow suppression-related thrombocytopenia dose adjustment in subsequent cycles may be effective for prevention of thrombocytopenia. Antibody testing and bone marrow investigation could

Address for Correspondence: Prof. Dr. Wouter W. van Solinge, Department of Clinical Chemistry and Haematology, University Medical Center Utrecht, Mailstop G03.550, PO Box 85500, 3508GA Utrecht, The Netherlands. Tel.: +31(0)887557604. Fax: +31(0)887555418. E-mail: WSolinge@umcutrecht.nl

(Received 16 April 2010; revised 15 September 2010; accepted 20 September 2010)

ISSN 1354-750X print/ISSN 1366-5804 online © 2011 Informa UK, Ltd.
DOI: 10.3109/1354750X.2010.526243

http://www.informahealthcare.com/bmk

provide information on the underlying mechanism, but cytostatic drug-related antibody tests are not widely available and bone marrow investigation is a burden for the patient. Therefore, a simple parameter (i.e. a noninvasive, fast, and inexpensive measurement) that could provide information about the mechanism underlying the thrombocytopenia in chemotherapy treatment would be useful in clinical practice. Indices related to platelet size that can be measured with modern hematology analyzers, including mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR), may be useful for this purpose. In general, in immune-mediated thrombocytopenia the normal bone marrow will release younger and larger platelets to keep up with ongoing losses, resulting in an increase in platelet size indices (Wazny and Ariano, 2000; Kenney and Stack, 2009). In bone marrow suppression-related thrombocytopenia, these platelet size indices are considered to be normal or even smaller (Wazny and Ariano, 2000; Kenney and Stack, 2009). Recent studies have shown that MPV, PDW, and P-LCR have sufficient validity and accuracy in discriminating thrombocytopenia resulting from an increased consumption or destruction of platelets in the peripheral circulation involving antibodies (e.g. idiopathic thrombocytopenic purpura (ITP)) and thrombocytopenia resulting from a decreased production of platelets due to myelosuppression (e.g. aplastic anemia, high-dose chemotherapy in hematologic cancer patients) (Bowles et al., 2005; Kaito et al., 2005; Ntaios et al., 2008; Borkataky, 2009; Chandra, 2010). We hypothesize that these platelet indices also have discriminative value for immune-mediated and bone marrow suppression-related thrombocytopenia caused by cytostatic agents. Although the MPV is considered to provide valuable information in the presence of immune-mediated drug-induced thrombocytopenia (Wazny and Ariano, 2000), its discriminative value for this purpose has not been investigated before. We conducted a retrospective study within a cohort of oncology patients treated with chemotherapy to test the hypothesis that MPV and PDW have discriminative value for immune-mediated and bone marrow suppression-related CIT.

Material and methods

Setting

For this study, data from a cohort of oncology patients treated with nonclinical trial chemotherapy regimens were used. The cohort, recently described in more detail (ten Berg et al., in press), concerns patients with solid tumors who received nonclinical trial chemotherapy treatment at the University Medical Center Utrecht (UMC Utrecht) in the 3-year period of 2004–2006. The cohort was drawn based upon data on chemotherapy exposure from the Utrecht Patient Oriented Database (UPOD). UPOD has been described in detail elsewhere (ten Berg et al., 2007). In brief, UPOD is a data platform encompassing automated data collected during clinical care on patient demographics, hospital discharge diagnoses, medical procedures, medication orders, and laboratory tests for all patients treated at the UMC Utrecht. In addition to these data, UPOD comprises a database with hematological data obtained with Cell-Dyn 4000 and Cell-Dyn Sapphire hematology analyzers (Abbott Diagnostics, Santa Clara, CA) used in routine blood cell analysis at the UMC Utrecht since January 2005. From the blood sample, all blood cell parameters that are measured by the analyzer (Müller et al., 2006) are collected within the database, providing complete and validated automated hematological data, including absolute cell counts, cell volume indices, and morphological data (ten Berg et al., 2007).

Patients

Patients who were treated with chemotherapy in 2005–2006 were selected from the UPOD oncology cohort. In each patient, the first period of consecutive exposure to a specific chemotherapy regimen was studied. This period was called a course of chemotherapy treatment. The course was constructed from consecutive automated medication orders for cycles of chemotherapy (i.e. one round of chemotherapy). For each patient, the last complete blood count obtained before the start of the course of chemotherapy treatment was identified within the UPOD hematology database. This blood count was considered the baseline measurement. In addition, all complete blood cells counts within the course of chemotherapy exposure were selected. Based on these data, three selective groups of patients were identified:

1. *Isolated thrombocytopenia*: Defined as patients with an event of isolated thrombocytopenia at least once. An event of isolated thrombocytopenia was defined as the presence of a platelet count $<100\times10^9$/L without concurrent anemia (hemoglobin ≤9.7 g/dL) and/or leukopenia (leukocyte count $\leq4.0\times10^9$/L) and/or neutropenia (neutrophil granulocyte count $\leq1.6\times10^9$/L) based on the same complete blood count. The complete blood count of the first event in time within the course was identified in each patient and considered as the event measurement. Isolated thrombocytopenia was considered as a proxy for immune-mediated CIT (Wazny and Ariano, 2000).
2. *Non-isolated thrombocytopenia only*: Defined as patients with only events of non-isolated thrombocytopenia. An event of non-isolated thrombocytopenia was defined as a platelet count $<100\times10^9$/L with concurrent anemia (hemoglobin ≤9.7 g/dL) and/or leukopenia (leucocyte count $\leq4.0\times10^9$/L)

and/or neutropenia (neutrophil granulocyte count $\leq 1.6 \times 10^9$/L) based on the same complete blood count. The complete blood count for the first event in time within the course was identified in each patient and considered as the event measurement. Non-isolated thrombocytopenia was considered to be a proxy for bone marrow suppression-related CIT (Wazny and Ariano, 2000).

3. *No thrombocytopenia*: Defined as patients with only platelet measurements $\geq 100 \times 10^9$/L during the course of chemotherapy treatment. The complete blood count with the lowest platelet count within the course was identified in each patient and considered as the event measurement.

Platelet size indices

For all patients, the values of MPV and PDW for the baseline measurement and the event measurement were identified. MPV was calculated by the hematology analyzer as the arithmetic mean from the impedance platelet histogram and was reported in femtoliter (fL). In each patient, it was determined whether the MPV was abnormally high, defined as >9.5 fL based on the upper limit of the reference range used at the UMC Utrecht. PDW was calculated by the hematology analyzer from the impedance platelet histogram and was reported 10 times the geometric standard deviation (GSD).

Data analysis

For each patient, platelet count, MPV, and PDW values of the baseline and event measurement were checked for normality by comparison of the mean and median, by comparison of the mean, median, and the standard deviation, by visual inspection of the distribution histogram and the normal plot, and by testing for normality using the Kolgomorov–Smirnov test. For normally distributed data a parametric test (Student's *t*-test) was used, whereas for non-normally distributed data a non-parametric test (Mann–Whitney *U*) was applied. For both tests, a *P*-value <0.05 was considered statistically significant. In each group, the percentage of patients with an abnormally high MPV at baseline and event measurement was determined. Between-group differences in percentage of patients with an abnormally high MPV were tested for statistical significance using a chi-square test considering a *P*-value <0.05 as statistical significant. Data analysis was performed using SPSS 16.0 (SPSS Inc. Chicago, IL).

Results

We included 402 patients in the study: 34 patients with isolated thrombocytopenia (8.6%), 63 patients with non-isolated thrombocytopenia (15.7%), and 305 patients without thrombocytopenia (75.7%). Patient demographics are presented in Table 1. Patients with isolated thrombocytopenia were more frequently male compared with patients with non-isolated thrombocytopenia and patients without thrombocytopenia. On average, patients with isolated thrombocytopenia were older than patients with non-isolated thrombocytopenia and patients without thrombocytopenia.

Chemotherapy exposure differed between the three groups. Considering all groups, patients were exposed to one of 47 different chemotherapy regimens. In the group of patients with isolated thrombocytopenia, 18 different regimens were used; the combination therapy of gemcitabine and cisplatin was most prevalent ($n = 6$, 17.6%). In the group of patients with non-isolated thrombocytopenia, 22 different regimens were used; the combination therapy consist cyclophosphamide, doxorubicine, and etoposide ($n = 8$, 12.7%), and monotherapy with carboplatin ($n = 7$, 11.1%) was most prevalent. In the group of patients without thrombocytopenia, 41 different regimens were used; the combination therapy consist fluorouracil, epirubicine, and cyclophosphamide ($n = 48$, 15.7%), and monotherapy with cisplatin ($n = 47$, 15.4%) was most prevalent.

Mean baseline values for platelet indices in each group are presented in Table 1. Platelet count, MPV, and PDW were not significantly different for the three groups at baseline. Mean and median MPV, mean and median PDW, and the percentage of patients with an abnormally high MPV based on the event measurement are presented for each group in Table 2. No significant difference in MPV was found between patients with isolated thrombocytopenia and patients with non-isolated thrombocytopenia. Significant differences were found between patients with isolated thrombocytopenia and patients without thrombocytopenia as well as between patients with non-isolated thrombocytopenia and patients without thrombocytopenia. For PDW, only a significant difference was found between patients with isolated thrombocytopenia and patients without thrombocytopenia. For the percentage of patients with an abnormally high MPV, no significant difference was found between patients with isolated thrombocytopenia and patients with non-isolated thrombocytopenia, although the percentage of the patients with either isolated or non-isolated thrombocytopenia was significantly different from the percentage of patients with an abnormally high MPV among patients without thrombocytopenia.

Discussion

We observed no differences in MPV, PDW, and the percentage of patients with an abnormally high MPV

Table 1. Comparison of demographic characteristics and platelet indices at baseline patients with isolated thrombocytopenia, non-isolated thrombocytopenia, and without thrombocytopenia.

		Isolated thrombocytopenia ($n=34$)	Non-isolated thrombocytopenia only ($n=63$)	No thrombocytopenia ($n=305$)	*P*-value isolated vs. non-isolated thrombocytopenia	*P*-value isolated vs. no thrombocytopenia	*P*-value non-isolated vs. no thrombocytopenia
Female	Number (%)	11 (32.3)	29 (46.0)	154 (50.5)	0.192	0.045	0.519
Age	Mean (SD)	57.9 (11.2)	56.0 (12.4)	53.5 (13.0)	0.555	0.059	0.095
Platelet count ($\times 10^9$/L)	Mean (SD)	311 (120)	300 (106)	316 (122)	0.988	0.776	0.655
MPV (fL)	Mean (SD)	7.4 (1.0)	7.3 (1.0)	7.4 (1.0)	0.874	0.431	0.442
	Median (range)	7.1 (5.9–10.3)	7.3 (5.1–10.1)	7.4 (5.6–12.6)			
MPV >9.5 fL	Number (%)	2 (5.9)	2 (3.2)	11 (3.6)	0.522	0.512	0.866
PDW (10GSD)	Mean (SD)	16.3 (0.6)	16.2 (0.6)	16.1 (1.4)	0.348	0.052	0.314
	Median (range)	16.4 (15.3–18.0)	16.0 (14.8–17.5)	16.0 (14.5–38.1)			

n: Number of patients; SD: standard deviation; MPV: mean platelet volume; PDW: platelet distribution width; fL: femtoliter; 10GSD: 10 times the geometric standard deviation.

Table 2. Comparison of platelet indices at event date between patients with isolated thrombocytopenia, non-isolated thrombocytopenia, and with thrombocytopenia.

		Isolated thrombocytopenia ($n=34$)	Non-isolated thrombocytopenia only ($n=63$)	No thrombocytopenia ($n=305$)	*P*-value isolated vs. non-isolated thrombocytopenia	*P*-value isolated vs. no thrombocytopenia	*P*-value non-isolated vs. no thrombocytopenia
Platelet count ($\times 10^9$/L)	Mean (SD)	81 (18)	75 (23)	201 (91)	0.463	<0.001	<0.001
MPV (fL)	Mean (SD)	9.0 (2.1)	8.7 (1.2)	7.6 (1.0)	0.793	<0.001	<0.001
	Median (range)	8.8 (5.8–17.1)	8.6 (6.2–11.4)	7.5 (5.0–12.9)			
MPV >9.5 fL	Number (%)	10 (29.4)	17 (27.0)	14 (4.6)	0.799	<0.001	<0.001
PDW (10GSD)	Mean (SD)	16.5 (2.8)	15.8 (1.2)	16.0 (1.3)	0.566	0.726	0.749
	Median (range)	15.9 (10.3–28.1)	15.9 (10.4–18.1)	16.0 (10.1–35.2)			

n: Number of patients; SD: standard deviation; MPV: mean platelet volume; PDW: platelet distribution width; fL: femtoliter; 10GSD: 10 times the geometric standard deviation.

between patients with isolated thrombocytopenia and patients with non-isolated thrombocytopenia. These results suggest that MPV and PDW have no discriminate value for immune-mediated thrombocytopenia and bone marrow suppression-related CIT.

Our hypothesis was based on recent studies in which MPV, PDW, and P-LCR were found to be useful to discriminate immune-mediated thrombocytopenia from thrombocytopenia due to bone marrow suppression (Borkataky, 2009; Chandra, 2010) or inherited macrothrombocytopenias (Noris, 2009). In these studies, significant differences in MPV, up to 2.0 fL, were observed between patients with these two types of thrombocytopenia (Bowles et al., 2005; Kaito et al., 2005; Chandra, 2010). In the current study, we only observed a non-significant difference of 0.3 fL in mean MPV between patients with isolated thrombocytopenia versus patients with non-isolated thrombocytopenia. Kaito et al. (2005) found a significant difference in PDW between patients with ITP and patients with aplastic anemia. In addition, Borkataky et al. reported that PDW was significantly different between patients with thrombocytopenia due to peripheral platelet destruction and patients with thrombocytopenia due to non-megaloblastic hypoproliferation (Borkataky, 2009). In contrast to these results, we did not find any significant difference in mean PDW between patients with isolated thrombocytopenia and patients with non-isolated thrombocytopenia. Finally, Kaito et al. (2005) also found a significant difference in P-LCR between patients with ITP and patient with aplastic anemia. In addition, Borkataky et al. (Borkataky, 2009) did not find a significant difference in P-LCR between patients with destructive thrombocytopenia and patients with hypoproductive thrombocytopenia. In the current study, P-LCR was not investigated because the Abbott Cell-Dyn hematology analyzer does not report this parameter.

Compared with the previous studies, we observed a relatively low MPV for patients with immune-mediated thrombocytopenia. Immune-mediated CIT is considered as an acute event. In this group of patients, MPV and PDW may be not as high as in patients with ITP, because here the increase in MPV and PDW following the occurrence of thrombocytopenia develops over time. The observation of the relatively high mean MPV in patients with non-isolated thrombocytopenia was unexpected. This may suggest that in CIT due to bone marrow suppression the MPV increases and partly affected bone marrow may be able to respond to thrombocytopenia by increasing the megakaryocytic activity. MPV is considered to be influenced by several conditions. Increased platelet size has been shown, for example, in ITP, diabetes, obesity, sepsis, DIC and myocardial infarction (Kim et al., 1986; Yetkin, 2008). Recently, it was shown that chronic hypertension is associated with increased MPV in ischemic stroke patients (Ntaios, 2010). In addition, a lower MPV was also reported to be associated with the presence of bone marrow metastasis in patients with solid tumors (Aksoy et al., 2008). Information on co-morbidity and presence of bone marrow metastasis at time of chemotherapy treatment was not available for our study population, and therefore we could not investigate whether differences in presence of such conditions contributed to our findings. The finding that MPV was different between patients with thrombocytopenia, either isolated or non-isolated, and patients without thrombocytopenia suggests that increased MPV is associated with thrombocytopenia. An inverse relation between platelet count and MPV has been described (Bessman et al., 1981; Levin and Bessman, 1983; Bain, 1985; Buckley et al., 2000). Our observation of a relatively high mean MPV in patients with either isolated or non-isolated thrombocytopenia could simply be explained by the presence of thrombocytopenia. To our knowledge, such a relation has not been described for PDW.

Some potential limitations of our study need to be addressed, which may explain to some extent why we did not observe a difference in MPV and PDW between patients with isolated thrombocytopenia and patients with non-isolated thrombocytopenia. First, the proxies we used for immune-mediated thrombocytopenia and bone marrow suppression-related thrombocytopenia may have had limited sensitivity and specificity for these conditions. We had to use proxies for these conditions because no antibody tests and bone marrow biopsies or aspirations were performed in these patients. We considered isolated thrombocytopenia as a proxy for immune-mediated thrombocytopenia, because immune-mediated drug-induced thrombocytopenia in general presents as isolated thrombocytopenia (Wazny and Ariano, 2000). However, we acknowledge that isolated thrombocytopenia can also be the result of selective bone marrow suppression on the level of the megakaryocyte cell line in the bone marrow. Second, our study may have lacked power to detect a difference between patients with isolated and patients with non-isolated thrombocytopenia. We compared group of 34 patients with isolated thrombocytopenia with group of 63 patients with non-isolated thrombocytopenia. With these numbers, only a difference of at least 0.7 fL in MPV between these groups could be detected with statistical significance. However, the differences identified in earlier studies were >0.7, so power should not have been a problem. As mentioned earlier, several conditions and disease are associated with increased MPV. Since we did not investigate the presence of co-morbidity among patients with isolated and non-isolated thrombocytopenia, we cannot exclude the possibility that differences in the presence of co-morbidity among the studied groups influenced the results. The final potential limitation of this study concerns the method that was used to obtain

the platelet count data for this study. The analyzer used in our study measures the MPV and PDW using an electronic impedance signal, which has an upper threshold (i.e. 20 fL). Due to the threshold, very large platelets are excluded from the platelet count (Ntaios, 2009), leading to a lower MPV than truly present in the patient. For an investigation as the current study, this would have a negative influence. Based on the observed MPV data, which are not near the 20 fL, we believe it is unlikely that this is the case in our study.

Despite these limitations, we believe our study suggests that MPV and PDW have little value as biomarkers for the identification of the mechanism of CIT. However, a large prospective study, in which potential cases could extensively be evaluated for the underlying mechanism of CIT might give additional information. In addition, there are other biomarkers for which the potential to serve as biomarker for CIT should be investigated. For example, the reticulated platelet count or immature platelet fraction might have potential to serve as biomarker for the mechanism of CIT. These platelet indices reflect thrombopoiesis activity in the bone marrow (Briggs et al., 2004; Abe et al., 2006).The reticulated platelet count has been reported to provide similar information as MPV about the underlying mechanism of thrombocytopenia, as the reticulated platelet count tends to vary proportionately with bone marrow function and very high counts can be seen in the setting of peripheral platelet destruction (Kenney and Stack, 2009). The immature platelet fraction has been reported to a marker for bone marrow recovery after chemotherapy (Abe et al., 2006). The reticulated platelet count and immature platelet fraction may have additional value to discriminate bone marrow suppression-related and immune-mediated chemotherapy-related thrombocytopenia.

Conclusions

These results of this study suggest that MPV and PDW have no discriminate value for immune-mediated thrombocytopenia and bone marrow suppression-related CIT. Further research should focus on the value of reticulated platelet count and immature platelet fraction for this purpose.

Acknowledgements

The authors are grateful to their colleagues at the Utrecht Institute for Pharmaceutical Sciences (UIPS) and the University Medical Center Utrecht (UMC Utrecht) for their support in establishing the Utrecht Patient Oriented Database (UPOD). They thank Ludi van Dun from Abbott Diagnostics, Hoofddorp, The Netherlands, for his support in collecting the data from the Abbott Cell-Dyn analyzers.

Declaration of interest

The authors did not have a potential conflict of interest. The department of pharmacoepidemiology and pharmacotherapy employing authors MB, PB, TE, and WS has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private–public funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health.

References

Abe Y, Wada H, Tomatsu H, Sakaguchi A, Nishioka J, Yabu Y, Onishi K, Nakatani K, Morishita Y, Oguni S, Nobori T. (2006). A simple technique to determine thrombopoiesis level using immature platelet fraction (IPF). *Thromb Res* 118:463–469.

Aksoy S, Kilickap S, Hayran M, Harputluoglu H, Koca E, Dede DS, Erman M, Turker A. (2008). Platelet size has diagnostic predictive value for bone marrow metastasis in patients with solid tumors. *Int J Lab Hematol* 30:214–219.

Bain BJ. (1985). Platelet count and platelet size in males and females. *Scand J Haematol* 35:77–79.

Bessman JD, Williams LJ, Gilmer PR Jr. (1981). Mean platelet volume. The inverse relation of platelet size and count in normal subjects, and an artifact of other particles. *Am J Clin Pathol* 76: 289–293.

Borkataky S, Jain R, Gupta R, Singh S, Krishan G, Gupta K, Kudesia M. (2009). Role of platelet volume indices in the differential diagnosis of thrombocytopenia: a simple and inexpensive method. *Hematology* 14:182–186.

Bowles KM, Cooke LJ, Richards EM, Baglin TP. (2005). Platelet size has diagnostic predictive value in patients with thrombocytopenia. *Clin Lab Haematol* 27:370–373.

Briggs C, Kunka S, Hart D, Oguni S, Machin SJ. (2004). Assessment of an immature platelet fraction (IPF) in peripheral thrombocytopenia. *Br J Haematol* 126:93–99.

Buckley MF, James JW, Brown DE, Whyte GS, Dean MG, Chesterman CN, Donald JA. (2000). A novel approach to the assessment of variations in the human platelet count. *Thromb Haemost* 83:480–484.

Chandra H, Chandra S, Rawat A, Verma SK. (2010). Role of mean platelet volume as discriminating guide for bone marrow disease in patients with thrombocytopenia. *Int J Lab Haematol* 32:498–505.

Jelic S, Radulovic S. (2006). Chemotherapy-associated thrombocytopenia: current and emerging management strategies. *Am J Cancer* 5:371–382.

Kaito K, Otsubo H, Usui N, Yoshida M, Tanno J, Kurihara E, Matsumoto K, Hirata R, Domitsu K, Kobayashi M. (2005). Platelet size deviation width, platelet large cell ratio, and mean platelet volume have sufficient sensitivity and specificity in the diagnosis of immune thrombocytopenia. *Br J Haematol* 128:698–702.

Kenney B, Stack G. (2009). Drug-induced thrombocytopenia. *Arch Pathol Lab Med* 133:309–314.

Kim KY, Kim KE, Kim KH. (1986). Mean platelet volume in the normal state and in various clinical disorders. *Yonsei Med J* 27:219–226.

Levin J, Bessman JD. (1983). The inverse relation between platelet volume and platelet number. Abnormalities in hematologic

disease and evidence that platelet size does not correlate with platelet age. *J Lab Clin Med* 101:295–307.

Müller R, Mellors I, Johannessen B, Aarsand AK, Kiefer P, Hardy J, Kendall R, Scott CS. (2006). European multi-center evaluation of the Abbott Cell-Dyn sapphire hematology analyzer. *Lab Hematol* 12:15–31.

Ntaios G, Papadopoulos A, Chatzinikolaou A, Girtovitis F, Kaiafa G, Savopoulos C, Hatzitolios A. (2009). Evaluation of mean platelet volume in the differential diagnosis of thrombocytopenia. *Int J Lab Hematol* 31:688–689.

Ntaios G, Papadopoulos A, Chatzinikolaou A, Saouli Z, Karalazou P, Kaiafa G, Girtovitis F, Kontoninas Z, Savopoulos C, Hatzitolios A, Alexiou-Daniel S. (2008). Increased values of mean platelet volume and platelet size deviation width may provide a safe positive diagnosis of idiopathic thrombocytopenic purpura. *Acta Haematol* 119:173–177.

ten Berg MJ, Huisman A, van den Bemt PM, Schobben AF, Egberts AC, van Solinge WW. (2007). Linking laboratory and medication data: new opportunities for pharmacoepidemiological research. *Clin Chem Lab Med* 45:13–19.

ten Berg MJ, van den Bemt PMLA, Shantakumar S, Bennett D, Voest EE, Huisman A, van Solinge WW, Egberts TCG. Thrombocytopenia in adult oncology patients receiving chemotherapy: incidence and relative risk estimates from a retrospective hospital-based cohort study using laboratory data. (2009). Doctoral Thesis Ten Berg MJ. Utrecht University. Submitted for publication.

Wazny LD, Ariano RE. (2000). Evaluation and management of drug-induced thrombocytopenia in the acutely ill patient. *Pharmacotherapy* 20:292–307.

Yetkin E. (2008). Mean platelet volume not so far from being a routine diagnostic and prognostic measurement. *Thromb Haemost* 100:3–4.