SHORT COMMUNICATION

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Thrombocytopenia in Adult Cancer Patients Receiving Cytotoxic Chemotherapy

Results from a Retrospective Hospital-Based Cohort Study

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Abstract

Background: Data on the frequency and relative risk (RR) of chemotherapy-induced thrombocytopenia (CIT) in patients with solid tumours receiving chemotherapy in clinical practice are limited.

Objective: The aim of the study was to estimate the frequency and RR of thrombocytopenia in adult patients with solid tumours receiving chemotherapy treatment.

Methods: For this retrospective, hospital-based study, adult patients with solid tumours who received chemotherapy at the University Medical Center Utrecht in the period 2004–6 were identified from the Utrecht Patient Oriented Database. We examined the frequency of (i) overall thrombocytopenia (defined as platelet count $<100\times10^9$/L) with or without other cytopenias; (ii) isolated thrombocytopenia (i.e. without other cytopenias); and (iii) the frequency and RR of overall thrombocytopenia and isolated thrombocytopenia associated with different cytotoxic agents.

Results: A total of 614 patients receiving one of 37 different chemotherapy regimens was included. Overall thrombocytopenia frequency was 21.8% and isolated thrombocytopenia frequency was 6.2%. The highest frequencies of thrombocytopenia were observed in patients receiving carboplatin monotherapy (81.8%) and combination therapies that included carboplatin (58.2%), gemcitabine (64.4%) or paclitaxel (59.3%). The highest RRs of

thrombocytopenia, compared with cisplatin-based therapy, were observed for combination therapies of carboplatin/gemcitabine (RR 10.1; 95% CI 5.5, 18.5) and carboplatin/paclitaxel/etoposide (RR 11.8; 95% CI 6.7, 20.8). In 54% of cases, the thrombocytopenia was of grade 2–4, which are considered to be the most clinically relevant grades. The highest frequencies of isolated thrombocytopenia were found with combination therapies that included oxaliplatin (28.6%) or gemcitabine (28.9%).

Conclusions: The results suggest that CIT is a relevant problem in clinical practice. Further research is necessary to investigate the clinical consequences of thrombocytopenia. The observed frequencies of thrombocytopenia were lower than those observed in older studies, but comparable with that observed in a recent US-based study. The observed increased risks for possible immune-mediated thrombocytopenia associated with exposure to oxaliplatin and gemcitabine contribute to the suspicion that these drugs can cause immune-mediated thrombocytopenia, and warrant further investigation. For clinicians, the mechanism has important consequences because in immune-mediated thrombocytopenia the drug must be avoided, while in dose-dependent thrombocytopenia a dose reduction may be sufficient.

Background

Many cytotoxic agents are known to cause thrombocytopenia in normal doses by inducing hypoplasia of the bone marrow megakaryocytic cells.[1,2] Cytotoxic agents can also cause thrombocytopenia by immune-mediated mechanisms, albeit less frequently.[1] Data on the frequency of thrombocytopenia with cytotoxic drugs are limited and are mostly derived from clinical trials. Data from population-based observational studies, which typically have fewer inclusion and exclusion criteria than clinical trials, may provide results that are more generalizable to broad patient populations. In the current study, we report the frequency and relative risk (RR) of thrombocytopenia in a population of Dutch adult cancer patients receiving chemotherapy for solid tumours.

Material and Methods

Study Design, Data Sources and Setting

The study was a retrospective, single-centre cohort study using data from the Utrecht Patient Oriented Database (UPOD) and the Regional Cancer Registry Middle Netherlands (RCR). UPOD, which has been described in detail elsewhere,[3] encompasses administrative and clinical data collected for all patients treated at the University Medical Center Utrecht (UMC Utrecht), a 1042-bed academic teaching hospital located in the central region of the Netherlands. The RCR is a patient registry of disease- and treatment-related information of all new cancer patients in the central region of the Netherlands and is embedded in the Comprehensive Cancer Center Middle Netherlands (CCCMN). UPOD data acquisition and management are in line with current Dutch privacy and ethics regulations. At the time of study design, no electronic data on cancer diagnoses were available within the UPOD, therefore a UPOD-RCR linkage was established for the first time. The study has been approved by the supervisory committee of the RCR.

Study Population

The study population comprised adult cancer patients (≥18 years, attending in- or outpatient

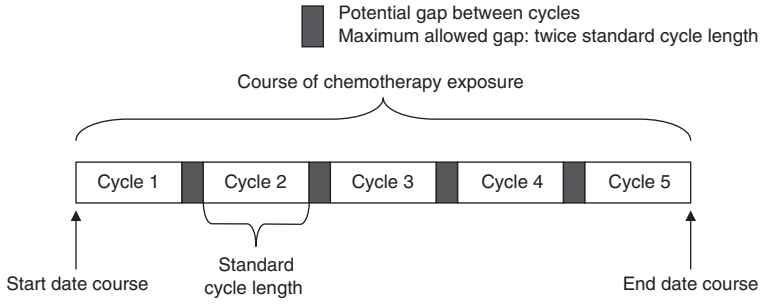

Fig. 1. Definition of a cycle and a course of chemotherapy treatment.

clinics of the UMC Utrecht between 1 January 2004 and 31 December 2006) who received chemotherapy for solid tumour treatment. The selection of the study population followed several consecutive steps. Initially, patients who received a non-clinical trial chemotherapy regimen indicated for the treatment of a solid tumour within the study period at the UMC Utrecht were identified from the UPOD. Patients who had received chemotherapy at the UMC Utrecht before the start of the study period were excluded. Also, patients whose course continued after the end of the study period were excluded in order to only include patients with complete exposure data. If patients received more than one course of chemotherapy during the study period, data from the first course in this period were selected (figure 1). Next, patients' data on solid tumour diagnoses (topography codes C00–C41 and C44–C80 and the morphology codes 800–958 according to the *International Classification of Diseases for Oncology, 3rd edition* [ICD-O-3]),[4] were obtained from the RCR. Patients without diagnostic tumour information or diagnosed with haematological malignancy within the RCR were excluded. Because of privacy restrictions, access to data from other regional cancer registries was prohibited; therefore, data on patients who could not be found within the RCR were not available. Finally, data on platelet measurements were selected from the UPOD. Patients without a baseline platelet count (i.e. within 30 days before the start of the course), without follow-up platelet counts during the course or with a platelet count of $<100\times10^9$/L at baseline were excluded.

Chemotherapy Exposure

Patient's exposure to one period of a specific chemotherapy regimen was studied and labelled as the *course* of chemotherapy treatment. The course consisted of consecutive *cycles* of the same chemotherapy regimen (i.e. one round of chemotherapy), as illustrated in figure 1. In instances where cycles of chemotherapy of the same regimen did not follow each other immediately in time, a maximum gap between cycles of no more than twice the standard cycle length was considered as continuation of the treatment. When patients switched to another regimen, follow-up was discontinued in order to prevent misclassification of chemotherapy exposure. The start date of the first cycle was considered the start date of the course. The theoretical end date of the last cycle, calculated as the start date of the last cycle plus the standard length of the cycle, was considered as the end date of the course. For each course, the individual cytotoxic agents that were part of the regimen were identified.

Thrombocytopenia

Occurrence of thrombocytopenia within the course was investigated by using platelet measurements from the UPOD. Thrombocytopenia was defined according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) for Adverse Events version 3, as a platelet count below the local lower limit of normal,[5] i.e. 100×10^9 platelets/L. In our definition, thrombocytopenia could occur with or without other concurrent cytopenias. Moreover, grades of severity of thrombocytopenia were defined

according to the NCI-CTC criteria version 3: grade 1 (75–100 $\times 10^9$/L); grade 2 (50–74 $\times 10^9$/L); grade 3 (25–49 $\times 10^9$/L); and grade 4 (<25 $\times 10^9$/L).[5] For patients with thrombocytopenia, the date and value of the first platelet count below 100 $\times 10^9$/L, as well as the lowest platelet count within the course, were identified. The lowest platelet count was considered as the platelet count nadir. The occurrence of isolated thrombocytopenia within the course of chemotherapy was also determined. Isolated thrombocytopenia was defined as a platelet count <100 $\times 10^9$/L without anaemia (haemoglobin <9.7 g/dL), leukopenia (leukocyte count <4.0 $\times 10^9$/L) and/or neutropenia (neutrophil granulocyte count <1.6 $\times 10^9$/L) at the same time.

Data Analysis

The frequency of thrombocytopenia, defined as the percentage of patients who developed thrombocytopenia, was determined and stratified by grades of severity based on the platelet count nadir and by exposure to specific cytotoxic agents. The RR for thrombocytopenia following exposure to a specific cytotoxic agent was estimated. Exposure to cisplatin monotherapy was chosen as the reference category because this was the most frequently used regimen in the study population. For the most frequently used regimens, the cytotoxic agents associated with a high frequency of thrombocytopenia were identified. For these regimens, the frequency and RR of thrombocytopenia were determined. Additionally, the frequency of isolated thrombocytopenia, defined as the percentage of patients who developed isolated thrombocytopenia, was determined. The association between isolated thrombocytopenia and exposure to a specific cytotoxic agent was investigated by stratifying the frequency of isolated thrombocytopenia by exposure to the specific cytotoxic agent. For cytotoxic agents that were used in mono- and combination therapy, separate frequency and RR estimates for mono- and combination therapy were calculated.

Results

Initially, we identified 676 adult patients receiving chemotherapy during the study period. A total of 62 patients were excluded: (i) 36 patients could not be found in the RCR; (ii) 7 patients had lymphoma; (iii) 8 patients had no available platelet count; (iv) 5 patients had no follow-up platelet count data; and (v) 6 patients had thrombocytopenia at baseline.

Clinical characteristics at the start of the course for the 614 included patients are presented in table I. Patients were treated for a median length of 65 days (minimum–maximum range 43–105), with one of 37 different regimens, including monotherapy and combination therapy of 19 unique cytotoxic agents. Details on regimens and their frequency are shown in Appendix 1 (Supplemental Digital Content, http://links.adisonline.com/DSZ/A54).

Thrombocytopenia occurred in 134 patients, resulting in a frequency of 21.8%. The frequency of thrombocytopenia stratified by grade of severity is presented in table II. First onset of thrombocytopenia was detected in a median number of 35 days (minimum–maximum range 14–57) following the start date of the course of chemotherapy. The platelet count nadir in patients with thrombocytopenia, median 69 $\times 10^9$/L (interquartile [IQR] range 39–86 $\times 10^9$/L), occurred in a median of 43 days (minimum–maximum range 15–67). Chemotherapy regimens associated with the highest frequencies (i.e. a frequency of >55%) of thrombocytopenia were carboplatin monotherapy and combination therapy regimens that included carboplatin, gemcitabine or paclitaxel (table III). The RR of thrombocytopenia per cytotoxic agent, either in mono- or combination therapy, compared with cisplatin monotherapy is presented in table III. The highest RRs were observed with carboplatin monotherapy and gemcitabine-based combination therapy. Figure 2 presents the severity of thrombocytopenia, based on the platelet count nadir, for all patients and for patients treated with any chemotherapy regimen that included carboplatin, gemcitabine or paclitaxel.

Isolated thrombocytopenia occurred in 38 patients, with a frequency of 6.2%. The median platelet count nadir in patients with isolated thrombocytopenia was 78 $\times 10^9$/L (IQR range 62–90 $\times 10^9$/L). The frequency of isolated thrombo-

Table I. Characteristics of adult patients with solid tumours receiving chemotherapy (n = 614)

Characteristic	Value
Patient demographics	
Female [n (%)]	312 (50.8)
Average age at start of first chemotherapy treatment within the study period [y (SD)]	54 (13)
Proportion of patients by age range [n (%)]	
18–39 y	87 (14.2)
40–59 y	278 (45.3)
≥60 y	249 (40.6)
Primary tumour site[a] [n (%)]	
Breast	109 (17.8)
Lip, oral cavity and pharynx	90 (14.7)
Respiratory system and intrathoracic organs	86 (14.0)
Male genital organs	84 (13.7)
Female genital organs	78 (12.7)
Digestive system	72 (11.7)
Skin	23 (3.7)
Urinary tract	20 (3.3)
Unknown primary site	18 (2.9)
Eye, brain and other parts of the CNS	14 (2.3)
Retroperitoneum and peritoneum	9 (1.5)
Connective, subcutaneous and other soft tissue	7 (1.1)
Peripheral nerves and autonomic nervous system	2 (0.3)
Thyroid and other endocrine glands	2 (0.3)
Blood cell counts at baseline	
Median platelet count [$\times 10^9$/L (IQR range)]	294 (242–378)
Median haemoglobin [g/dL (IQR range)][b]	13.1 (11.8–14.2)
Haemoglobin <9.7 g/dL [n (%)]	16 (2.6)
Median leukocyte count [$\times 10^9$/L (IQR range)][b]	8.2 (6.5–10.6)
Leukocyte count <4.0 $\times 10^9$/L [n (%)]	12 (2.0)
Median neutrophil granulocyte count [$\times 10^9$/L (IQR range)][c]	5.7 (4.2–7.8)
Neutrophil granulocyte count <1.6 $\times 10^9$/L [n (%)]	3 (0.5)

a Classified according to the *International Classification of Diseases for Oncology, 3rd edition*.[4]

b Mean value calculated for study population for whom data were available (n = 602). Missing values were for patients who had no baseline leukocyte count reported.

c Mean value calculated for study population for whom data were available (n = 427). Missing values were for patients who had no baseline neutrophil granulocyte count reported.

IQR = interquartile.

cytopenia stratified by grade of severity is presented in table II, and the frequency of isolated thrombocytopenia stratified by type of cytotoxic agent, either in mono- or combination therapy, is presented in table III. The frequency of isolated thrombocytopenia was highest in patients treated with combination therapies that included oxaliplatin or gemcitabine.

Discussion

In this study, thrombocytopenia was found to occur in approximately one in five adult cancer patients treated with regimens of chemotherapy for solid tumours. In 54% of cases, thrombocytopenia was of grade 2–4, which is considered clinically relevant because of an increased risk of

Table II. Frequency of overall and isolated thrombocytopenia classified by grade of severity based on the platelet count nadir

Grade	Frequency [n (%)]	
	overall thrombocytopenia	isolated thrombocytopenia
Overall	134 (21.8)	38 (6.2)
1[a]	61 (9.9)	23 (3.7)
2[b]	31 (5.0)	11 (1.8)
3[c]	22 (3.6)	4 (0.7)
4[d]	20 (3.3)	0 (0.0)

a 75–100 $\times 10^9$ platelets/L; the lower limit of normal was defined as 100 $\times 10^9$ platelets/L.

b 50–74 $\times 10^9$ platelets/L.

c 25–49 $\times 10^9$ platelets/L.

d <25 $\times 10^9$ platelets/L.

bleeding.[1] Regimens that included carboplatin, gemcitabine or paclitaxel were associated with the highest risk of thrombocytopenia, and the highest frequencies of isolated thrombocytopenia occurred in patients receiving regimens that included oxaliplatin or gemcitabine.

There is a paucity of population-based data available in the published literature with which to compare our findings. Data from two retrospective studies (published in 1984 and 1990) indicate that grade 3–4 thrombocytopenia occurs in approximately 19–24% of patients receiving chemotherapy for solid tumours or lymphoma.[6,7] We observed a much lower frequency (6.8%) of grade 3–4 thrombocytopenia in patients with solid tumours and all types of chemotherapy. A retrospective analysis of gynaecological cancer patients published in 1994 showed a thrombocytopenia frequency of 36.3%.[8] We observed thrombocytopenia in 20.5% of patients with gynaecological cancer (ICD-0-3 category female genital organs, C51–C58)[4] using the same platelet cut-off level of <100 $\times 10^9$/L. Differences in the frequencies of thrombocytopenia between the current study and these older studies may be explained by a higher thrombocytopenic potential of older chemotherapeutic agents. More recent population-based data on the frequency of thrombocytopenia in oncology patients were obtained in two US-based studies.[9,10] In the study by Kuderer et al.,[10] thrombocytopenia (platelet count <150 $\times 10^9$/L) occurred in 47% of patients, and grade 2–4 thrombocytopenia (platelet count <75 $\times 10^9$/L) was observed in 12.4% of patients. The latter estimate is comparable to our observation of 11.8%.[10] Wu et al.[9] reported the prevalence of thrombocytopenia (NCI-CTC criteria version 3) by class of cytostatic agent. The prevalence of grade 2–4 thrombocytopenia ranged from 4.3% for taxane-based regimens to 23.2% for gemcitabine-based regimens. These estimates are much lower than our findings, which may in part be explained by the different approaches in assigning exposure. In the study by Wu et al.,[9] if patients were exposed to more than one class of cytostatic agent, they were assigned to a single class, i.e. the one considered to be most haematotoxic. This approach may have resulted in an underestimation of the prevalence of thrombocytopenia for a given class of cytostatic agent, as the authors acknowledge. In our study, when patients were exposed to a regimen of more than one cytostatic agent, thrombocytopenia was attributed to each of the individual agents, which may have resulted in an overestimation of the frequency of thrombocytopenia for a given agent.

The frequency of thrombocytopenia was stratified by type of cytostatic agent. When interpreting the estimates for agents that were used in combination therapy, one needs to consider that other drugs in the regimen, or the combination of drugs in the regimen, may have been responsible for the observed thrombocytopenia. Detailed investigation into the causal agent was not performed and may be inconclusive since agents are often administered on the same day or on consecutive days. In addition, from a clinical perspective, information on the risk of thrombocytopenia associated with the regimen is more practical since, in most regimens, combinations of cytostatic agents are used. We observed the highest frequency of thrombocytopenia in patients treated with carboplatin, either in monotherapy or combination therapy. Organoplatinum agents, especially carboplatin, are well known for causing dose-limiting thrombocytopenia.[1] The area under the plasma concentration-time curve targeted in dosing carboplatin is correlated with the platelet count nadir.[11] The observed frequency of thrombocytopenia in cis-

platin monotherapy was much lower than that for carboplatin. Of note is the difference in frequency of thrombocytopenia in patients with cisplatin in combination therapy compared with patients treated with cisplatin monotherapy. Since cisplatin is frequently administered in

Table III. Frequency and relative risk (RR) of thrombocytopenia

Type of cytotoxic drug	Mono- or combination therapy	No. of patients	Frequency of overall thrombocytopenia [n (%)]	RR of overall thrombocytopenia compared with cisplatin monotherapy [RR (95% CI)]	Frequency of isolated thrombocytopenia [n (%)]
Alkylating agents					
Ifosfamide	Combination	14	5 (35.7)	4.2 (1.7, 10.4)	0 (0.0)
Temozolomide	Mono	13	3 (23.1)	2.7 (0.9, 8.5)	1 (7.7)
Cyclophosphamide	Combination	131	17 (13.0)	1.5 (0.7, 3.1)	3 (2.3)
Dacarbazine	Mono	21	2 (9.5)	1.1 (0.3, 4.7)	0 (0.0)
Antimetabolites					
Gemcitabine	Combination	45	29 (64.4)	7.6 (4.2, 14.0)	13 (28.9)
Capecitabine	Combination	17	5 (29.4)	3.5 (1.4, 8.8)	3 (17.6)
	Mono	5	0 (0.0)	NA	0 (0.0)
Fluorouracil	Combination	114	19 (17.5)	2.1 (1.0, 4.1)	11 (9.6)
	Mono	5	0 (0.0)	NA	0 (0.0)
Methotrexate	Combination	1	0 (0.0)	NA	0 (0.0)
	Mono	22	2 (9.1)	1.1 (0.2, 4.5)	1 (4.5)
Plant alkaloids					
Paclitaxel	Combination	27	16 (59.3)	7.0 (3.7, 13.4)	3 (11.1)
Etoposide	Combination	84	31 (36.9)	4.4 (2.3, 8.2)	3 (3.6)
Docetaxel	Combination	8	0 (0.0)	NA	0 (0.0)
	Mono	30	2 (6.7)	0.8 (0.2, 3.4)	0 (0.0)
Cytotoxic antibiotics and related substances					
Mitomycin	Combination	25	7 (28.0)	3.3 (1.4, 7.7)	1 (4.0)
Bleomycin	Combination	37	6 (16.2)	1.9 (0.8, 4.8)	2 (5.4)
Doxorubicin	Combination	67	13 (19.4)	2.3 (1.1, 4.8)	1 (1.4)
	Mono	11	0 (0.0)	NA	0 (0.0)
Epirubicin	Combination	84	10 (11.9)	1.4 (0.6, 3.2)	5 (5.9)
Mitoxantrone	Mono	11	0 (0.0)	NA	0 (0.0)
Platinum compounds					
Carboplatin	Combination	55	32 (58.2)	6.9 (3.7, 12.6)	9 (16.4)
	Mono	11	9 (81.8)	9.7 (5.1, 18.2)	0 (0.0)
Oxaliplatin	Mono	2	1 (50.0)	5.9 (1.3, 26.4)	0 (0.0)
	Combination	28	9 (35.7)	4.2 (2.0, 9.0)	8 (28.6)
Cisplatin	Mono	130	11 (8.5)	1.0 (reference)	2 (1.5)
	Combination	131	44 (33.6)	4.0 (2.1, 7.3)	14 (10.7)
Combination therapies, including cytotoxic agents most frequently associated with high risk of thrombocytopenia					
Gemcitabine + carboplatin	Combination	14	12 (85.7)	10.1 (5.5, 18.5)	5 (35.7)
Gemcitabine + cisplatin	Combination	31	17 (54.8)	6.5 (3.4, 12.4)	8 (25.8)
Paclitaxel + carboplatin	Combination	19	9 (47.4)	5.6 (2.7, 11.7)	3 (15.8)
Paclitaxel + carboplatin + etoposide	Combination	7	7 (100)	11.8 (6.7, 20.8)	0 (0.0)
Carboplatin + docetaxel	Combination	8	0 (0.0)	NA	0 (0.0)

NA = not applicable.

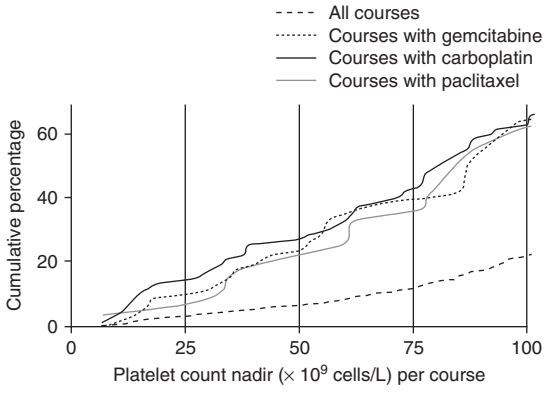

Fig. 2. Cumulative frequency of the platelet count nadir per course of chemotherapy treatment. The vertical lines represent the cut-off values for the various grades of severity of thrombocytopenia.

combination regimens with gemcitabine, and this agent was identified as having an increased RR of thrombocytopenia, this possibly explains the high frequency of thrombocytopenia with cisplatin combination therapies. Dose-limiting thrombocytopenia has been reported to be common during treatment with nitrosourea compounds, anthracyclines, podophyllotoxins, most alkylating agents and anthraquinones.[1] We could not estimate the frequency of thrombocytopenia for treatment with nitrosourea compounds because no such agents were used in our population. Our results suggest that the frequency of thrombocytopenia in patients treated with the anthracycline drug doxorubicin, the podophyllotoxin etoposide and the alkylating agent ifosfamide are relatively high.

In most cases, chemotherapy-induced thrombocytopenia (CIT) is caused by myelosuppression, although cytotoxic agents can also cause thrombocytopenia by immune-medicated mechanisms.[1] Because of the low frequency, immune-mediated adverse drug reactions are often not detected in clinical trials, but they can be clinically relevant when the drug is used in large populations of patients.[12] Large observational database studies have previously been used successfully to pick up signals of rare adverse events.[9,13] Although we acknowledge that isolated thrombocytopenia can also be the consequence of selective suppression of the megakaryocytopoiesis, isolated thrombocytopenia could be considered as a specific proxy for thrombocytopenia caused by an immune-mediated mechanism.[14] We observed the highest frequency of isolated thrombocytopenia in patients treated with combination therapies that included oxaliplatin and gemcitabine. We did not investigate further which individual drug from the regimen was most likely to be the causal agent of the isolated thrombocytopenia, nor did we confirm that the isolated thrombocytopenia was caused by immune-mediated mechanisms by determining the presence of drug-related antibodies. However, we believe that observation of the high frequency of isolated thrombocytopenia in patients receiving oxaliplatin is of special interest because several case reports have recently been published on thrombocytopenia due to hypersensitivity reactions to oxaliplatin.[15-18] We propose further research, including testing for drug-related antibodies, to determine the frequency of immune-mediated thrombocytopenia in patients treated with chemotherapy.

The strength of this study is the use of platelet measurement data to determine the presence of thrombocytopenia. The use of laboratory information is a sensitive, valid and objective method to determine a clinical condition compared with the use of hospital discharge diagnoses data, which have been historically used in other pharmacoepidemiological investigations of the aetiology of thrombocytopenia.[19,20] The use of hospital discharge diagnoses for thrombocytopenia can lead to under-identification of patients with thrombocytopenia.[19,20] In two recent database studies, thrombocytopenia frequency of 0.6% and 5.5% (in combination with neutropenia) were found for breast cancer patients treated with chemotherapy.[21,22] In our current study, we found a thrombocytopenia frequency of 6.4% for breast cancer patients (ICD-0-3 category breast cancer, C50).[4]

Limitations

Several potential limitations of this study need to be mentioned. First, the UPOD comprises data of only one institution. Consequently, exposure data are limited in numbers, possibly

limiting the statistical power of the study. Because of the relatively low number of patients exposed to certain regimens, caution should be taken in drawing conclusions from the results for these subgroups. In addition, because of possible differences in patient population or treatment practice we have to be careful in extrapolating the results from our study to other settings. The academic signature of the UMC Utrecht also means that this cancer patient population may not be representative of the patient population treated at general hospitals. Second, in clinical practice, platelet counts are obtained at fixed points in time, i.e. when the patient comes for evaluation during the cycle. The day the blood count is checked may not necessarily be the day that the platelet count nadir occurs. For that reason, platelet count nadirs of $<100 \times 10^9$/L may have remained undetected, resulting in an underestimation of the true frequency of thrombocytopenia. However, it seems unlikely that these potentially missed thrombocytopenias were clinically relevant. Finally, only the risk of thrombocytopenia associated with specific cytostatic agents was investigated; however, the type of cytostatic agent may not be the only factor influencing a patients' risk for CIT. The identification of potential patient- and treatment-related risk factors, as well as potential biomarkers for thrombocytopenia, may be useful for the management of thrombocytopenia, enabling chemotherapy to be administered on-schedule and with a full dose. Potential risk factors, not investigated in the current study but which require further investigation, include setting (e.g. patients in the adjuvant setting are more likely to complete a full course compared with patients in the metastatic setting and may therefore have a higher chance of developing CIT); line of treatment (i.e. higher risk for CIT with consecutive courses); additional types of treatment (i.e. radiotherapy); dose and dosage interval (i.e. the risk for myelosuppression is dose related); and co-medications and co-morbidities.

Conclusions

With thrombocytopenia occurring in one in five patients with a solid tumour treated with cytotoxic agents, and with a clinically relevant grade of severity occurring in 54% of patients, our observations suggest thrombocytopenia is a clinically relevant problem in this population. Further research is necessary to investigate the consequences of thrombocytopenia (e.g. bleeding, dose reduction, dose delay) and its impact on survival.

Few other studies are available that we can compare our data with; however, the frequencies of thrombocytopenia observed in our population were lower than estimates from previous observational studies from the 1980s and 1990s.[6-8] In addition, the frequency of overall thrombocytopenia is comparable to the frequency observed in a recent US population-based study.[10] Finally, our estimates are higher than the estimates from a recent US-based retrospective observational study,[9] which may be explained by differences in study design.

Data on the frequency and RR for thrombocytopenia provided by this study contribute to our knowledge of the risk of thrombocytopenia in adult patients with solid tumours treated with cytostatic agents in the clinical practice setting.

The observations of the increased risks of possible immune-mediated thrombocytopenia associated with exposure to oxaliplatin or gemcitabine contribute to the suspicion that these drugs may cause immune-mediated thrombocytopenia. For clinicians, the mechanism associated with thrombocytopenia has important consequences because in immune-mediated thrombocytopenia the drug must be avoided, while in dose-dependent thrombocytopenia a dose reduction may be sufficient. These observations require additional investigation.

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Ethics: The UPOD data acquisition and data management are in line with current Dutch regulations concerning privacy and ethics, and has been approved by the Medical Ethics Committee of the UMC Utrecht. This committee felt that reviewing the regimen for this study was not necessary. The data that were used for this study were collected for patient-care purposes and were used retrospectively. The design and data abstraction process of the current study have been approved by the supervisory committee of the RCR.

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