Evaluation of current practice: management of chemotherapy-related toxicities

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Adverse effects induced by cytotoxic chemotherapy (CT) have been mostly evaluated in clinical trials. The aim of this study was to assess in a nonselected patients group the incidence of CT-related toxicities and to identify risk factors in daily practice. Patients treated with CT (except cisplatin-based or carboplatin-based CT), for a solid tumour, were included in a prospective multicentre observational study. Clinical parameters, renal function and albumin level were assessed at baseline. Multivariate logistic regression was used to identify risk factors of CT-related toxicities. A total of 502 patients were recruited in different types of oncology departments. During CT, 62% of patients experienced grade 2–4 toxicities. Haematological toxicities affected 34% of patients and 20% of patients developed an infection requiring antibiotics. For 55% of patients, toxicities induced dose reduction (59% of cases), CT delay (25%) or discontinuation (16%) according to the management habits in the investigating centre. Performance status ≥ 1, breast cancer, lymphopenia, hypoalbuminaemia and clearance creatinine < 60 ml/min were risk factors for haematological toxicity. Performance status ≥ 1, hypoalbuminaemia, proteinuria and clearance creatinine < 90 ml/min were risk factors for change of CT schedule. A majority of patients receiving CT experienced significant toxicity leading to change of standard CT protocol. Albumin, creatinine clearance and lymphocyte should be routinely monitored at baseline to manage CT and to prevent their toxicities. ***Anti-Cancer Drugs*** **22:919–925** © **2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Despite the upcoming of targeted therapy, cytotoxic chemotherapy (CT) still keeps its leading role in the treatment of solid tumours. Adverse effects induced by CT have been mostly evaluated in clinical trials with selected patients. Nevertheless, as most patients managed in current practice do not match the eligibility criteria required for inclusion in clinical trials, the routine evaluation of toxicities has been little explored. However, toxicities modify the medical care and could change the CT standard protocol with no benefit/risk ratio data. Except for cisplatin-based and carboplatin-based CT that are prescribed according to renal function, anticancer drug dosage is usually based on findings from clinical trials and is calculated while considering the body surface area (BSA) since 1972 [1]. However, several studies have already shown that the estimation of BSA does not contribute to explain pharmacokinetic (PK) variations [2–5]. Few recommendations are available to adapt non-cisplatin-based CT for patients in routine practice [6–8]. Thus, age is related to modifications of PK drugs and is now well taken into account [9,10]. The International Society of Geriatric Oncology therefore suggests dose recommendations according to renal function for elderly patients [11]. Renal function indeed participates in each step of cytotoxic PK drugs [12]; in addition, most of the CTs are excreted in urine [6]. According to the Renal Insufficiency and Anticancer Medications-1 study, 57.4% of patients with cancer presented an abnormal renal function, as assessed using the Cockcroft–Gault formula [13]. Moreover, as most CT drugs bind to protein in blood plasma, the poor nutritional status could increase the free-drug fraction related to toxicity [14–16]. In this context, we assumed that these parameters could be useful to predict CT-induced toxicities and to manage CT. The aim of this study was to prospectively assess the incidence of CT-related toxicities in nonselected patients with cancer and to identify risk factors that could be potentially be useful in daily practice.

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Materials and methods

Study design

It was a prospective, observational and multicentre study conducted in six oncology departments in Normandy, France (one comprehensive cancer centre, two communitarian hospitals, one university hospital and one private hospital). At inclusion, sex, age, type of tumour, number of previous lines of CT and the CT regimen were registered. The following data were collected at baseline and at each CT cycle: weight, performance status (PS), proteinuria, blood count, serum albumin, creatinine and hepatic assessment. The renal function was estimated by calculating the creatinine clearance (CrCl) using the Cockroft–Gault formula [17]. Renal function was staged according to the clinical practice guidelines published by the Working Group of the National Kidney Foundation [18]. Renal insufficiency was defined while considering two different thresholds: a CrCl < 90 ml/min, which corresponds to a greater than or equal to grade 2 renal insufficiency, and a CrCl < 60 ml/min, which defines a greater than or equal to grade 3 renal insufficiency. At each cycle, according to routine practice, the physician noted the CT dose and spontaneously reported documented toxicities; all these data were collected in hospital medical records. The evaluation of toxicities and grades were based on the schedule Common Terminology Criteria for Adverse Events version 3 (*http://ctep.cancer.gov*) [19]. Thus, considered toxicities were as follows: digestive toxicities (nausea, vomiting, diarrhoea, constipation), neurological toxicities (dysesthesias, defined by a disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation), dermatological toxicities (palmar-plantar erythrodysesthesia syndrome, cutaneous rash, nail ridging, conjunctivitis), cardiac and lung toxicities (cardiac insufficiency, drug-related pneumopathia) and haematological toxicities [febrile neutropenia (FN), neutropenia, thrombopenia, anaemia].

Study population

Patients were included if they began a first cycle of CT, whatever the line was. Targeted therapies were allowed if they were associated with a CT regimen. Patients were excluded if they were below 18 years of age, treated with cisplatin or carboplatin or were suffering from an end-stage renal disease that required renal replacement therapy. This study was approved by the local ethics committees, and the patients gave their written informed consent.

Statistical analysis

Statistical analyses were carried out using STATA software version 10 (Texas, USA). The type I error rate was 0.05 for all analyses. The primary endpoint was to estimate the prevalence of toxicities of CT in current practice. Overall grade 2 or 3 toxicities were defined by FN, greater than or equal to grade 2 infections (requiring antibiotics), anaemia, thrombopenia, dysesthesia, dermatological, cardiac and lung toxicities as well as greater than or equal to grade 3 neutropenia and digestive toxicities, according to the Common Terminology Criteria for Adverse Events version 3 [19]. Haematological toxicities were defined by FN, anaemia, thrombopenia and greater than or equal to grade 3 neutropenia.

The second endpoint was to determine the prevalence of changes in CT protocol, which were defined by a dose reduction, a delay or a discontinuation of CT.

Descriptive statistical data evaluation was based on medians for continuous variables and on frequencies for categorical variables. It was performed for the whole study population and according to the indication of CT (adjuvant/metastatic).

The third endpoint was to identify useful risk factors related to the occurrence of overall and haematological toxicities and of changes in CT protocol. These evaluations were made among the whole study population and according to the CT indication. Multivariate logistic regression models containing all variables with a *P* value less than 20% in univariate analyses were performed. Results were expressed as adjusted odds ratios (OR) with their 95% confidence interval.

Results

Population

Between October 2007 and December 2008, 502 patients with various solid cancers were included. The mean age was 58 years (range: 22–85 years), and 70% of patients were women. Breast cancer (54%) and colorectal cancer (30%) were the most common cancers in our population. The other localizations were lung (7%), prostate (5%), ovary (3%) and sarcoma (1%). The CT indication was neoadjuvant treatment (3%), adjuvant treatment (51%) and metastatic disease (46%). Patients aged above 65 years, with metastatic disease, represented 68% of patients treated in a general hospital and 47% of patients treated in a specific hospital. Table 1 shows the baseline characteristics of the whole study population. At baseline, although 78% of patients had a normal serum creatinine level (< 80 µmol/l), approximately half the patients (47%) presented a decreased glomerular filtration rate of less than 90 ml/min. A majority of abnormal parameters at baseline were observed in a metastatic setting.

Different drugs were prescribed (Table 2), and patients received 5.6 CT cycles on average. The most frequent CT protocols were FEC100 (5-fluorouracil, epirubicin and cyclophosphamide; 37%), Folfox (oxaliplatin and 5-fluorouracil; 14%) and Folfiri (irinotecan and 5-fluorouracil; 7%). Main prescribed targeted therapies were trastuzumab and cetuximab, associated to CT in 46 patients (9%). Previous treatments before enrolment included surgery for 79% of patients, radiotherapy for

Table 1 Characteristics of the study population at baseline (*N*=502)

	N (%)[a]		
	Whole population [*N*=502 (%)]	Neoadjuvant/adjuvant cancer [*n*=272 (%)]	Metastatic cancer [*n*=230 (%)]
Male sex	149 (30)	26 (10)	123 (53)
Age>65 years	156 (31)	44 (16)	112 (49)
PS>0[b]	145 (29)	30 (11)	115 (50)
Cancer			
Breast cancer	271 (54)	221 (82)	50 (18)
Gastrointestinal cancer	150 (30)	51 (19)	99 (43)
Other			
Weight loss	168 (33)	74 (27)	94 (41)
Serum creatinine (>80 μmol/l)	108 (22)	24 (9)	84 (38)
Creatinine clearance (<90 ml/min)[c]	226 (47)	89 (34)	137 (62)
Albumin (<35 g/l)	141 (30)	48 (19)	93 (44)
Bilirubin (>17 UI/l)	21 (5)	8 (3)	13 (6)
AST/ALT (<37 UI/l)	82 (18)	34 (13)	48 (23)
Absolute neutrophil count (<1500/mm^3)	2 (0.4)		
Lymphocyte (<800/mm^3)	43 (9)		

AST, aspartate transaminase; ALT, alanine aminotransferase.
[a]Number of patients may vary because of missing information.
[b]Performance status.
[c]Using the Cockroft–Gault formula.

Table 2 Anticancer drugs most often prescribed to patients in the study

Anticancer drugs	Number of prescriptions
5-Fluorouracil	303
Epirubicin	195
Cyclophosphamide	191
Docetaxel	82
Oxaliplatin	80
Gemcitabine	49
Irinotecan	46
Paclitaxel	25
Pemetrexed	24
Targeted therapy (trastuzumab, cetuximab)	46

24% of patients and previous chemotherapies for 40% of patients with a mean of 1.8 lines.

Chemotherapy prescription

During the study period, 270 patients (54%) had a modification of the standard CT protocol. In 44% of cases, these modifications were observed in neoadjuvant or adjuvant setting. The modalities of change of CT were a dose reduction (59%), a delay (25%) or a discontinuation (16%) of CT. The reasons for these dose-intensity reductions were toxicities, age or PS deterioration. A dose reduction was initially prescribed at cycle 1 for only 24 patients (5%) due to their age and due to deteriorated PS. The CT modifications were more often observed in general hospitals than in specific cancer hospitals.

During CT, 60 and 197 patients, respectively, received erythropoietin-stimulating agents (ESA; 12%) and granulocyte colony-stimulating factor (G-CSF; 39%). In metastatic cancer (230 patients), ESA and G-CSF were, respectively, prescribed for 36 (16%) and 60 (26%) patients. In adjuvant setting (272 patients), ESA and G-CSF were, respectively, prescribed for 24 (9%) and 137 (50%) patients. Patients aged above 65 years ($n = 156$), respectively, received ESA and G-CSF in 17% (26 patients) and in 29% (45 patients) of cases. Lastly, ESA and G-CSF were given to 10% (34 patients) and to 44% (152 patients) of patients aged below 65 years.

Toxicities

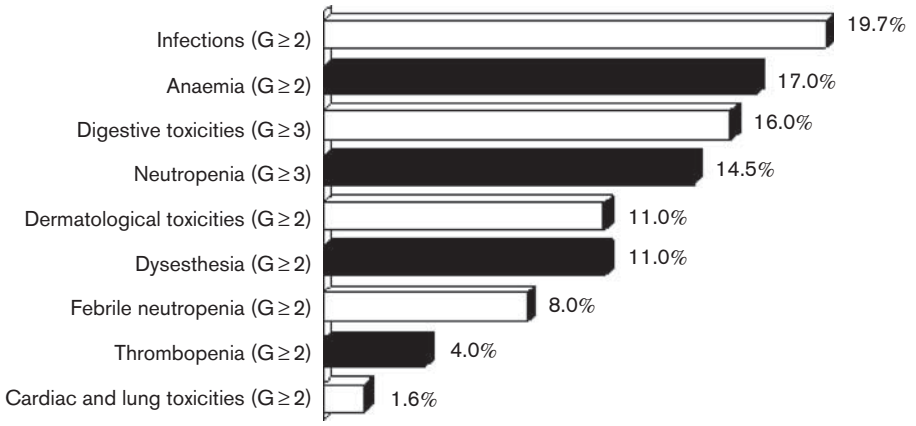
Overall grade 2 or 3 toxicities were observed for 62% of the 502 studied patients (Fig. 1). More precisely, 45% of patients presented a toxicity greater than or equal to grade 3 or an infection requiring antibiotic prescription. These toxicities occurred on cycle 3 on average, whatever the type of CT protocol was. The main observed toxicities were haematological toxicities that occurred in 34% of patients and were more often observed in metastatic setting (38%) than in adjuvant one (31%). An FN was reported for 42 patients (8%). The blood sample analyses identified a grade greater than or equal to 3 neutropenia in 68 patients (14%), a grade greater than or equal to 2 anaemia in 85 patients (17%) and a grade greater than or equal to 2 thrombocytopenia in 20 patients (4%).

Predictive factors of toxicity onset

In the whole study population, PS > 0 (OR = 2.51, $P = 0.002$) and hypoalbuminaemia (OR = 2.21, $P = 0.005$) at baseline were found to increase the risk of overall toxicities (Table 3). PS deterioration (OR = 2.76, $P = 0.002$) and hypoalbuminaemia (OR = 2.11, $P = 0.025$) remained predictive factors of toxicities in metastatic CT indication. Conversely, no parameter was significantly related to overall toxicities in adjuvant situation.

Patients with breast cancer, PS > 0, lymphopenia, CrCl < 60 ml/min and hypolbuminaemia were identified at higher risk of developing haematological toxicity (Table 4). Change in CT regimen was more frequent for patients with breast cancer, gastrointestinal cancer, PS > 0, CrCl < 90 ml/min

Fig. 1



Profile and frequency of patients' toxicities (G = grade; $N = 502$).

Table 3 Multivariate analyses of risk factors for toxicities in the whole population ($n = 502$)

Parameters at baseline	Adjusted OR	CI (95%)	*P* value
PS[a]			
= 0	1		
> 0	2.51	(1.39–4.54)	0.002
Albumin (g/l)			
> 35	1		
< 35	2.21	(1.27–3.86)	0.005
Cancer			
Other cancer	1		
Breast cancer	2.01	(0.76–5.27)	0.155
Gastrointestinal cancer	1.31	(0.62–2.73)	0.472
Weight			
Stable	1		
Gain	0.7	(0.37–1.31)	0.27
Loss	1.06	(0.62–1.81)	0.823
AST/ALT (UI/l)			
< 37	1		
> 37	1.38	(0.74–2.56)	0.298
Sex			
Male	1		
Female	1.25	(0.61–2.58)	0.529
Age (years)			
< 65	1		
> 65	0.92	(0.50–1.68)	0.802
Indication CT line			
Adjuvant	1		
Metastatic	0.76	(0.39–1.48)	0.429
CrCl (ml/min)[b]			
≥ 90	1		
< 90	1.03	(0.62–1.71)	0.893

CI, confidence interval; CrCl, Creatinine clearance; CT, chemotherapy; OR, odds ratio; AST, asparate aminotransferase; ALT, alanine aminotransferase.
[a]Performance status.
[b]Using the Cockroft–Gault formula.

Table 4 Multivariate analysis of risk factors for haematological toxicity ($n = 502$)

Parameters at baseline	Adjusted OR	CI (95%)	*P* value
PS[a]			
= 0	1		
> 0	2.02	(1.18–3.45)	0.011
Albumin (g/l)			
> 35			
< 35	1.63	(1.01–2.62)	0.047
Cancer			
Other cancer	1		
Breast cancer	4.35	(1.70–11.1)	0.002
Gastrointestinal cancer	1.26	(0.62–2.55)	0.519
CrCl (ml/min)[b]			
≥ 60	1		
< 60	1.92	(1.02–3.60)	0.043
Lymphocyte (mm^3)			
≥ 800	1		
< 800	2.27	(1.10–4.70)	0.026
Indication CT line			
Adjuvant	1		
Metastatic	1.84	(0.92–3.67)	0.084
Previous radiotherapy			
No	1		
Yes	0.91	(0.49–1.69)	0.76
Sex			
Male	1		
Female	1.18	(0.59–2.37)	0.633

CI, confidence interval; CrCl, Creatinine clearance; CT, chemotherapy; OR, odds ratio.
[a]Performance status.
[b]Using the Cockroft–Gault formula.

and hypoalbuminaemia (Table 5). In adjuvant situation, PS > 0 (OR = 4.09, $P = 0.016$), proteinuria (OR = 5.43, $P = 0.005$) and CrCl < 90 ml/min (OR = 2.49, $P = 0.005$) were the main risk factors for CT modification. In metastatic indication, breast cancer (OR = 4.78, $P = 0.003$), PS > 0 (OR = 2.29, $P = 0.023$) and hypoalbuminaemia (OR = 2.46, $P = 0.017$) were found to predict a CT change.

Discussion

This is one of the largest prospective studies that evaluated toxicities of CT in current practice. The assessment of chemotherapy-induced toxicities was therefore based on toxicities spontaneously reported by physicians. In such conditions, as no predefined checklist of toxicities was established, the toxicity rate may be underestimated. Nevertheless, we aimed at realizing a 'snapshot' of CT-induced toxicities among a nonselected population. We found a high rate of significant toxicities as well as of standard CT modification. Simple predictive risk factors

Table 5 Multivariate analysis of risk factors for change CT protocol in the whole population ($n=502$)

Parameters at baseline	Adjusted OR	CI (95%)	*P* value
PS[a]			
=0	1		
>0	2.9	(1.60–5.24)	<0.0001
Cancer			
Other cancer	1		
Breast cancer	3.69	(1.57–8.70)	0.003
Gastrointestinal cancer	2.80	(1.34–5.84)	0.006
CrCl (ml/min)[b]			
≥ 90	1		
<90	1.85	(1.15–2.98)	0.011
Albumin (g/l)			
>35	1		
<35	1.76	(1.07–2.91)	0.026
Proteinuria			
No	1		
>0	1.99	(0.98–4.05)	0.058
Indication CT line			
Adjuvant	1		
Metastatic	1.78	(0.89–3.55)	0.102
Previous radiotherapy			
No	1		
Yes	1.33	(0.70–2.52)	0.384
Age (years)			
<65	1		
>65	0.82	(0.45–1.47)	0.496

CI, confidence interval; CrCl, creatinine clearance; CT, chemotherapy; OR, odds ratio.
[a]Performance status.
[b]Using the Cockroft–Gault formula.

such as PS > 0, decreased renal function, lymphopenia and hypoalbuminaemia were identified to be helpful for the management of CT.

During CT, 62% of patients developed early significant toxicities so that they could not receive the standard CT protocol in 55% of cases. Targeted therapies associated with CT were included in our study. Such associations only concerned 9% of our whole study population; some of these patients developed toxicities related to targeted therapies but these toxicities did not occur in early cycles and were not haematological toxicities. These observations confirmed that the usual prescription of CT dose according to patient's BSA is not adapted to the drug exposition level and may be responsible for a high rate of toxicities [20]. A retrospective nationwide study showed the same frequency of protocol deviations in routine among 20 799 patients treated for adjuvant breast cancer [21]. We prospectively confirmed that most patients needed an adaptation of CT protocol in current practice, whatever the line and the type of CT were. The adaptation of CT protocol in response to toxicities was heterogeneous between hospitals, such differences in CT management could result from various patients' profiles according to the participating hospital and from the lack of standard guidelines. The impact on CT efficiency as well as the modalities and the issues of such modifications have been poorly described and needs to be evaluated. This is particularly important in adjuvant setting where the treatment goal is curative and CT efficiency is probably related to dose intensity. This observation promotes the interest of phase IV study to better understand the tolerance profile of drug. Information is indeed needed once the drug is marketed to optimize its use and consequently its efficiency.

Although a change in CT protocol resulted from toxicities for a majority of patients, dose adjustment was rarely performed at baseline. The identification of simple predictive parameters at baseline is therefore important to manage CT and to improve the prevention of toxicities.

In our prospective study, PS > 0 and hypoalbuminaemia are the two main predictive factors of overall toxicities occurrence. PS > 0, breast cancer, CrCl < 60 ml/min, lymphopenia and hypoalbuminaemia at baseline were identified to increase the risk of further haematological toxicities, which are the most common toxicities, whatever the CT indication is.

The PS deterioration has already been shown as a risk factor for toxicities [22]. This parameter is assessed according to the Karnofsky and Eastern Cooperative Oncology Group scales: it is not objective and depends on intraobserver and interobserver variabilities [23] and may reflect different clinical or biological situations.

We prospectively showed that renal insufficiency is involved in haematological toxicities. A previous retrospective analysis reported a more than three-fold increased risk of haematological toxicities in case of CrCl < 50 ml/min among women, aged above 65 years, with breast cancer [24]. Similarly, another study noted a relationship between CrCl ranging from 35 to 66 ml/min and the risk of neutropenia among patients treated with irinotecan [25]. The large Renal Insufficiency and Anticancer Medications 2 study reported an association between a reduced cancer survival and renal insufficiency. Patients with cancer with abbreviated Modification of the Diet in Renal Disease < 60 ml/min seemed to be at a higher risk of death for the following 2 years, even in the nonmetastatic situation. However, the link between CT toxicities or protocol modifications and survival was not established.

We confirmed the high prevalence of renal insufficiency in patients with cancer, despite normal creatinine level [26]. As renal insufficiency increased the risk of haematological toxicities, the evaluation of glomerular filtration rate needs to be assessed before CT prescription, even with CT regimens not containing cisplatin or carboplatin, to calculate the appropriate CT dose and to manage potential haematological toxicities. Furthermore, in patients with decreased renal function at baseline, cautious selection and analysis of concomitant medications should be also performed.

Lymphopenia less than 700/mm^3 at baseline has been already shown to predict anaemia [27] and thrombopenia [28] in multivariate models. Our study confirmed that

a grade 2 lymphopenia (< 800/mm^3) before CT administration is engaged in comprehensive haematological toxicities. This parameter is easily assessable at baseline and should be considered routinely.

Previous studies have reported a relationship between hypoalbuminaemia and FN in univariate analyses [29–31]; our study confirmed such a strong association in multivariate models. A prospective study observed the predictive role of hypoalbuminaemia on the risk of FN but the relationship did not remain significant in multivariate analysis [32], probably due to a threshold for albumin level equal to 25 g/l, which was not discriminating.

In our study, we could not identify age as predictive of haematological toxicities. Age could be associated with a physiological GRF decrease [33], but was not an individual predictive factor of this parameter. This finding could result from the observational method, as the oncologists could modify the CT management for older patients.

Various complex models have been proposed to predict haematological toxicities, but they are either difficult to apply routinely or are restricted to a subset of patients. A prospective study conducted among 107 patients established a significant score called 'Nutritional and Inflammatory Status' to identify a group of patients at risk [34]. The Nutritional and Inflammatory Status could be calculated with this formula: (C-reactive protein × alpha-1 acid glycoprotein)/(albumin × prealbumin). This score is difficult to implement routinely and is consequently little used. Inversely, our study identified simple risk factors of toxicities that are easy to use in current practice to target patients at high-risk for CT-induced toxicities. Severe acute toxicity frequently requires a decrease in dose, an extension of the interval between treatments or even a discontinuation of treatment. Such changes may therefore quickly lead to a reduced efficiency, which is notably a problematic issue in the adjuvant setting, as discussed above. Severe toxicity may also be responsible for unscheduled hospitalizations, inconvenience or handicaps, thus increasing treatment cost. These toxicities are particularly important for metastatic patients for whom the main objective is to improve the quality of life. This group usually represents the 'unfit' patients who are often excluded from clinical trials due to altered criteria at baseline. However, these patients received CT in current practice. In our study, they experienced more haematological toxicities but received less G-CSF than patients treated with adjuvant CT. Primary prophylaxis is recommended for CT regimens associated with a risk of FN of at least 20% and is also appropriated for patients at high-risk for receiving regimens with FN rates less than 20% [35,36]. Patients with metastatic cancer could be considered as high-risk patients in case of CrCl < 60 ml/min, lymphopenia or hypoalbumin.

In the whole study population, a renal dysfunction based on a GRF decrease and on proteinuria seems to have an impact on the modification of CT protocol. It may be correlated to less drug elimination, thus leading to drug accumulation, which requires a change of CT protocol. The impact of renal function impairment was well identified in adjuvant CT indication but not among metastatic patients. In this situation, the main risk factors were PS deterioration and hypoalbuminaemia. The differences between the patient's characteristics in adjuvant and metastatic indications could explain this finding. Other clinical predictive factors for the modification of CT protocol were identified in a retrospective study as follows: age > 65 years, type of CT, schedule of 28 days, BSA > 2 m^2 and no G-CSF prevention [37]. Nevertheless, due to its retrospective design, this study could not assess specific biological parameters.

We prospectively studied a nonhomogenous population of patients with cancer receiving different types of CT. However, our original observational study was an informative overview of current practice of CT, which provided simple parameters, easily assessable at baseline. Such a study could help the CT management with supportive measures to control acute toxicities and to develop useful prevention tools. Further studies with a longer follow-up could be conducted to evaluate the risk/benefit ratio, especially in metastatic patients.

Conclusion

This prospective, multicentric study established data on CT management in current practice and showed a high level of toxicities and modifications of standard CT dose, leading to the interest of phase IV studies.

In multivariate analysis, PS, albumin, CrCl and lymphocytes count at baseline were identified to be correlated with an increased risk of CT-induced toxicity. These simple parameters should be routinely monitored to improve the CT management and to prevent toxicities by appropriate supportive measures.

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Conflicts of interest

There are no conflicts of interest.

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