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Predictors of tolerance to chemotherapy in older cancer patients: a prospective pilot study

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Abstract

Few data are available to help predict which older cancer patient is at risk of developing chemotherapy-related toxicity. This study was a pilot for a project designing a predictive risk score. Chemotherapy patients aged 70 years and older were prospectively enrolled. Chemotherapies were adjusted for their published toxicity. 60 patients were enrolled, 59 were evaluable. Mean dose-intensity was 90.3%, range 33.3–129.0%. 47% of the patients experienced grade 4 haematological and/or grade 3-4 non-haematological toxicity. Published toxicity (MAX2), diastolic blood pressure, marrow invasion and lactate dehydrogenase (LDH) were all associated with toxicity ($P<0.1$); Body Mass Index, previous chemotherapy, red blood cells, platelets, polymedication with dose-intensity; and polymedication with FACT-G change. After adjustment for the published toxicity, the variables retained their significance, except for LDH and polymedication (for dose-intensity). Although the size of this pilot study imposes a cautious interpretation, patient-related and chemotherapy-related variables correlated independently with toxicity. Designing a composite predictive score to use in assessing the toxicity of multiple chemotherapy regimens therefore appears to be a valid undertaking.

Keywords: Chemotherapy toxicity; Aged; Aged >80 years; Predictive factors; Comprehensive geriatric assessment

1. Introduction

Cancer is a disease of the elderly: in developed countries, including the United States, 60% of all incident tumours and 70% of all cancer mortality occur in those aged 65 years and over. This proportion will increase with the expected increase in the size of the older population in the next decades. Therefore, a major question faced by oncologists treating older cancer patients is to identify the variables that influence their tolerance to chemotherapy. Predicting chemotherapy toxicity is particularly critical in the palliative setting, for example in patients with metastatic breast or prostate cancer, since control or delay of symptoms is the main objective. Identifying patients at risk of complications may allow the physician to propose alternative forms of treatment, include supportive measures, or make rational dose reductions. It may also help identify a subgroup of patients who would tolerate treatment better than average, and therefore may be offered other additional options. Despite reports of an association of various predictor variables with toxicity from chemotherapy, no reliable prognostic system is as yet available, especially any that takes into account the multidimensional problems of older cancer patients. Previous studies have also focused on a limited number of toxicity endpoints, such as neutropenia, febrile neutropenia or anaemia [1–3]. These endpoints are important, but insufficient, to encompass the whole array of complications chemotherapy can cause in older individuals, notably non-haematological toxicities, which can be major considerations in the choice of a therapeutic option. Therefore, a global approach to toxicity risk prediction would have a high relevance for clinical practice. Most toxicity from chemotherapy is dose-dependent. Furthermore, a study using docetaxel suggests that a haematological toxicity—neutropenia—and a non-haematological toxicity—fluid retention—share similar predictors [2]. This

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led us to hypothesise that a model considering toxicity from chemotherapy from a global perspective could be constructed.

At present, pharmacokinetic modelling is the best-known and most precise way of predicting toxicity. However, its use is impractical in the everyday clinical setting. It also becomes fairly complex if multidrug regimens are used. Another possible approach is to try to predict toxicity based on clinical and routine laboratory variables, that are ideally obtained before treatment. Various attempts have been made to correlate clinical variables and toxicity. However, the studies trying to design multifactorial models were retrospective in nature and typically included very few clinical parameters with a high relevance for older cancer patients, such as comorbidity, cognition, depression or nutrition [1–4]. They also used very targeted toxicity endpoints. Another limitation of such studies is that outside of clinical studies, toxicity is not systematically assessed and tends to be underreported. This is particularly true for non-haematological toxicities. In addition, the implementation of treatment is not uniform. The number of pretreatment variables that are evaluable may also be limited by the quality of the records. Therefore, a prospective approach offers the optimal strategy to rigorously control both treatment and pretreatment variables, notably the specific geriatric elements, which maximises the power to detect significant correlations with toxicity. This pilot was the first step of our prospective approach. Its goals were:

- To determine whether patient-specific factors influencing toxicity could be identified independently from the variations in toxicity severity that are linked to the regimen chosen itself.
- To design a practical way of ranking published toxicities of chemotherapy regimens for inclusion in a prognostic model.
- To determine the toxicity endpoint offering the best feasibility and discriminatory power to build a risk model for toxicity from chemotherapy.
- To assess the proportion of patients experiencing toxicity, the accrual rates, and the practical feasibility of an assessment including geriatric assessment tools.

2. Patients and methods

Patients treated at H. Lee Moffitt Cancer Center, aged 70 years or more, were prospectively and sequentially accrued in the study. They were to receive a well-defined chemotherapy regimen for a solid tumour or a non-leukaemic haematological malignancy, without concomitant radiation therapy. Any stage of disease and any line of treatment were accepted. Patients in phase I studies, and those receiving myelosuppressive chemotherapy (e.g. for acute leukaemia) were not eligible. A pretreatment history and physical examination, complete blood count (CBC), and chemistry panel were assessed, as well as a set of questionnaires (see below). The variables were chosen in an exploratory manner to represent a broad spectrum of pretreatment laboratory, clinical, and geriatric parameters with potential interest as predictors. The following variables were analysed for their association with outcome: Age, sex, marital status, presence of a caregiver, body mass index (BMI), blood pressure, bone marrow invasion (defined as any radiological or cytological evidence of tumour infiltration), tumour response, previous treatment, polymedication (three medications or more), Eastern Co-operative Oncology Group (ECOG) Performance Status, Lawton's Instrumental Activities of Daily Living (IADL) [5], Geriatric Depression Scale, short form (GDS) [6], Mini-Mental Status (MMS) [7], Mini-Nutritional Assessment (MNA) [8], Functional Assessment of Cancer Treatment-General v.3 (FACT-G) [9], Comorbidity data extracted using the Cumulative Illness Rating Scale-Geriatric (CIRS-G) [10], and the Charlson comorbidity index [11], CBC, hepatic tests, lactate dehydrogenase (LDH), albumin, creatinine clearance and MAX2. No short synthetic way to summarise and compare the toxicity of various chemotherapy regimens was available for mathematical analysis. To address this need, the MAX2 index (Table 1) was designed empirically at the beginning of this pilot (i.e. prior to the analysis of the results) as a means to compare the published toxicity of the various chemotherapy regimens with low or moderate toxicity. It was extracted from published articles of chemotherapy studies treating at least 20 patients with the same chemotherapy regimen. We defined as severe toxicity a grade 4 haematological toxicity and/or grade 3 or 4 non-haematological toxicity. These levels of toxicity are in most protocols considered as dose-limiting toxicities that prompt a delay, a reduction in dosage or a cessation of treatment. The incidence of the most frequent grade 4 haematological toxicity and of the most frequent grade 3 and 4 non-haematological toxicity were added, then divided by two. The result was a number between 0 and 1. Alopecia was excluded. For example, a regimen having as the most frequent toxicities a 25% incidence of grade 4 neutropenia and a 13% incidence of grade 3 and 4 diarrhoea would have a MAX2 of $(0.25+0.13)/2=0.19$. If haematological toxicity was listed only as a leucopenia, grade 4 neutropenia was calculated as (grade 3 + 4 leucopenia) * 0.6, if grade 4 leucopenia was less than 30%, and * 0.8, if above. This corresponds to the median ratios found in a sample of 15 studies evaluating 20 chemotherapy regimens that provided both leucopenia and neutropenia data. The MAX2 index builds on the fact that the most frequent toxicities of a regimen are

Table 1
The MAX2 index: an index allowing adjusting the toxicity of different chemotherapy regimens for comparison (see text for details)

$$\frac{\text{Most frequent grade 4 haematological toxicity} + \text{most frequent grades 3+4 non-haematological toxicity}}{2}$$

Example
25% grade 4 neutropenia → $\text{MAX2} = \frac{0.25 + 0.13}{2} = 0.19$
13% grade 3+4 diarrhoea

Notes
Alopecia is not counted
When only WBC nadirs are reported, ANC is extracted as follows:
0.6* G3+4 leucopenia, if G4 leucopenia <30%
0.8* G3+4 leucopenia, if G4 leucopenia 30% and above

WBC, white blood cell; ANC, absolute neutrophil count.

usually reported in detail, with, in the last decade, standardised and similar models: e.g. the Common Toxicity Criteria, or the World Health Organization (WHO) criteria. Therefore, it has low sensitivity to publication bias. Indeed, for example, in three studies using the cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimen, the MAX2 was 0.41, 0.35, and 0.37, respectively [12–14]. It also has good stability across tumours: gemcitabine given as 1.25 g on days 1, 8, 15 every 4 weeks has a MAX2 of 0.03 and 0.09 in non-small cell lung cancer, 0.065 in non-Hodgkin's lymphoma, and 0.07 in Hodgkin's disease [15–18]. By linearising a composite of haematological and non-haematological toxicity, the MAX2 index also allows ranking of regimens that have different haematological or non-haematological toxicity.

Patients had a comprehensive evaluation (FACT-G included) initially, at 3 months, and at the end of treatment. If the end of treatment was before 3 months, the 3-month evaluation was skipped. Follow-up was truncated at 6 months to minimise the influence of outliers.

There were three endpoints: (1) Occurrence of grade 4 haematological toxicity and/or grade 3 or 4 non-haematological toxicity (hereafter endpoint toxicity), using the Common Toxicity Criteria v.2 [19]. Alopecia was not counted. These levels of toxicity were chosen because in most studies, they are considered dose-limiting toxicities and trigger dose modifications. (2) Dose-intensity of the chemotherapy, in percentage of the planned dose-intensity [20]. (3) Change in quality of life, as assessed by changes in the FACT-G score from baseline.

2.1. Statistical analysis

Univariate logistic regression was used to study the association of each variable with toxicity, expressed as a dichotomous dependent variable: occurrence or not of endpoint toxicity (see definition above). This pilot was not powered to allow a full multivariate analysis. Rather, the key endpoint of interest was assessing whether patient-based parameters would correlate with toxicity in a measurable independent way from the intrinsic toxicity of the chemotherapy regimen. Therefore, bivariate logistic regression was used to adjust each variable for the toxicity of the chemotherapy (MAX2). The association of each variable with the continuous endpoint measures (dose-intensity and FACT-G change) was determined with univariate linear regression. The analysis was repeated with adjustment for MAX2 with bivariate linear regression. A P value of <0.1 was considered significant. We chose this threshold for two reasons. $P<0.1$ is a cut-off value often used when selecting candidate variables for a multivariate analysis. Since this pilot was also of limited size and a screening study for prognostic factors, we wanted to have a high sensitivity for potential predictors.

The Institutional Review Board of the University of South Florida approved this protocol. Each patient signed a written informed consent form prior to inclusion in the study.

3. Results

60 patients were enrolled and underwent an initial assessment over 16 months. They represented approximately a quarter of the older patients receiving chemotherapy at H. Lee Moffitt Cancer Center during the accrual period. Another quarter had concomitant radiation therapy, a quarter were planned to continue treatment outside of Moffitt after a short period of time, and others were either receiving myelosuppressive chemotherapy, refused to participate, had physical impairments rendering them ineligible (e.g. deafness), were missed or were not enrolled for technical reasons. The main technical reason for non-enrolment was that, due to accrual in multiple clinics, the research nurse assigned to the study was not always available for enrolment due to competing engagements.

One patient died before initiation of chemotherapy. 59 patients were evaluable for toxicity. The median age of the evaluable patients was 75 years (range 70–87 years). 14% of them were 80 years or older. The

Table 2
Patients' baseline characteristics

Patients' characteristics	Out of 59 evaluable
Median age (years)	75 (70–87)
Male/female	29/30
ECOG Performance Status	
0	40
1	14
2-3	5
IADL dependent	37
Geriatric Depression Scale >5	6
Mini Mental Status $\leqslant 25$	9
Mini-nutritional assessment	At risk: 31 Malnourished: 2
Comorbidity	Charlson +: 35 CIRS-G +: all CIRS-G, 3 or more categories: 38
Polymedication ($\geqslant 3$ drugs)	40
With caregiver	43
Tumour types	See text
Metastatic disease	37
Bone marrow invasion	15
Previous treatment[a]	49
•chemotherapy	20
•hormonal therapy	8
•radiotherapy	20
•surgery	35
BMI >25	22
Median initial RBC count (range)	4.02×10^{12}/cells/l (3.0–4.79)
Median initial platelet count (range)	232×10^{9} cells/l (104–520)
Median initial diastolic blood pressure (range)	74 mmHg (56–92)
Median initial LDH[b] (range)	517 U/l (318–834)

BMI, body mass index; RBC, red blood cell; CIRS-G, Cumulative Illness Rating Scale-Geriatric; LDH, lactate dehydrogenase; ECOG, Eastern Co-operative Oncology Group; IADL, Lawton's Instrumental Activities of Daily Living.

[a] A patient could have had several modalities.

[b] Normal 313–618 U/l.

patients' characteristics are listed in Table 2. 11 patients had colorectal cancer, 11 breast cancer, 10 lung cancer (1 also had prostate cancer), 6 non-Hodgkin's lymphoma, 5 gastrointestinal tumours other than colon, 5 prostate cancer (1 with lung cancer), 4 ovarian cancer, 2 uterine cancer, 3 other genito-urinary tumours, 1 multiple myeloma, 1 melanoma and 1 squamous skin cancer. 37 patients had stage IV disease, 15 of them with marrow invasion. 49 patients had received one or more previous treatments. 35 had received surgery, 20 radiation therapy, 8 hormonal therapy, and 20 chemotherapy. The chemotherapy regimens prescribed to the patients are listed in Table 3 and reflect the wide variety of tumours treated. 2 patients received one course of another regimen during the study period (carboplatin–paclitaxel for vinorelbine–gemcitabine and reciprocally). Since the MAX2 of these regimens were similar, these patients were retained for analysis. 5 patients received granulocyte-colony stimulating factor (G-CSF) as part of their initial treatment plan (e.g. doxorubicin (Adriamycin)-ifosfamide + G-CSF). 7 received G-CSF after having experienced severe toxicity from their treatment. 3 patients received erythropoietin: 2 were already on this treatment at the time of initiation of the study of chemotherapy, and 1 started it during chemotherapy.

28 patients (47%) experienced endpoint toxicity. 12 of them (20%) experienced grade 4 haematological toxicity, and 22 of them (37%) experienced grade 3 or 4 non-haematological toxicity. The details of the toxicities experienced are shown in Table 4. The reasons for ending chemotherapy were completion of treatment: 29, progression of disease: 14, toxicity: 8, other: 6 (surgery 1, transfer–move out 4, patient withdrawal 1), death: 2. 1 patient died of progressive disease, and another died of a myocardial infarction. That patient had a known history of ischaemic disease, and was receiving mitoxantrone and prednisone for prostate cancer. The mean

Table 3
Chemotherapy drugs received[a]

	MAX2	Patients
Carboplatin–paclitaxel	0.148	9
doxorubicin–(Adriamycin)-cyclophosphamide ± paclitaxel	0.211	7
Gemcitabine–vinorelbine	0.138	6
5-FU-leucovorin	0.098 (weekly), 0.222 (Mayo)	5
Irinotecan	0.255	5
CHOP ± rituximab	0.375	5
Mitoxantrone–prednisone ± VX710	0.074	4
Carboplatin–etoposide	0.294	2
Gemcitabine	0.070	2
Cisplatin–paclitaxel	0.487	2
Docetaxel	0.385 (q3weeks)	2
Capecitabine	0.088	2
Irinotecan–5-FU	0.255	2
Other	–	6

5-FU; 5-fluorouracil; q, every; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone.

[a] Further details about the MAX2 calculation, doses and references used in this study can be obtained directly from the corresponding author.

Table 4
Toxicities: number of patients affected

Toxicity	Grade			
	1	2	3	4
Leucopenia	7	9	6	7
Neutropenia	10	2	7	9
Anaemia	16	24	5	1
Thrombopenia	4	5	1	3
Mucositis	10	1	–	1
Diarrhoea	9	3	4	1
Constipation	10	2	1	–
Nausea/vomiting	17	6	1	–
Bloody stools	1	–	–	–
Dehydration	3	2	4	–
Oedema	6	2	–	1
Rash	7	2	1	–
Blurred vision	2	–	–	–
Pain	11	2	2	–
Fatigue	16	25	6	–
Dizziness	9	2	–	–
Weight loss	25	1	–	–
Weight gain	6	2	–	–
Fever	6	2	4	–
Bruising	1	–	–	–
Unsteady gait	2	1	–	–
Confusion	3	–	–	–
Headache	8	1	–	–
Stumbling	1	–	–	–
Infection	3	3	1	–
Cardiological	–	1	2	2
Hypertension	1	–	–	–
Hypotension	4	1	1	–
Neurological	3	5	2	1
Hyperglycaemia	4	7	5	1
Hyponatraemia	4	1	1	–
Hypokalaemia	2	–	2	–
Hyperkalaemia	1	–	–	–
Hypercalcaemia	–	1	–	–
Recorded, not counted in totals				
Alopecia	4	18	–	-
Lymphopenia	3	5	21	8

dose intensity received was 90.3% of planned dose (standard deviation (S.D.): 16.3%). The median was 100% (range 33.3–129.0%).

The completion of the initial assessment was easy to conduct, demanding 20 min of research nurse's time with the patients. The tolerance of the patients to the repetition of the questionnaires was good and very few refused the follow-up evaluations. However, other circumstances prevented several patients from completing the whole set of follow-up questionnaires. 37 patients completed the follow-up comprehensive assessments. Among the others, 2 refused, 1 had surgery, 2 radiation therapy, 5 were transferred to another hospital or hospice, 3 died after starting chemotherapy, and 9 did not return the questionnaires or lost contact. Because of a large number of patients who finished treatment before 3 months because of progression or toxicity, or had their end of treatment assessment at 3 months, only 18 patients had an independent comprehensive assessment at 3 months. Therefore, only the end of treatment results are reported here for FACT-G change. 34 were evaluable for FACT-G changes between the beginning and end of treatment. The mean initial FACT-G for all 59 patients was 84.68 ± 15.26. For the 34 patients evaluable for a change in FACT-G, the mean initial score was 86.82 ± 14.24, and the mean final FACT-G was 83.04 ± 14.81. The mean change was -3.78 ± 15.64.

The variables associated with the occurrence of endpoint toxicity, dose-intensity, and FACT-G change are listed in Table 5. The MAX2 score was strongly associated with toxicity: Odds Ratio (OR) 166.6 for the MAX2 range of 0 to 1 (95% confidence interval (CI) 1.32- > 1000) ($P = 0.038$). Bone marrow invasion had an OR of 3.17 (95% CI 0.93–10.67) ($P = 0.066$). Diastolic blood pressure was associated with an OR of 1.06/mmHg (95% CI 0.99–1.13) ($P = 0.082$), higher blood pressure being associated with a higher incidence of toxicity. LDH was also positively associated with toxicity: OR 1.03 per international unit (95% CI 1.001–1.05) ($P = 0.040$). A higher BMI was associated with higher dose intensity (1.2% per unit of BMI, standard error (S.E.) 0.6%) ($P = 0.047$). Previous treatment with another chemotherapy was associated with a lower dose intensity (−9.2%, S.E. 4.4%) ($P = 0.040$). Patients taking three medications or more also had a lower dose-intensity (−7.9%, S.E. 4.5%) ($P = 0.083$). The initial red blood cell count was positively associated with dose-intensity: 8.6% per million/microlitre (S.E. 4.9%) ($P = 0.087$). The initial platelet count was also positively associated: 0.04% per thousand/microlitre (S.E. 0.02%) ($P = 0.094$), most likely as a close correlate of the red blood cell count. Polymedication was again associated with FACT-G change, but this time positively: 11.1 points (S.E. 5.48) ($P = 0.052$). Interestingly, despite the strong association of MAX2 with toxicity, most variables maintained their significance in the bivariate analysis, highlighting the independent measurable contribution of patient-related factors and chemotherapy-related factors to the overall risk of toxicity.

The best endpoint was the occurrence of grade 4 haematological toxicity and/or grade 3-4 non-haematological toxicity. It was documented consistently and well retrievable from the records and primary oncologists, even in patients stopping treatment early due to progression or toxicity. The percentage of planned dose-intensity posed some analytical problems in patients supposed to be treated until progression. It may also have been sensitive to the administration of G-CSF after severe toxicity. FACT-G changes, although conveying information on the patient's well being, proved several times to be difficult to obtain, with as a result a sub-optimal amount of follow-up data for FACT-Gs being available.

Table 5
Statistically significant associations[a]

Initial parameters	Odds Ratio (95 %CI)	Univariate *P* value	Bivariate *P* value
Association with endpoint toxicity			
MAX2 (complete range)	166.6 (1.32–>1000)	0.038	Adjustment variable
Diastolic blood pressure (/mmHg)	1.06 (0.99–1.13)	0.082	0.08
Bone marrow invasion	3.17 (0.93–10.67)	0.066	0.09
LDH (/unit)	1.03 (1.001–1.05)	0.040	NS
Association with dose intensity % change (standard error)			
BMI (/unit)	1.2% (S.E. 0.6%)	0.047	0.055
Previous chemotherapy	−9.2% (S.E. 4.4%)	0.040	0.029
Polymedication (⩾3 drugs)	−7.9% (S.E. 4.5%)	0.083	NS
Red blood cells (/10E6/ul)	8.6% (S.E. 4.9%)	0.087	0.091
Platelets (1000/ul)	0.04% (S.E. 0.02%)	0.094	0.055
Association with FACT-G change point change (standard error)			
Polymedication	11.1 points (S.E. 5.48)	0.052	0.060

95% CI, 95% confidence interval; S.E., standard error; NS, non significant; LDH, lactate dehydrogenase; BMI, body mass index; FACT-G, Funcional Assessment of Cancer Treatment-General v.3.

[a] Analyses were conducted on each of the initial parameters mentioned in the Methods. Only the significant results are shown. See text for details and comments.

4. Discussion

This pilot study is, to our knowledge, the first to address tolerance to chemotherapy in an unselected population of older cancer patients treated in a tertiary cancer centre. It is also the first to prospectively address globally predictors of toxicity in cancer patients. In this patient population, most of whom would not have been eligible for therapeutic trials, the ability to deliver chemotherapy was excellent, with a mean dose-intensity of 90.3%, a median of 100%, and only 8 patients stopping treatment due to toxicity. However, many patients experienced significant side-effects. However, the use of support structures such as a tertiary care centre and a specialised geriatric oncology programme (where half of the study patients were treated) clearly allowed the continuation of treatment despite these toxicities, emphasising the need for skilled support. Practicing oncologists may be less familiar with this specific approach in the treatment of these older patients, although this is rapidly becoming mainstream practice in oncology. For example, the use of a geriatric assessment is now recommended in the National Comprehensive Cancer Network Guidelines [21].

This pilot study assessed whether there was a significant enough association between pre-treatment variables and outcome to build a predictive index. Our results indicate that this seems to be the case. Of note is the low level of interaction between chemotherapy-related variables (MAX2) and patient-related variables in the analysis, supporting the hypothesis of a mostly independent input with regard to the prognosis (Table 5). Obviously, this pilot is of a small size and contains multiple analyses; therefore false-positives and -negatives are likely. Despite our legitimate eagerness to offer our patients better predictive tools, these results should not be over-interpreted. Further testing will be needed prior to determining a validated index for clinical use, and the size of this study does not allow a reliable dichotomisation of continuous variables, such as LDH for example. Most of the associations, however, were clinically plausible. The MAX2 index had a significant association with the endpoint toxicities from treatment. Therefore this index could potentially be used to compare chemotherapies in terms of toxicity and deserves further exploration. On the other hand, many patient-related predictors retained their significance when the correlations were adjusted for MAX2, indicating that patient factors independent from those leading to the choice of the chemotherapy were influencing tolerance. Among them, previous chemotherapy or radiation therapy is a well-known predictor of tolerance to chemotherapy. Dose adaptations are often made, although not always along systematic guidelines. Tumoral marrow invasion is another well-known predictor of toxicity. One interesting finding from our study was with regard to the red blood cell count. There is significant incorporation of several chemotherapy agents into erythrocytes (e.g. methotrexate, 5-FU, anthracyclines) [22]. This aspect has as yet received little attention, but now that corrective measures are available, should be explored further for its clinical significance. Absent from the significant variables in this study were ECOG performance status and comorbidity. As these have been demonstrated to be related to tolerance to treatment in other studies [23], we assessed whether it was because performance status, comorbidity, age, or initial FACT-G led to the choice of a less toxic chemotherapy regimen. There was no significant correlation between MAX2 and these variables.

Therefore this negative results might reflect a beta-error. The correlation of body-mass index with dose-intensity may reflect sub-optimal dose adjustment in overweight patients. The occurrence of diastolic blood pressure as a predictive factor is intriguing: it might underlie a pathophysiological relationship (such as cardiovascular condition, arteriosclerosis, or concomitant medications) or be an indicator of general condition. The impact of polypharmacy on the metabolism and effectiveness of chemotherapy is only just beginning to be explored [24]. Age was not by itself associated with tolerance to chemotherapy.

Retrospective studies have highlighted a correlation between treatment intensity and the level of comorbidity or age [25,26]. Functional status impairment, glomerular filtration rate, nutritional status, have also been correlated individually with chemotherapy toxicity (reviewed in Ref. [27]) [28,29]. A retrospective study conducted in breast cancer patients receiving adjuvant chemotherapy assessed age, menstrual history, time from surgery and type of surgery, oestrogen receptor (ER) and progesterone receptor (PR) status, initial blood count, first cycle nadir counts, and type of chemotherapy. Pretreatment variables were not predictive of neutropenia, dose-reduction, or delay, whereas a model based on first cycle nadir neutrophil count was predictive of subsequent events (c-statistic = 0.78–0.87) [1]. A similar study in lymphoma patients analysed sex, age, performance status, tumour stage, marrow involvement, albumin, LDH, Beta-2-microglobulin, histology, and tumour necrosis factor (TNF) levels. Intensity of chemotherapy, stage, B symptoms, albumin, Beta-2 microglobulin, and TNF levels were associated with grade 4, prolonged, or febrile neutropenia [4]. A study conducted in cancer patients treated with various chemotherapy regimens identified a predictive model for the risk of anaemia. The variables analysed were age, sex, number of previous chemotherapies, use of a high risk chemotherapy, cisplatin-containing therapy, performance status, 'comorbidities that could influence the choice for blood transfusion', pretreatment haemoglobin, lymphocyte, and neutrophil counts. A model built on pretreatment haemoglobin level, lymphocyte count, and performance status allowed classification of patients into groups with a probability of receiving transfusions of 1, 4, 11 and 30%, respectively [3]. In a retrospective analysis of phase I and II studies with docetaxel, Bruno and colleagues identified alpha-1 acid glycoprotein, docetaxel exposure (as measured by various pharmacokinetic parameters during the initial cycle of chemotherapy), baseline neutrophil count, and number of previous chemotherapy regimens as predictors of grade 4 neutropenia. Total protein, alpha-1 acid glycoprotein, initial docetaxel exposure and cumulative dose of docetaxel were predictors of fluid retention [2]. The other variables analysed were age, sex, performance status, body surface area, presence of hepatic metastases, hepatic tests, proteins, albumin, creatinine. As mentioned in the introduction, the four retrospective studies mentioned above have typically included very few clinical parameters with relevance for older cancer patients, used very targeted toxicity endpoints, and are limited by the quality of the available records. More recently, a prospective study from Thailand was reported, exploring predictors of the risk of neutropenia and febrile neutropenia in lymphoma patients receiving CHOP. These were mostly young patients (20% were 60 years and older). Age, sex, histological subtype, B symptoms, bulky disease, bone marrow invasion, number of extranodal sites, LDH, stage, WHO performance status, international prognostic index, CBC, bilirubin, alanine aminotransferase, creatinine, and albumin were explored. Albumin $\leqslant 3.5$ g/l, LDH, and bone marrow involvement permitted the identification of three risk groups for neutropenia and febrile neutropenia during the first course of CHOP [30].

A prospective approach such as the one used in this study offers the optimal setting to control rigorously both treatment and pretreatment variables, notably specific geriatric elements, which maximises the power to detect significant correlations with toxicity. It also proved to be very feasible with good data quality, with the exception of a significant loss of patient data for the quality of life evaluation. This pilot demonstrates that designing a larger study to create a global predictive risk index for toxicity from chemotherapy is feasible and likely to be fruitful. Such an index should have two components: one assessing the intrinsic toxicity from the chemotherapy (such as the MAX2 index), and the other based on patient-related variables.

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