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Chemotoxicity recurrence in older patients: Risk factors and effectiveness of preventive strategies. A prospective study

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Abstract

Purpose—The Common Terminology Criteria for Adverse Events(CTCAE) and adjustment rules after severe toxicity are derived by consensus, but little is known about the determinants of toxicity recurrence, especially in the elderly.

Patients and Methods—We prospectively accrued 200 patients (≥ 65 years) prior to chemotherapy. For those with grade 3–4 non-hematologic or grade 4 hematologic toxicity (severe toxicity), we recorded duration and functional impact, treatment modifications, and severe toxicity recurrence. The regimen's toxicity was adjusted with the MAX2 index.

Results—Median patient age was 73 years(range 65–90). Among 163 patients evaluable for toxicity after 1 treatment cycle (receiving on average 4.73 cycles), 82 had severe toxicity, 10 were discontinued for toxicity, 6 for other reasons, and 5 died. Sixty-one patients had further chemotherapy, 41 without dose modification (16 with secondary prevention measures) and 20 with dose modifications. Without modification, 19(46%) had a recurrence (0 death). With modification, 7(35%) had a recurrence (1 death). In univariate analysis, treatment intent, hospitalization, and duration-adjusted Activities of Daily Living (ADL), quality of life impact, and fatigue were associated with dose modification. ADL remained associated in multivariate analysis($p=0.02$). In univariate analysis for toxicity recurrence, ECOG PS and MAX2 score showed an association, with only the latter remaining significant in multivariate analysis($p=0.04$).

Conclusions—If a severe toxicity does not have a long ADL impact, oncologists are less inclined to modify treatment. With proper supportive measures, this leads to recurrence risks similar to those shown in patients with modified treatment, with low risks of toxic deaths overall.

Keywords

Chemotherapy; elderly; chemotherapy toxicity; management of chemotherapy toxicity; MAX2 index; geriatric oncology; functional status; quality of life; CTCAE

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Introduction

Assessing the severity of side effects from chemotherapy in a reproducible manner is a familiar issue for clinical trialists. Over the years, the National Cancer Institute has developed a consensus definition: The Common Terminology Criteria for Adverse Events (CTCAE), now in its fourth version.¹ Clinical trials often recommend treatment modification in cases of grade 4 hematologic or grade 3–4 non-hematologic toxicity. Although grade 3 hematologic toxicity is often lumped in the group, dose modifications are rarely recommended for grade 3 neutropenia or leukopenia, the most frequent of them by far. Grade 4 hematologic toxicity and/or grade 3–4 non-hematologic toxicity (hereafter called “severe toxicity”) is experienced by half or more of older cancer patients in a clinical setting.^{2,3} However, we observed that the functional impact of those toxicities is variable and that chemotherapy is often continued at good doses.² When we explored further the appropriateness of this management approach, we were surprised to note that, in clinical practice, 2/5 of older patients did not have dose modifications and that this appeared to be safe, with actually less recurrences of toxicities in the patients without dose modifications.⁴ Since no direct correlation with patients’ baseline characteristics was noted, this suggested some factor recognized by the clinician at the time of toxicity. We hypothesized that, if a severe toxicity was short and did not have a functional impact, it would be safe to continue the chemotherapy at full dose. Furthermore, identifying older patients at low risk of further toxicity has a clear potential for improving treatment delivery and patient outcomes. In this study, we addressed two questions: 1) Do short toxicities with low functional impact correlate with maintenance of treatment dose by the oncologist? 2) Does that targeted dose maintenance lead to an equal or lower recurrence of toxicity versus that shown in patients who had dose modification after toxicity?

Methods

This was a prospective observational cohort study of patients treated with chemotherapy at Moffitt Cancer Center. Patients had to be >65 years old and have a histologically or cytologically documented malignant tumor. A chemotherapy regimen that included at least one classic chemotherapy agent had to be planned. The chemotherapy regimen and management were left to the discretion of the treating oncologist, as long as it was a published regimen and was not an aplasiant treatment (e.g., an acute leukemia or a transplant regimen). The toxicity of the regimen was rated with the MAX2 index.^{2,5} Briefly, The MAX2 index is the average of the most frequent grade 4 hematologic toxicity and the most frequent grade 3–4 non hematologic toxicity reported in publications of a regimen and correlates well with the average overall risk of severe toxicity for that regimen. Exclusion criteria were diagnosis of dementia, chemotherapy within less than 3 weeks, life expectancy less than 3 months, and concomitant radiation therapy. Palliative radiation to less than 25% of bone marrow was allowed but had to be completed before chemotherapy. All other radiation needed to be completed at least 4 weeks prior to chemotherapy. Adequate English and cognitive skills were required to provide written informed consent and answer the study questionnaires. Baseline functional status was assessed with ECOG Performance Status (PS),⁶ Katz’ Activities of Daily Living (ADL),⁷ and Lawton’s 9-item Instrumental ADL (IADL).⁸ Fatigue was assessed with the Fatigue Symptoms Inventory (FSI),⁹ using the

interference score (0 being best). Comorbidity was assessed with the Cumulative Illness Rating Scale-Geriatric.¹⁰ Toxicity assessment was prospective. Weekly complete blood counts (CBC) were required. Initially, these were required for the entire treatment duration; however, the protocol was later amended to allow low-risk patients (i.e., patients who did not experience any neutropenia during the first cycle and had a regimen with a MAX2 score <0.20¹¹) to forgo weekly CBCs after the first cycle. Patients were assessed at each pre-chemotherapy visit according to CTCAE v.4, and occurrences of grade 4 hematologic toxicity or grade 3–4 non-hematologic toxicity (severe toxicity) were recorded, as well as whether treatment was modified as a consequence. Modifications of dose or drugs in the chemotherapy as well as modifications of supportive measures were tallied. The functional impact of the toxicity was rated with ECOG PS, ADL, IADL, FSI interference score, and a quality of life (QOL) impact question, rated from 0 (not at all) to 10 (terrible). We chose a unidimensional QOL scale for the following reasons: such scales have been validated by Sloan et al., and their performance compares well with multidimensional QOL instruments¹²; rating symptom intensity on a scale of 0 to 10 is familiar to patients; and, as we sought to identify factors that influence oncologists' decision making, we wanted a measure close to clinical practice, where typically simple short QOL questions are asked. Function and QOL were assessed at the first visit after severe toxicity occurrence, and duration of the toxicity (either patient-reported or clinically measured) was recorded. Patients were reassessed at each subsequent pre-chemotherapy visit with the same functional/QOL assessment, with recurrence of severe toxicity recorded. Follow-up was until the end of the last chemotherapy cycle or an upper time limit of 6 months. The magnitude of the dose modifications was calculated using Hryniuk's relative dose-intensity method.¹³ The study was approved by the Institutional Review Board of the University of South Florida.

Statistical analysis

A sample size of 200 patients was calculated as having an 80% power of detecting odds ratios for treatment change of 1.5 or greater on logistic regression with a nominal alpha of 0.05, and deemed feasible within the 2-year duration of our funding grant. The same analytic approach was used for both outcome variables: treatment modification (in increasing severity: none, modified, stopped) and toxicity recurrence (yes/no). First, we conducted univariate analyses to identify clinical and toxicity parameters that, by themselves, were correlated with outcome. Next, we entered univariate factors with correlates having a *p* value of 0.05 or less into a multivariate regression model to identify which factors accounted for unique variance in outcome likelihood. A hierarchical linear regression model was used to test treatment modification status. Because our hypothesis was that treatment would be maintained in case of short low-impact toxicity, we ran the analysis with two models: one in which the duration and functional impact of the toxicity were treated independently, and one where the functional impact scores were multiplied by the duration of the severe toxicity. A binary logistic regression model was used to test toxicity recurrence. We explored both the absolute value of the variable (e.g., IADL score) and the value expressed as a change from baseline (e.g., baseline IADL - toxicity IADL).

Results

Two hundred patients were accrued between October 2009 and May 2011. The evolution of patients throughout their chemotherapy is presented in Figure 1 (CONSORT diagram). One hundred sixty-three patients were fully evaluable for toxicity. The median age of the patients was 73 years (range 65–90). The baseline characteristics were similar between the patients who did and those who did not experience severe toxicity, with the following exception: Whereas 45% of the cohort was female, 87% of those with toxicity were female vs. 3% of those without (Table 1). This is not a common finding in similar studies.^{3,14,15} One explanation lies in the fact that women did on average receive more toxic chemotherapies (mean MAX2 F: 0.15; mean MAX2 M: 0.12; $p=0.04$). Although there may have been additional selection factors or random effects, no other baseline variable was significantly different. The regimens used and their MAX2 indexes are listed in Table 2. The most frequent regimen was single-agent gemcitabine (25% of patients). For the remainder, 35% were platinum-containing combinations, 23% taxane-containing regimens, 10% anthracycline-containing regimens (with some overlaps), and 12% were regimens containing none of these 3 types of agents.

The median time to first toxicity was 29 days (range 1 to 180). Forty-six percent of patients experienced their first severe toxicity during the first cycle, 24% during the second cycle, 17% during the third cycle, and 12% beyond the third cycle. The median duration of the initial toxicity was 7 days (range 0 to 20), and 30 patients were hospitalized (23 continued treatment). Fifty patients experienced a grade 3–4 non-hematologic toxicity, and 33 patients had a grade 4 hematologic toxicity (one had both). The median perceived impact of the toxicity on QOL was 7 (0–10), the median number of impaired ADL was 0 (0–4), the median IADL score was 25 (14–29), the median ECOG PS was 1 (0–4), and the median FSI interference score was 13 (0–59). The mean number of cycles received was 4.61(SD 1.28) vs. 4.89(SD 1.43) in the group with and without toxicity, respectively, allowing a good follow-up after first toxicity. The median received dose-intensity was 87%(range 17–117%). It was 94%(33–117) in patients without severe toxicity, and 79%(17–102) in the patients with it. Among the latter, dose intensity received was 96%(33–102) in those with dose unchanged at the time of first severe toxicity, 73%(41–93) in those with a dose change, and 67%(17–100) in those who stopped (wide range interval due to heterogeneous reasons for stopping).

Treatment adaptation

Of the 82 patients who had a severe toxicity, 5 died, 6 discontinued treatment for unrelated reasons, and 10 discontinued treatment for toxicity. Sixty-one patients continued treatment, of which 20 had a change in their regimen. The other 41 had no dose change but 16 had secondary prevention measures: 5 had antibiotic prophylaxis; 3 anticoagulation, 2 granulocyte growth factors; 2 pain medicines; and 5 had other measures (some patients had multiple measures). There were no clear differences in tumor type, stage, or toxicity subtype between patients who did or did not receive secondary prevention measures. Recurrences of toxicity occurred in both subsets. On univariate analysis without duration adjustment, the characteristics associated with treatment modifications were treatment with curative intent

($p < 0.05$), hospitalization ($p < 0.05$), impact on QOL ($p < 0.05$), and ADL score ($p < 0.01$) (Table 3). In the multivariate analysis, no variable was significant at the $p < 0.05$ level, although ADL showed a trend at 0.08 (Table 4). This overall model had an adjusted R^2 of 0.11. In the duration-adjusted analysis, treatment with curative intent ($p < 0.05$), hospitalization ($p < 0.05$), and impact on QOL*duration ($p < 0.05$), ADL*duration ($p < 0.01$), and FSI*duration ($p < 0.05$) were associated with treatment modification. On multivariate analysis, one variable, ADL*duration, remained significant ($p = 0.02$), whereas hospitalization showed a trend ($p = 0.092$), with a better overall performance of the variables (Table 5). This model explained nearly twice as much variance in modification (adjusted $R^2 = 0.21$) as did the model that was not duration-adjusted. We repeated the analyses using the degree of change from baseline, but the absolute values at the time of toxicity provided more precise results (results not shown). A significant amount of variance remains unexplained. Part of that may be due to our relatively low number of patients, and the R^2 for the same variables might increase in a larger sample. We suspect that, in the absence of well-established data and guidelines, a good amount of residual variance simply reflects inter-physician variation. We explored whether comorbidity level might explain part of this variance. However, the baseline CIRS-G total score was not associated with treatment change (OR=0.99, CI=0.89–1.11, $p = 0.88$)

Recurrence of severe toxicity

For this analysis, 61 patients were available, since the 10 patients who stopped chemotherapy for toxicity could not provide recurrence information. Sixteen patients had a grade 4 hematologic toxicity and 10 a grade 3–4 non hematologic toxicity. Thirteen patients recurred with the same toxicity as the original one, whereas 13 recurred with a different toxicity. The recurrence rate was 46% (95% CI: 31–62%), no death, in the group without modification, and 35% (95% CI: 14–56%), one death, in the group with modification. On univariate analysis, the MAX2 score (0.13 ± 0.07 in the group without recurrence vs. 0.17 ± 0.09 in the group with) and the ECOG PS (0:16%; 1–2:84% vs. 0:39%; 1–2 54%; 3–4:7%) were the only variables associated with toxicity recurrence ($p < 0.05$) (Table 6). Specific secondary prophylaxis had no additional impact. In the multivariable analysis, the MAX2 score remained associated with toxicity recurrence (OR=1.96, 95% CI 1.05–2.79, $p < 0.05$), whereas ECOG PS results were not significant (OR=1.47, 95% CI = 0.57–3.79, $p = .42$). We explored whether baseline comorbidity influenced recurrence of toxicity. The baseline CIRS-G total score was not associated with recurrence (OR=0.99, CI= 0.89–1.12, $p = 0.97$).

Effectiveness of dose-adjustment strategies

We performed a series of analyses to identify an effective dose modification approach for possible use in future clinical trials. There were two dominant patterns of dose modifications: dose delay alone and dose reduction with or without delay. After dose delay alone, 6/8 patients had a recurrence of toxicity vs. 1/12 with reduction and 19/41 without ($p = 0.009$). Therefore, dose delay alone was not an effective dose modification strategy. We analyzed whether patients with uncomplicated grade 4 neutropenia were relapsing simply with an uncomplicated grade 4 neutropenia. However, the pattern of recurrence was heterogeneous with both hematologic and non-hematologic severe toxicity. Although our numbers are small, they do not support treating grade 4 neutropenia fundamentally

differently from other toxicities (although it is less likely to have QOL and functional impact). We analyzed hospitalization, low ADLs, impact on QOL, and duration of toxicity alone and in combination in order to model the most discriminative approach in terms of prevention of recurrent toxicity. However, due to our limited numbers and heterogeneous impact of dose modification strategies, we could not identify a clearly dominant strategy.

Discussion

There is surprisingly little published data on the recurrence of toxicity from chemotherapy. Typical clinical trials report the most severe grade of a given toxicity but not the number of times the toxicity occurred in a given patient. Some studies have focused on specific toxicities, such as neutropenia or cardiac toxicity, usually in relationship to a specific secondary prevention (e.g.^{16,17}). To our knowledge, our study is the first to investigate the global effectiveness of management of toxicity in daily practice. Our findings suggest that the present CTCAE, established by expert consensus, might be improved by integrating the functional impact of a given toxicity. We hypothesized that severe toxicities by CTCAE 4.0 that are brief and of low functional impact would be associated with maintenance of treatment plan and that this approach would be safe. Our results support the validity of our hypotheses, although confirmation and development in larger cohorts will be needed. The best correlation with treatment modifications was obtained by variables that combined toxicity duration and functional impact. One might argue that the duration of a severe functional impact might have been better measured with patient diaries. However, our primary goal was to understand which factors influence the decisions of an oncologist in daily practice. Diaries are not typically available in this setting, but recall information at the subsequent visit is. Future trials more oriented toward identifying a threshold functional impact and its duration to inform post-toxicity decisions might opt for using a diary approach. From a safety point of view, all the treatment-related deaths, except one, occurred at the time of the first toxicity, early in the treatment. This is compatible with other literature data. For example, in a study in older lymphoma patients treated with CHOP and G-CSF, 22/35 treatment-related deaths occurred during the first cycle.¹⁸ The present study, however, highlighted a heterogeneous effectiveness of the management strategies in preventing a recurrence of severe toxicities. The approach that was purely delaying treatment without dose reduction did not appear to be effective. This finding might be taken into consideration when designing toxicity management schemes in future clinical trials.

The only factor associated with recurrence of toxicity was the MAX2 score ($p=0.04$). This constitutes a further validation of this useful index in conducting comparisons between chemotherapy regimens. However, it should be noted that the total number of severe toxicity recurrences was small (26); therefore, the proportions in each treatment group have wide overlapping confidence intervals.

The median time to first toxicity was short: 29 days. In the CRASH trial, it was 22 days.³ Taken together with the amount of complications from first toxicity (Figure 1), this highlights the critical need for a proper design of the chemotherapy plan in the elderly. Recently, several models have become available that may assist with decision making.^{3,14,15,19} Some aim at predicting the risk of CTCAE severe toxicity,^{3,14} whereas

others focus on the ability to complete chemotherapy.^{15,19} Collectively, they highlight the importance of considering geriatric parameters when planning chemotherapy. Future research should focus on the best way to use these models in clinical trial design, so that an appropriate chemotherapy dose can be given at the first cycle: both high enough to be effective and low enough to decrease the important drop-out due to severe initial complications. A formal study of dose-adjustment strategies that integrate functional impact of the first toxicity might compare the dose intensity achieved with this alternate strategy versus standard dose reduction schemes. Observing such a difference would be a first step in our attempt to improve the outcomes of older patients treated with chemotherapy.

Our study has limitations. It is a single institution study in a large academic center. Oncologists in other settings such as private practice might apply different rules and our findings might not extend to them. Our results should not be used in clinical practice until validated by studies conducted in other populations. Our study size is also relatively small. This limits the generalizability of our findings, notably the negative ones, and other variables may be found in future studies that also influence recurrence of severe toxicity. Larger studies will help refine our understanding of this important clinical issue.

In conclusion, if a severe toxicity does not have a long ADL impact, oncologists in an academic setting are less inclined to modify treatment. With proper supportive measures, this strategy appears to lead to recurrence risks similar to those shown in patients who had modified treatment, with low risk of toxic deaths overall. This finding needs to be confirmed and further detailed in larger studies. Our study confirmed the overall safety of the dose reduction strategies used, although their effectiveness could be optimized. In clinical trials, adjusting dose reduction recommendations to duration and functional impact of toxicity might lead to less dose reductions and better dose intensity throughout the trial. Further research is needed to find the best way to design these adjustments.

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Figure 1.
CONSORT diagram

Table 1

Baseline patient and cancer characteristics and treatment patterns

	Total(n=163)	Severe toxicity (n=82)	No severe toxicity (n=81)
Age, years: median(range)	73(65–90)	73(65–89)	73(65–90)
Men/women, %	55/45	13/87	97/3
Race, %			
African American	4	2	6
Asian	1	0	1
White	95	98	93
ECOG PS, %			
0	42	38	46
1	42	43	42
2	12	15	10
3–4	4	5	3
ADL, %			
Independent	90	89	91
Impaired	10	11	9
IADL, %			
Independent(28–29)	44	42	46
Dependent(<28)	56	58	54
FSI - TDI score, mean(SD)	14.54(14.08)	17.34(15.01)	11.7(12.53)
CIRS-G total score	8.42(3.82)	8.67(3.94)	8.17(3.70)
Number of medications, mean(SD)	8.94(4.49)	9.48(4.81)	8.41(4.10)
Tumor type, %			
Breast	15	17	14
GI	45	41	43
GU	4	4	4
Hematologic	13	15	12
Lung	17	16	19
Other	5	1	9
Tumor stage, %			
I	4	7	1
II	16	16	16
III	16	21	11
IV	63	56	70
Prior treatment, %	64	60	68

	Total(n=163)	Severe toxicity (n=82)	No severe toxicity (n=81)
Treatments' average MAX2 score			
M	0.12	0.15	0.12
F	0.15**	0.14	0.16
Treatment intent, %			
Adjuvant/curative	37	43	31
Palliative	63	57	69
Primary growth factors support, %	19	24	14
Tumor response, %			
Adjuvant	14.3	14.8	13.4
Complete response	1.4	2.1	0
Partial response	6.0	4.8	8.0
Stable disease	7.1	6.9	7.5
Progressive disease	3.1	3.0	3.2
Non-assessable *	56.9	56.5	57.8
Number of cycles received, mean (SD)	4.73(1.35)	4.61(1.28)	4.89(1.43)

* Non-measurable at baseline, or end of treatment before next response assessment.

** Statistically different between men and women, p=0.04.

CIRS-G, Cumulative Illness Rating Scale-Geriatric.

Table 2

Regimens used and their MAX2 index.

Regimen	MAX2
5-FU (de Gramont) *	0.025
5-FU (Roswell-Park)	0.183
5-FU/mitomycin *	0.029
AC	0.223
Bendamustine + R	0.101
Capecitabine 2g/m2	0.06
Carboplatin/paclitaxel q3w	0.149
Carboplatin/paclitaxel q4w *	0.139
Carboplatin/paclitaxel weekly *	0.094
Carboplatin/irinotecan weekly *	0.074
Carboplatin/pemetrexed	0.089
CEOP-R *	0.341
CHOP	0.341
CHOP-R *	0.341
Cisplatin/etoposide	0.277
Cisplatin/gemcitabine	0.117
Cisplatin/irinotecan	0.262
Cisplatin/pemetrexed	0.079
Cisplatin/vinblastin/temozolomide *	0.165
CVP + R *	0.043
Docetaxel q3w	0.193
Docetaxel/carboplatin + H *	0.189
Docetaxel/carboplatin + H weekly *	0.094
Docetaxel/cyclophosphamide (TC) *	0.235
Docetaxel/cyclophosphamide + H *	0.235
ECF	0.149
FEC 100/docetaxel *	0.117
FOLFIRI + B *	0.075
FOLFOX	0.119
FOLFOX + B *	0.119
Gemcitabine/carboplatin	0.135
Gemcitabine weekly [#]	0.077
Gemcitabine/docetaxel *	0.132

Regimen	MAX2
Gemcitabine/docetaxel/capecitabine(GTX) *	0.174
Irinotecan/cetuximab *	0.306
Nab-paclitaxel weekly + H *	0.051
Nab-paclitaxel weekly *	0.051
Nab-paclitaxel/mitomycin *	0.051
Pegylated doxorubicin	0.089
Vinorelbine weekly [#]	0.111
XELOX	0.134

If leucocyte growth factors are included as primary prophylaxis, the MAX2 score is decreased by 0.06.

Abbreviations: 5-FU=5-fluorouracil; AC=doxorubicin/cyclophosphamide; B=bevacizumab; CEOP=cyclophosphamide/epirubicin/vincristine/prednisone; CHOP=cyclophosphamide/doxorubicin/vincristine/prednisone; CVP=cyclophosphamide/vincristine/prednisone; ECF=cisplatin/epirubicin/5-FU; FEC100=5-FU/epirubicin/cyclophosphamide; FOLFIRI=5-FU/leucovorin/irinotecan; FOLFOX=5-FU/leucovorin/oxaliplatin; H=trastuzumab; R=rituximab; XELOX=capecitabine/oxaliplatin.

* Optimally, the MAX2 score is derived from 3 studies with good quality toxicity reporting. Scores with * are derived from studies with lesser quality reporting or less than 3 studies.

[#] may include a “skip week” e.g. 3 out of 4 weeks schedule.

Table 3

Characteristics associated with treatment plan modifications after first severe toxicity: univariate analysis

	Unchanged (n=41)	Modified (n=20)	Stopped (n=10)	Total(n=71)	P value
Age, years, mean (SD)	72.44(5.29)	72.85(4.85)	73.13(5.34)	72.69(5.12)	NS
Sex, % female	100	85	100	96	NS
Treatment intent, %curative	56	25	33	43	<0.05
MAX2 score ^{d)} , mean (SD)	.16(.09)	.12(.07)	.15(.08)	.15(.08)	NS
Severe toxicity type (Hematologic versus non-hematologic), %G4H	46	50	20	42	NS
Toxicity subtype, %					NS
Neutropenia	39	50	7	35	
GI	8	10	27	12	
Infection/FN	5	5	20	8	
Other	49	35	47	45	
Severe toxicity duration, days, mean (SD)	7.12(3.35)	8.7(4.58)	8.43(3.78)	8.08(3.79)	NS
Hospitalization for severe toxicity, % Yes	21	30	60	31	<0.05
Severe toxicity QOL ^{a)}	5.45(4.11)	5.70(4.04)	8.92(1.98)	6.15(3.97)	<0.05
Severe toxicity ADL ^{a)}	.18(.69)	.25(.72)	.77(.93)	.31(.77)	<0.01
Severe toxicity IADL ^{b)}	25.21(3.20)	24.25(2.67)	24.23(3.00)	24.76(3.02)	NS
Severe toxicity ECOG PS, % ^{a)}					NS
0	29	20	15	24	
1-2	69	75	70	71	
3-4	3	5	15	5	
Severe toxicity FSI ^{a)}	16.7(12.99)	15.60(11.01)	20.08(14.89)	17.01(12.75)	<0.05

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^{a)} Higher score = worse;
^{b)} higher score = better.

ADL =Activities of Daily Living; ECOG PS =ECOG performance status; FSI =Fatigue Symptom Inventory; G4H, grade 4 hematologic toxicity; IADL =Instrumental ADL; QOL =quality of life.

Characteristics associated with treatment plan modifications: multivariable analysis without impact duration adjustment

Table 4

Model	Unstandardized Coefficients		Standardized Coefficients		t	Sig.
	B	Std. Error	Beta			
1	Constant	0.214			0.415	0.680
	Severe toxicity hospitalization	0.422		0.173	1.374	0.174
	Severe toxicity QOL	0.055		0.196	1.527	0.131
	Severe toxicity ADL	0.305		0.209	1.749	0.085
	Intent of treatment	0.040		0.018	0.144	0.886

For coefficients, the dependent variable was modification. ADL=Activities of Daily Living; QOL =Quality of Life

Table 5

Characteristics associated with treatment plan modifications: multivariable analysis with duration-dependent variables

Model	Unstandardized Coefficients		Standardized Coefficients		t	Sig.
	B	Std. Error	Beta			
(Constant)	0.584 -0.200	0.454			1.286	0.203
Intent of treatment		0.256	-0.2000.094		-0.2000.781	0.438
Severe toxicity hospitalization	0.471	0.276	0.204		1.711	0.092
ST QOL*duration	0.005	0.003	0.197		1.590	0.117
ST ADL*duration	0.051	0.020	0.305		2.470	0.016
ST FSI*duration	0.000	0.001	0.034		0.253	0.801

For coefficients, the dependent variable was modification.

ST =Severe toxicity, QOL =quality of life, ADL =Activities of Daily Living, FSI =Fatigue Symptom Inventory.

Table 6

Characteristics associated with recurrence of severe toxicity: univariate analysis.

	No Recurrence	Recurrence	P value
Number of patients	35	26	
Age, years	73.21(4.70)	71.77(5.56)	NS
%Female	94	96	NS
Treatment intent, %curative	46	46	NS
Treatment change at first toxicity, %yes	39	27	NS
MAX2 score	0.13(0.07)	0.17(0.09)	<0.05
Severe toxicity type, %G4H	46	50	NS
%G4 Neutropenia	42	42	NS
Severe toxicity duration	8.39(3.95)	7.54(3.68)	NS
Severe toxicity hospital, %Yes	24	23	NS
Severe toxicity impact on QOL	5.56(3.95)	5.50(4.25)	NS
Severe toxicity impact on ADL	0.22(0.75)	0.19(0.63)	NS
Severe toxicity impact on IADL	24.84(2.97)	24.92(3.17)	NS
Severe toxicity impact on ECOG PS, %			<0.05
0	16	39	
1–2	84	54	
3–4	0	7	
Severe toxicity impact on FSI-TDI	15.50(11.98)	17.35(12.76)	NS
Specific 2 nd prophylaxis, %Yes	28	23	NS