MOX-Report No. 72/2022

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Novel longitudinal Multiple Overall Toxicity (MOTox) score to quantify adverse events experienced by patients during chemotherapy treatment: a retrospective analysis of the MRC BO06 trial in osteosarcoma

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Abstract

Aim: This work is intended to study the evolution of chemotherapy-induced toxicity over treatment, introducing a new method for summarize multiple toxic adverse events (AEs), i.e., the longitudinal Multiple Overall Toxicity (MOTox) score. A retrospective analysis of patients from MRC BO06/EORTC 80931 Randomized Controlled Trial for osteosarcoma was conducted.

Methods: Patients were randomised to six cycles of conventional versus dose-intense regimens of doxorubicin and cisplatin. Non-haematological toxicity data were collected prospectively and graded according to the Common Terminology Criteria for Adverse Events (CTCAE). The MOTox score was defined by condensing the worst AE and the overall toxic condition, including a time dimension. Multivariate models were constructed to assess the evolution of high overall toxicity, examining cycle-by-cycle the impact of personalized characteristics, such as achieved chemotherapy dose, previous toxic events, or biochemical factors.

Results: The flexible longitudinal depiction of MOTox score represents the strength of our method. A cycle-by-cycle dimension allowed to reconstruct different evolution patterns over treatment, leading to informative ramifications on patients' health statuses. Patient's toxic history played an important role in the quality of life over therapy, showing an autoregressive impact of previous toxicity. Conventional regimen had to be preferred to dose-intense one in terms of toxic AEs in the first half of the treatment.

Conclusion: This study shows that working in this direction is a difficult but profitable approach. The flexibility of our method, added to a cooperation with medical staff, could lead to improvements in the definition of useful tools for health care assessment and treatment planning.

Keywords: Osteosarcoma, Toxicity, Chemotherapy, Longitudinal data, Prediction models

1. Introduction

Osteosarcoma is a malignant bone tumour mainly affecting children and young adults. Although osteosarcoma is the most common primary malignant bone cancer, it is a rare disease and has an annual incidence of 3-4 patients per million (Smeland *et al.*, 2019). Multidisciplinary management including neoadjuvant and adjuvant chemotherapy with aggressive surgical resection (Ritter and Bielack, 2010) or intensified chemotherapy (Lewis et al., 2007) has improved clinical outcomes but over the past 40 years there have been no further improvements in survival.

In cancer trial, the relationship between chemotherapy dose and clinical efficacy outcomes are problematic to analyse due to the presence of a negative feedback between exposure to cytotoxic drugs and some peculiar aspects, such as latent accumulation of chemotherapy-induced toxicity. Toxic Adverse Effects (AEs), developed by patients through a chemotherapy cycle, affect subsequent exposure by delaying the next cycle or reducing its dosage, representing one of the principal reasons for treatment discontinuation (Souhami *et al.*, 1997). The introduction of the Common Terminology Criteria for Adverse Events (CTCAE) (U.S. Department of Health and Human Services, 2006) multimodality grading system greatly facilitated the standardized reporting of AEs and the comparison of outcomes between trials and institutions (Trotti *et al.*, 2003). According to CTCAE, AEs range in severity from minor, asymptomatic changes noted on physical examination to life-threatening injuries or death (Trotti *et al.*, 2003). CTCAE promoted a more complete recognition of toxicities, representing now the predominant set of toxicity criteria for cancer clinical trials and scientific meetings (Trotti *et al.*, 2003; Zhang, Chen and Wang, 2016). Characterisation of toxicity is of interest to patients and clinicians engaged in shared decision making about a treatment strategy (Thanarajasingam *et al.*, 2016). Toxicities are at the same time risk factors for mortality and predictors of future exposure levels, representing time-dependent confounders for the effect of chemotherapy on patient's status (Lancia *et al.*, 2019). Incorporating the dimension of time into analysis of toxicity is also important in accurately comparing different chemotherapy regimens or even multiple toxicities from the same regimen (Thanarajasingam *et al.*, 2015). For all these reasons, it is extremely important to provide an effective tool to assess the evolution of overall toxicity over chemotherapy treatment and to guide the diagnosis.

Since patients might have different types and amounts of adverse events, summarising the multiple facets of toxicity during treatment and understanding the true extent of toxic burden represent challenging problems in cancer research. Due to the complexity of longitudinal chemotherapy data, no uniform method exists for summarising the key elements of different AEs data into a concise score of overall risk. Toxicity data are usually considered in very simplistic ways in cancer prediction models, where they act as fixed maximum toxicity over time (*max-time*) or maximum grade among events (*max-grade*) (Trotti *et al.*, 2007; McTiernan *et al.*, 2012; Thanarajasingam *et al.*, 2015; Thanarajasingam *et al.*, 2016; Zhang, Chen and Wang, 2016). Both methods can summarise large volumes of data over time, discarding substantial amount of information. On one hand, using the *max-time* method, also known as the maximum-severity or worst-grade method (Trotti *et al.*, 2007), event data related to multiple temporal points are summarized into a single AE profile by using the worst (highest) grade over the entire treatment period for each toxic event. However, this approach treats isolated and repeated episodes in the same way. For example, an isolated episode of grade 2 mucositis ulcers during treatment is considered the same as grade 2 chronic mucositis ulcers occurring at each cycle, but the second case has a substantial cost to patient's quality of life which is not included in the toxicity assessment. On the other hand, the *max-grade* method summarises all the toxic AEs through the maximum grade among all types of events (Trotti *et al.*, 2007). However, this approach treats single and multiple episodes in the same way. For example, a patient who suffers a single grade 3 event and a patient with three separate grade 3 events have the same *max-grade*, since only one grade 3 event is counted by the summary. Moreover, both approaches discard valuable information related to longer-lasting lower-grade chronic toxicities, adverse event timing or its severity at a given cycle during treatment. The inclusion of time-related information could provide a more comprehensive depiction of adverse events and their evolution over time (Thanarajasingam *et al.*, 2016). All these aspects are of clinical

relevance and contain valuable information related to patient's status and quality of life which could give new insights for cancer treatment.

In this framework, alternative methods of longitudinal and graphical adverse event evaluation have been proposed (Atherton, 2003; Trotti *et al.*, 2007; Thanarajasingam *et al.*, 2016) but none of them is focused on an ongoing analysis to examine the evolution of high overall toxicity over chemotherapy treatment. To improve the methods for summarising and quantifying risk in oncology, a new longitudinal Multiple Overall Toxicity (MOTox) score is proposed. At each cycle, the developed MOTox score summarises multiple CTCAE-graded adverse events, capturing both the overall toxic status and the most severe risk event. Then, the evolution of high MOTox scores over cycles is studied using different logistic regression models to predict high overall toxicity at the end of the cycle using personalized patterns over time (i.e., achieved chemotherapy dose, previous toxicities, biochemical and haematological factors). Two main novelties are hence proposed: (i) the introduction of a new method for summarize multiple toxic AEs including time-dimension, i.e., the longitudinal MOTox score, and (ii) the cycle-by-cycle analysis of high overall toxicity over treatment, using personalized characteristics. Provided that longitudinal data are available from drug administrations (doses in mg/m^2, biochemical measurements and CTCAE-graded toxicity), the procedure presented here is really flexible and appropriate to analyse chemotherapy treatments in general.

To explore how chemotherapy-induced toxicities evolve in patients with high-grade osteosarcoma, a retrospective analysis was conducted on MRC BO06/EORTC 80931 Randomized Controlled Trial (Lewis et al., 2007) for patients treated with cisplatin (CDDP) and doxorubicin (DOX). CDDP and DOX are cytotoxic drugs commonly used in the treatment of various types of human cancers and are characterized by various toxic AEs, including nausea and neurotoxicity for CDDP (Gregg *et al.*, 1992; Aldossary, 2019) or cardiotoxicity for DOX (Zhou *et al.*, 2001; Zhao and Zhang, 2017). In this framework, longitudinal MOTox scores over therapy were computed considering non-haematological toxicity. Then, demographics, treatment-related and biochemical characteristics were used to examine high overall toxicity over cycles. The performed analyses were finally used to develop an intuitive webapp (http://osteowebapp.prod.s3-website.eu-central-1.amazonaws.com/) as support tools for clinicians.

The rest of this article is organized as follows. MRC BO06/EORTC 80931 Randomized Controlled Trial data are described in Section 2. Longitudinal MOTox scores and statistical methods are introduced in Section 3. Results are presented in Section 4. Section 5 ends with a discussion of strengths and limitations of the current approach, identifying some developments for future research.

2. MRC BO06 Randomized Clinical Trial data

2.1. Patients

Data from the MRC BO06/EORTC 80931 Randomized Clinical Trial (RCT) for patients with non-metastatic high-grade osteosarcoma recruited between 1993 and 2002 (Lewis *et al.*, 2007) were analysed. Patients were randomized between conventional (*Reg-C*) and dose-intense (*Reg-DI*) regimens. Both arms had six cycles of the same course of chemotherapy, 25 mg/m^2/d for 3 days of doxorubicin (DOX) plus 100 mg/m^2 of cisplatin (CDDP) as a continuous 24-h infusion on day 1, with different time schedule: in *Reg-DI* cycles were every two weeks, whereas in *Reg-C* they were every three weeks. Surgery to remove the primary tumour was scheduled at week 6 after starting treatment in both arms, that is, after two cycles in *Reg-C* and after three cycles in *Reg-DI*. Postoperative chemotherapy was intended to resume three weeks after surgery in both arms (see Figure 1). Full details of the trial are reported in Lewis *et al.* (2007).

The dataset included 497 eligible patients; 19 patients who did not start chemotherapy (13) or reported an abnormal dosage (i.e., +25% higher than planned) of one or both agents (6) were excluded. Only patients who completed all six cycles within 180 days after randomization were included in the analysis, while 93 patients who did not complete the therapy and 8 who did not terminate the last cycle within 180 days were

excluded. The final cohort of 377 patients included in the analyses (75.9% of the initial sample) is shown in Figure 2.

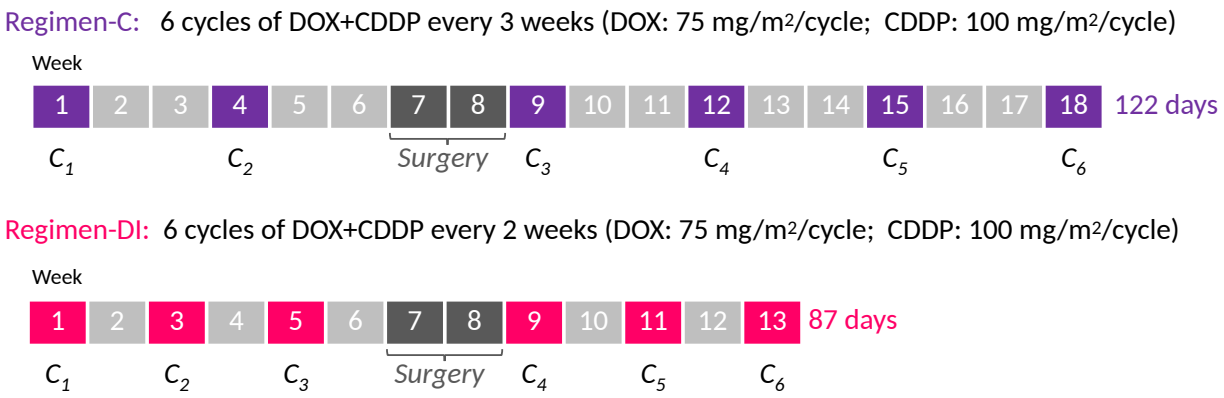

Figure 1. Patients are randomized at baseline to one of the two regimens, with the same anticipated cumulative dose (doxorubicin 25 mg/m²/d for 3 days + cisplatin 100 mg/m² as a continuous 24-h infusion on day 1) but different duration (3-weekly vs 2-weekly cycles).

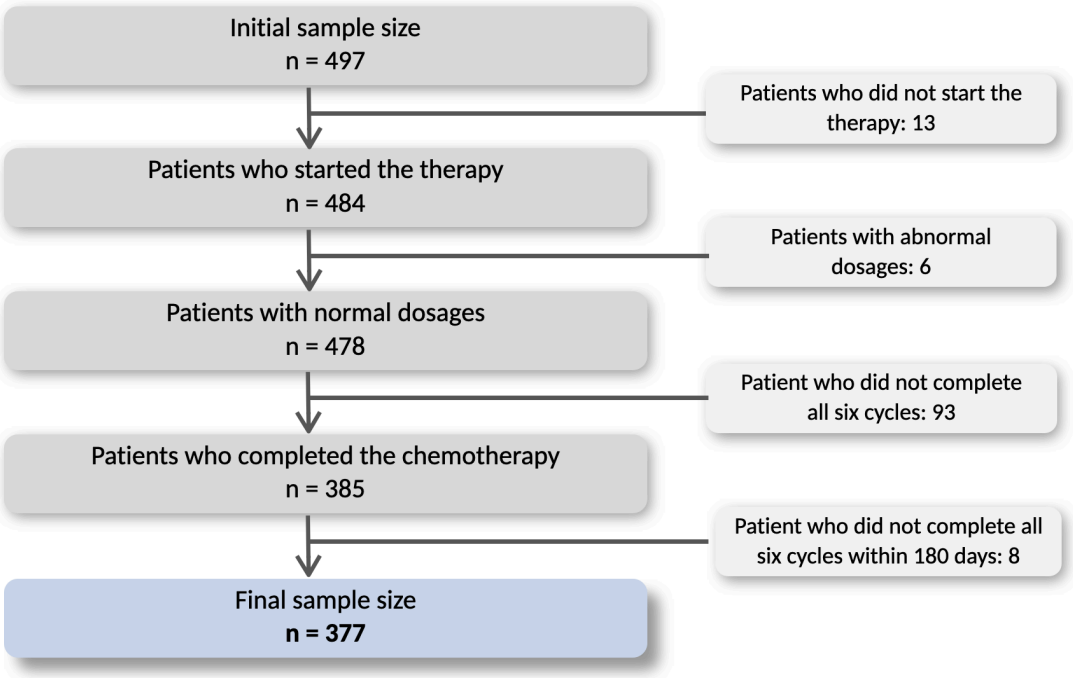

Figure 2. Flowchart of cohort selection.

2.2. Data

Patients characteristics and treatment-related factors were collected prospectively at each cycle of chemotherapy using standardised case-report forms. Baseline information were registered at randomization and included age, gender, allocated regimen (*Reg-C* or *Reg-DI*), site and location of the tumour. Treatment-related information comprehended administered dose of chemotherapy drugs, cycles delays, haematological and biochemical parameters, chemotherapy-induced toxicity and histological response to pre-operative chemotherapy (Lewis *et al.*, 2007). The resected specimen was examined histologically to assess response to pre-operative chemotherapy. *Good* histological response was defined as

≥ 90% necrosis in the tumour resected; 10% or more viable tumour after pre-operative chemotherapy was defined *poor*. Levels of renal clearance, alkaline phosphatase, lactate dehydrogenase, calcium and magnesium were determined before the beginning of each cycle (i.e., before the drugs administration) according to local practice. Blood counts (white blood cells, neutrophils, platelets) were obtained before each cycle and at the expected nadir of the course (day 10 of the cycle in *Reg-C*, day 8 in *Reg-DI*). Non-haematological chemotherapy-induced toxicity for nausea/vomiting, mucositis, neurological toxicity, cardiac toxicity, ototoxicity and infection were graded according to the Common Terminology Criteria for Adverse Events Version 3 (CTCAE v3.0) (U.S. Department of Health and Human Services, 2006), with grades ranging from 0 (none) to 4 (life-threatening) (see Table 1). Data on non-haematological toxicity were not available for 1.25% of measurements, which were treated as CTCAE 0-grades for clinical indication.

Since delays or chemotherapy dose reductions during treatment were possible in case of toxicity, chemotherapy dose at cycle k was analysed as percentage of achieved chemotherapy dose. For each patient i, it was defined as the percentage of the cumulative drugs administrated up to cycle k divided by the cumulative drugs planned up to k, that is:

$$p\delta_i^k = \frac{\text{cumulative drugs administated up to cycle } k}{\text{cumulative drugs planned up to cycle } k} \bullet 100\% = \frac{\sum_{c=1}^{k} (DOX_i^c + CDDP_i^c)/sa_i^c \ \left[\text{mg/m}^2\right]}{175 \ \left[\text{mg/m}^2\right] \bullet k} \bullet 100\%$$

where $k \in \{1, \ldots, 6\}$ is the cycle index, sa is patient's surface area in m^2, DOX and $CDDP$ are the administrated mg of doxorubicin and cisplatin, respectively.

3. Methods

3.1. Longitudinal chemotherapy-induced Multiple Overall Toxicity (MOTox) score

The longitudinal chemotherapy-induced Multiple Overall Toxicity (MOTox) score is now introduced. Let T be the set of different toxicity categories. Let $k \in \{1, \ldots, 6\}$ be the cycle index and $tox_{ij}^k \in \{0,1,2,3,4\}$ be the j-th toxicity level for the i-th patient at the k-th cycle, with $j \in T$. The chemotherapy-induced MOTox score for the i-th patient at cycle k is defined as:

$$MOTox_i^k = \frac{1}{|T|} \sum_{j \in \mathcal{T}} tox_{ij,k} + \max_{j \in T} \left(tox_{ij,k} \right). \qquad (1)$$

The MOTox score is a *cycle-dependent longitudinal mean-max* index that condensates the information of patients' collateral events in an effective and interpretative way. It considers the overall collateral effects experienced by patient i in the chemotherapy cycle k, the *mean* part, putting a specific stress on the worst-graded toxicity, the *max* part. This choice was made to take into account that (i) multiple lower-grade chronic toxicities may decrease patient's quality of life and (ii) huge level in one specific toxicity can cause severe effects and permanent consequences for the patient. Considering both aspects, the MOTox score can determine increasing ramifications on patients' health status and quality of life, resulting more informative with respect to traditional methods.

The median value of MOTox scores over all the patients in all the cycles, computed as

$$\tau = \underset{i,k}{median} \left(MOTox_i^k \right),$$

was named *global median MOTox value* and it was used as a threshold to define a longitudinal binary score for *high* (or *low*) overall toxicity, as follows:

$$high\text{-}MOTox_i^k = \begin{cases} 1 & \text{if } MOTox_i^k > \tau \\ 0 & \text{otherwise}. \end{cases} \qquad (2)$$

Table 1. Toxicity coding based on CTCAE (Common Terminology Criteria for Adverse Events) grade v3.0 (U.S. Department of Health and Human Services, 2006) for non-haematological chemotherapy-induced toxicity related to nausea/vomiting, mucositis, neurological toxicity, cardiac toxicity ototoxicity and infection.

Toxicity	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Nausea/ Vomiting	None	Nausea	Transient vomiting	Continuative vomiting	Intractable vomiting
Oral Mucositis	No change	Soreness / erythema	Ulceres: can eat solid	Ulcers: liquid diet only	Alimentation not possible
Infection	None	Minor infection	Moderate infection	Major infection	Major infection with hypotension
Cardiac toxicity	No change	Sinus tachycardia	Unifocal PVC arrhythmia	Multifocal PVC	Venticular tachycardia
Ototoxicity	No change	Slight hearing loss	Moderate hearing loss	Major hearing loss	Complete hearing loss
Neurological toxicity	None	Paraesthesiae	Severe paraesthesiae	Intolerable paraesthesiae	Paralysis

MOTox and high-MOTox scores represent new and interpretative indices to effectively measure patients' overall toxicity status preserving medical interpretability.

In MRC BO06/EORTC 80931 RCT, non-haematological chemotherapy-induced toxicity related to

- $naus$ Nausea/vomiting
- $oral$ Mucositis
- inf Infection
- car Cardiac toxicity (heart dysfunctions).
- oto Ototoxicity (hearing loss)
- $neur$ Neurological toxicity

were registered and graded according to CTCAE scale (see Table 1). Therefore, in our retrospective analysis, set $T = \{naus, oral, neur, car, oto, inf\}$ was considered to compute MOTox and high-MOTox scores over cycles for each patient, according to Equation (1) and Equation (2).

3.2. Statistical analysis

A retrospective analysis to examine prognostic factors for high/low overall toxicity over cycles was conducted. Baseline and treatment-related characteristics were examined. A two-sided significance level of 5% was adopted. R software (R Core Team, 2018) was used for the analysis.

No missing data were registered for baseline information, except for one missed location of the tumour. Other predictors presented different level of missingness. Data on non-haematological toxicity were not available for 1.25% of measurements, which were treated as CTCAE 0-grade for clinical indication. For treatment-related missing values (i.e., histologic response, biochemical and haematological markers), a Missing At Random (MAR) assumption was made and missing values were imputed using Multiple Imputations by Chained Equations (MICE) algorithm (van Buuren and Groothuis-Oudshoorn, 1999,2011).

At each cycle, the impact of factors on *high* overall toxicity was examined using multivariate logistic regression models and expressed by odds ratios (OR) (McCullagh and Nelder, 1989). An OR>1.0 indicates a greater risk of achieving a high overall toxicity in case of a 1-unit increase for numerical characteristics or

compared to the baseline category for categorical ones. Covariates with more than 15% of missing values in the original data were not included in the multivariate models. A stepwise backward selection procedure was applied to select the best set of covariates at each cycle based on Akaike Information Criterion (AIC). Variance Inflation Factor (VIF) was also used to remove non-significant and highly collinear covariates. Predictive capacities of models were expressed by sensitivity and specificity metrics and Area Under the receiver operating characteristic Curve (AUC) (Fawcett, 2006).

4. Results

4.1. Patient and treatment-related characteristics

Patient characteristics at randomization are shown in Table 2. Among 377 patients, 229 (60.7%) were males and regimen Dose-Intense was allocate in 52.3% of the patients (197). Median age was 15 years (IQR [11; 18]) and three age groups were defined according to Collins *et al.* (2013): *child* (male: 0-12 years; female: 0-11 years), *adolescent* (male: 13-17 years; female: 12-16 years) and *adult* (male: 18 or older; female: age 17 years or older). *Good* histological response was measured in 38.2% of the patients (144) and no response was reported for 47 patients (12.5%). A summary of the biochemical and haematological values measured over the entire dataset is shown in Table 3. Grades of chemotherapy-induced non-haematological toxicity over cycles are reported in Figure 3. Nausea/vomiting was reported at least once over cycles in 97.3% of patients (367/377), with a percentage that decreased over cycles from 84.9% in cycle 1 to 52.5% in cycle 6. The percentages of patients that reported oral mucositis or infections were more stable over cycles: 30.5%-43.3% for mucositis, with 78% (294/377) reporting oral AEs at least once, and 23.8%-31.3% for infection, with 69% (260/377) reporting infection AEs at least once. Other toxicities were less frequent (<25%): ototoxicity was reported at least once in 21.5% (81/377), cardiac toxicity in 14.1% (53/377) and neurological toxicity in 11.7% (44/377).

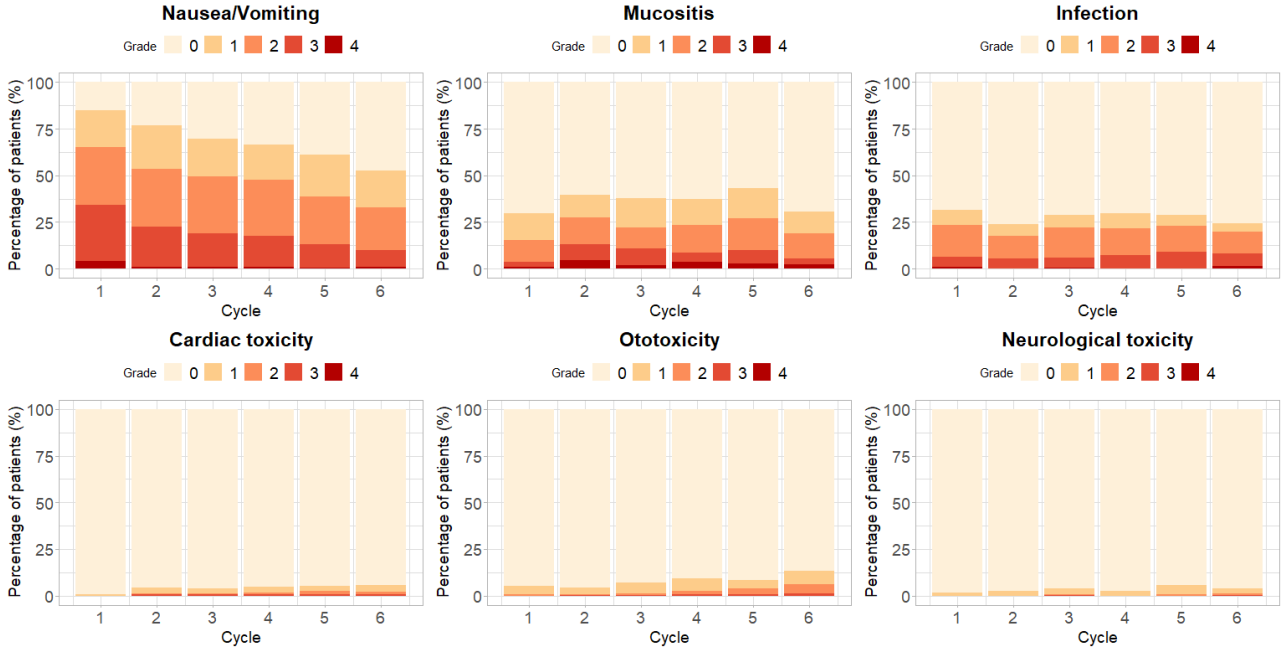

Figure 3. Bar-plots of chemotherapy-induced toxicity CTCAE grades over cycles (wheat: 0; light-orange: 1; orange: 2; red: 3; dark-red: 4). Each panel refers to a different type of toxicity: nausea/vomiting [top-left], mucositis [top-centre], infection [top-right], cardiac toxicity [bottom-left], ototoxicity [bottom-centre] and neurological toxicity [bottom-right].

Table 2. Patients' characteristics at randomization and histological responses.

Baseline characteristic	
Patients	377
Age [**years**]	
Median (IQR)	15 (11; 18)
Minimum/maximum	3/40
Child	109 (28.9%)
Adolescent	154 (40.9%)
Adult	114 (30.2%)
Gender	
Female	148 (39.3%)
Male	229 (60.7%)
Allocated treatment	
Regimen-C	180 (47.7%)
Regimen-DI	197 (52.3%)
Site of tumour	
Femur	227 (60.2%)
Fibula	22 (5.8%)
Humerus	37 (9.8%)
Radius	3 (0.8%)
Tibia	87 (23.1%)
Ulna	1 (0.3%)
Location of tumour	
Distal	217 (57.6%)
Mid-shaft	11 (2.9%)
Proximal	148 (39.2%)
Missing	1 (0.3%)
Histological Response	
Poor	186 (49.3%)
Good	144 (38.2%)
Missing	47 (12.5%)

Table 3. Descriptive of biochemical and haematological values over the entire dataset.

Biomarkers	**Mean** (**s.d.**)	**Median** (**IQR**)	**Min/Max**
White Blood Count [$\times 10^9$/L]	7.36 (8.25)	5.00 (3.10; 8.20)	0.10/117
Neutrophils [$\times 10^9$/L]	4.74 (6.93)	2.60 (1.12; 5.30)	0/83.38
Platelets [$\times 10^9$/L]	219.8 (157.5)	190 (99; 311)	2/999
Renal Clearance [ml/min/1.73 m^2]	112.3 (34.9)	110 (90; 132)	8/396
Alkaline Phosphatase [IU/L]	238.5 (279.1)	162.5 (98.0; 267.2)	14/3680
Lactate Dehydrogenase [IU/L]	447.0 (264.2)	394.0 (298.8; 531.0)	4/4310
Calcium [mmol/l]	2.34 (0.36)	2.35 (2.25; 2.45)	0.21/9.70
Magnesium [mmol/l]	0.71 (0.24)	0.69 (0.57; 0.80)	0.07/3.06

4.2. Non-haematological longitudinal Multiple Overall Toxicity scores

For each patient $i \in \{1, \ldots, 377\}$ and cycle $k \in \{1, \ldots, 6\}$, non-haematological chemotherapy-induced toxicity related to nausea/vomiting ($naus$), mucositis ($oral$), neurological toxicity ($neur$), cardiac toxicity (car), ototoxicity (oto) and infection (inf) were considered to compute the MOTox score $OTOX_i^k$ through Equation (1), with $T = \{naus, oral, neur, car, oto, inf\}$. A summary of the obtained scores over cycles is given in Table 4. Obtained MOTox scores ranged between 0 and 6 and their mean values decreased over cycles from 2.626 (cycle 1) to 1.953 (cycle 6). The global median MOTox value τ, i.e., the median value of overall toxicity over all the patients in all the cycles, was 2.333. An example of obtained longitudinal MOTox scores over cycles for five random patients is shown in Figure 4 (different colours refer to different patients). The global mean MOTox value τ is reported as solid black line. Different evolution patterns of longitudinal MOTox score over cycles are presented: increasing pattern (*orange:* patient A), decreasing pattern (*light blue:* patient B), isolated severe status (*violet*: patient C), low-values (*blue*: patient D) and high-values (*red*: patient E) over cycles.

To evaluate which regimens is characterized by higher overall toxicity over cycles, Table 5 reports the means of MOTox scores at each cycle k for patients allocated in *Reg-DI* and *Reg-C*, $\bar{OTOX}_{DI}^k$ and $\bar{OTOX}_{C}^k$ respectively. P-values are related to hypothesis tests concerning the difference between the two populations means for large independent samples. In cycles 1-3, mean overall toxicity for patients in *Reg-DI* was higher than for those in *Reg-C* ($p<0.05$), whereas from cycle 4 the difference was not statistically significant. To better characterize these differences, Figure 5 shows the mean values of each non-haematological toxicity $\{naus, oral, neur, car, oto, inf\}$ along with 95% Bonferroni's confidence intervals over cycles, stratified by regimens (purple: *Reg-C*; pink: *Reg-DI*). Each panel refers to a different type of toxicity: nausea/vomiting (top-left), mucositis (top-centre), infection (top-right), cardiac toxicity (bottom-left), ototoxicity (bottom-centre) and neurological toxicity (bottom-right). The biggest contribution to the difference in the mean MOTox scores by regimes was given by mucositis (top-centre panel), significantly higher in *Reg-DI* (pink) than in *Reg-C* (purple) at cycles 2 and 3.

The global median MOTox value τ was then used to compute the longitudinal dichotomous *low/high* MOTox scores over cycles according to Equation (2). Table 4 shows the percentages of patients with high MOTox score, which decrease from 57.8% (218/377) at cycle 1 to 36.6% (138/377) at cycle 6. There was evidence for an association between chemotherapy regimens and high overall toxicity at cycles 2-3 (p-value of Chi-squared tests for association < 0.05), confirming results obtained in Table 5. At each cycle, high overall toxicity was strongly associated with *low/high* MOTox at previous cycles.

Table 4. Longitudinal MOTox and high-MOTox scores characteristics over cycles.

Toxicity score	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**
MOTox						
Median	2.667	2.333	2.333	2.333	2.3333	2.333
IQR	[2.333; 3.500]	[1.167; 3.667]	[1.167; 3.500]	[1.167; 3.500]	[1.167; 3.500]	[0; 2.667]
Mean (s.d.)	2.646 (1.268)	2.450 (1.414)	2.327 (1.390)	2.297 (1.481)	2.284 (1.381)	1.953 (1.498)
Min/Max	0/5.667	0/5.667	0/5.667	0/6	0/5.833	0/6
			Global median MOTox value τ: 2.333			
High MOTox						
0 *(low)*	159 (42.2%)	189 (50.1%)	198 (52.5%)	193 (51.2%)	204 (54.1%)	239 (63.4%)
1 *(high)*	218 (57.8%)	188 (49.9%)	179 (47.5%)	184 (48.8%)	173 (45.9%)	138 (36.6%)

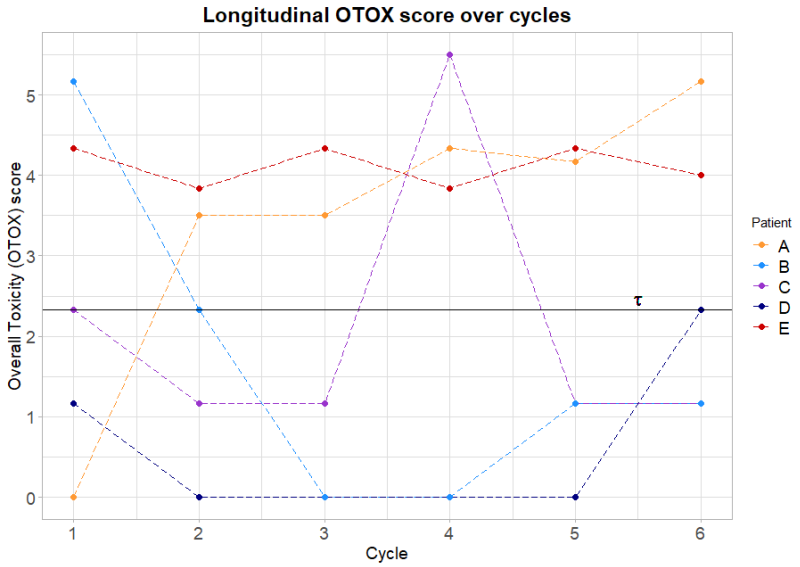

Figure 4. Example of different evolution of longitudinal Multiple Overall Toxicity (MOTox) scores over cycles for five random patients: increasing pattern (*orange:* patient A), decreasing pattern (*light blue:* patient B), isolated severe status (*violet*: patient C), low-values (*blue*: patient D) and high-values (*red*: patient E). Solid black line refers to the global median MOTox value τ=2.333.

Table 5. Overall toxicity differences between Dose-Intense (DI) and Conventional (C) regimens. $\overline{MOTox}^k_{DI}$ and $\overline{MOTox}^k_{C}$ are the means of MOTox scores at cycle k for patients allocated in *Reg-DI* and *Reg-C*, respectively.

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
$\overline{MOTox}^k_{DI}$	2.552	2.653	2.488	2.240	2.261	1.920
$\overline{MOTox}^k_{C}$	2.782	2.229	2.150	2.359	2.309	1.989
p-value of test	0.045	0.003	0.018	0.437	0.737	0.657

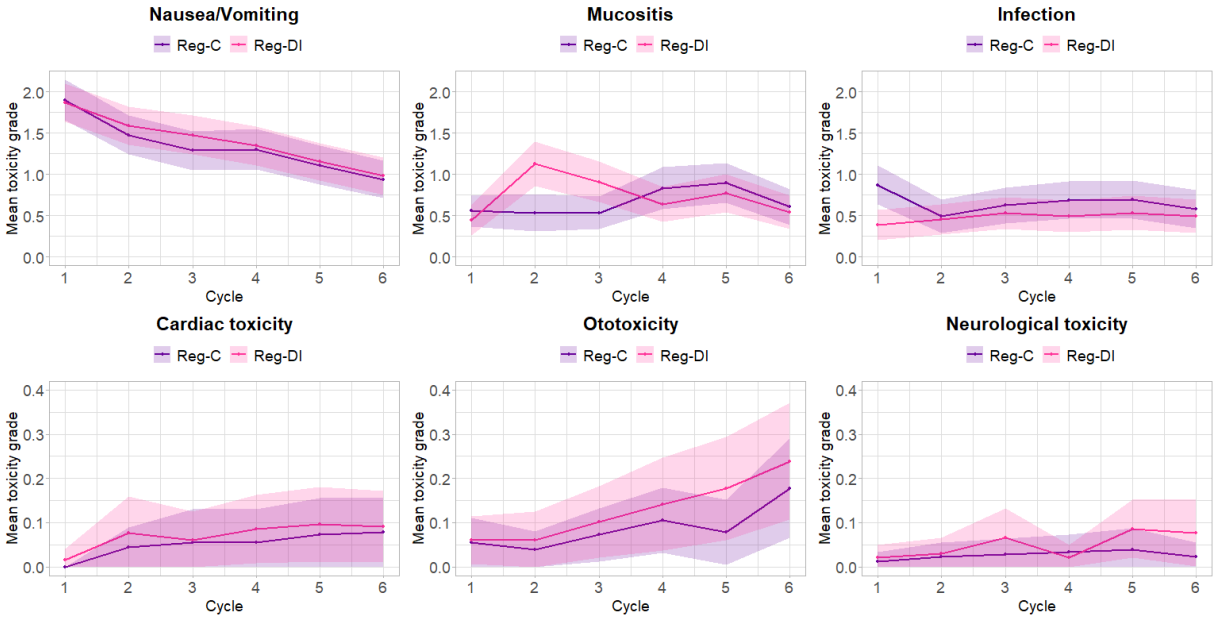

Figure 5. Mean value of chemotherapy-induced toxicity during cycles along with 95% Bonferroni confidence intervals, stratified by the regimens (purple: *Reg-C*; pink: *Reg-C*). Each panel refers to a different type of toxicity: nausea/vomiting [top-left], mucositis [top-centre], infection [top-right], cardiac toxicity [bottom-left], ototoxicity [bottom-centre] and neurological toxicity [bottom-right].

4.3. Multivariate logistic regression models for high overall toxicity over cycles

The evolution of longitudinal high-MOTox score over cycles defined in Equation (2) was analysed through multivariate logistic regression models, using a cycle-by-cycle approach. Starting from the second cycle, each model analysed high-MOTox at the of the cycle in terms of personalized characteristics and previous toxicity levels. Baseline and treatment-related information with less than 15% of missing values in the original dataset were considered as possible prognostic factors for toxicity prediction. In particular, among haematological and biochemical factors, measurements of neutrophils (N), platelets (PLT), alkaline phosphatase (ALP) and calcium (Ca) were considered before the beginning of each cycle (i.e., the administration of the course), whereas values of white blood count (WBC) both before administration and at the planned nadir of each cycle. Due to the skewed nature of biomarkers levels distributions, haematological and biochemical factos were included in the models as difference between the logarithmic measure and the logarithmic value measured at randomization. Neutrophils-white blood count ratio (NWR), i.e., the neutrophils count dived by the white blood cell count, and neutrophils-platelets score (NPS), a three-level systemic inflammation-based score (*good*: N $\leq$ 7.5 $\times 10^9$/L and PLT $\leq$ 400 $\times 10^9$/L; *intermediate*: N $>$ 7.5 $\times 10^9$/L or PLT $>$ 400 x10^9/L; *poor*: N $>$ 7.5 x10^9/L and PLT $>$ 400 $\times 10^9$/L) (Watt *et al.*, 2015; Liu *et al.*, 2016), were also included. For each model, multicollinear variables with VIF greater than 5 were removed. Then, stepwise backward procedures were used to select the best set of covariates according to AIC. The selected models were finally fitted on the whole dataset.

Table 6 reports selected covariates, estimated Odds Ratios (ORs) along with 95% Confidence Intervals (CIs) and overall performances (i.e., specificity, sensitivity and AUC) of each model. All the models retained a similar structure with comparable overall performances: sensitivity and specificity values ranged in 0.66-0.77, and AUCs were between 0.72 and 0.79. No effect was due to gender, when selected. In cycle 2 and 3, higher percentage of achieved chemotherapy dose reflected a higher risk for the development of high toxicity, especially for patient in *Reg-DI* (cycle 2). Haematological factors were selected in each model. In particular, both PLT before the administration of the course and WBC at nadir had a protective role on the risk of having high overall toxicity (OR$<$1). In particular, an increase in the dynamic difference between the logarithmic levels decreased the risk of high toxicity. Patients with previous *high* MOTox had higher risk to experience again high overall toxicity with respect to patients with previous *low* MOTox (OR$>$1), showing an autoregressive pattern. In particular, toxicity information related to different previous cycles were selected and statistically significant in the final models, meaning that global patient's history and not only the last condition had impact on his/her quality of life over the therapy.

The performed analyses were finally used to develop an intuitive webapp (http://osteowebapp.prod.s3-website.eu-central-1.amazonaws.com/) as support tool for clinicians. The structure of the webapp is presented in Appendix A.

5. Discussion

Due to the presence of multiple types of Adverse Events (AEs) with different extents of toxicity burden, to study the overall toxicity progression during chemotherapy is a challenging problem in cancer research. The development of statistical methods able to deal with the complexity of longitudinal chemotherapy data and to provide a uniform procedure for condensing the key elements of AEs data into a score of overall risk is necessary and of clinical relevance. This paper uniquely explored the evolution of chemotherapy-induced toxicity over treatment in patients with osteosarcoma. Data from the MRC BO06/EORTC 80931 randomized clinical trial were analysed. First, the Multiple Overall Toxicity (MOTox) score was developed to improve the methods for summarising and quantifying risk in oncology. Then, the cycle-by-cycle longitudinal evolution of high MOTox was analysed using multivariate logistic regression models to predict high overall toxicity at the end of the cycle trough dynamic personalized patterns.

Results showed that the inclusion of the cycle-dimension allowed to consider different evolution patterns over treatment, leading to more informative ramifications on patients' health statuses that could better

quantify and qualify the effect of AEs on patients' life with respect to traditional methods (i.e., *max-grade* or *max-time*). The use of previous personalized characteristics allowed to take into account the autoregressive nature of overall toxicity, showing that the last available toxic condition had the highest impact for a high MOTox risk but also the global patient's toxic history plays an important role in patient's quality of life over treatment. Moreover, given that no statistically significant difference in terms of mortality rate among regimes resulted from previous studies on the same data (Lewis et al., 2007), the analysis showed that the Conventional Regimen has ground to be preferred to the Dose-Intense one, at least in terms of induced cumulative toxicities in the first half of the therapy (i.e., up to the third cycle).

The proposed method represents a novel approach to analyse longitudinal chemotherapy data, designed to account for the multiplicity and time dimensions of AEs. Different possibilities for a summarising score were initially investigated. The final choice fell on the index presenting the highest accuracy in describing and discriminating patients' condition, i.e. the cycle-dependent longitudinal mean-max MOTox score over therapy in Equation (1). Starting from recorded CTCAE grades, the MOTox score summarised multiple AEs allowing to (i) capture the global toxic status, (ii) put a specific stress on the most severe collateral effect and (iii) incorporate the time-dimension of treatment cycles. In this way, various aspects which could cause severe and permanent consequences for the patient, such as worst-graded events or multiple lower-grade chronic toxicities, and their overall evolution were concomitantly analysed. MOTox and high-MOTox scores represent new and interpretative indices to effectively measure patients' overall toxicity status preserving medical interpretability. In particular, they can be intended as a proxy of patient's quality of life and can be used (i) to describe patient's response to therapy over cycles, (ii) to predict the upcoming overall toxicity level given patient's history and (iii) to drive the clinical decision, trying to reduce the impact of therapies in terms of toxic AEs.

From a modelling point of view, different statistical and machine learning methods for high/low binary classification were considered, among others support vector machines or ensemble methods (e.g., random forests or XGBoost). More complex methods showed no significant improvements in terms of predictive performances with respect to logistic regression models. Therefore, the final choice fell on favouring the clinical interpretability offered by the cycle-by-cycle logistic regression outputs, which also allowed to provide an easy usable, interpretable and operative support tool for clinicians, i.e., the *OsteoWebApp* (see Appendix A).

This retrospective exploratory analysis has some limitations, mainly due to the data quality and the complexity of the problem. Although the toxicity data was recorded using the standardised CTCAE grading system, there is a subjective element to assessing non-haematological toxicity and variations between individual investigators cannot be controlled. Other factors of potential interest were not routinely recorded during the trial, including among others nephrMOToxicity, lymphocytes count or tumour size. The analysis was performed on a single RCT in osteosarcoma. An external validation could help to verify if the models correctly generalize the problem or if it is necessary to integrate the analysis with richer data sources. Furthermore, since this study represents one of the first attempts to analyse summarized toxicity data in osteosarcoma using a cycle-by-cycle time perspective, toxicity grades, which are in fact categorical variables, have been improperly treated as numerical values that increase as the level of toxicity worsened. In this framework, a longitudinal categorical data approach could be developed. This is not a trivial task due to the complexity of the problem. Nevertheless, although the results have been derived from a single RCT and only non-haematological toxicities, the developed procedure is applicable to any cancer treatment and can be tailored according to the needs of the study. Provided that toxicities are recorded according to the CTCAE scale or traced back to it, the longitudinal MOTox score represents a uniform and general methods to analyse overall toxic risk in oncology, constituting a really flexible approach to qualify and quantify the personal behaviours and evolutions of toxic patterns in cancer patients.

Table 6. Multivariate logistic regression model for each cycle $k \in \{2,3,4,5,6\}$.

	Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Covariates	**ORs**	**95% CIs**	**ORs**	**95% CIs**	**ORs**	**95% CIs**	**ORs**	**95% CIs**	**ORs**	**95% CIs**
Baseline										
Gender (male)					1.458	[0.912; 2.33]	1.548	[0.967; 2.478]		
Regimen (Reg-DI)	2.379	[1.455; 3.889]								
Treatment-related factors										
Achieved dose (%)	1.112	[1.042; 1.187]	1.056	[1.008; 1.106]						
WBC							1.664	[0.978; 2.831]		
WBC at nadir	0.778	[0.615; 0.983]			0.701	[0.569; 0.864]	0.637	[0.499; 0.813]	0.748	[0.589; 0.950]
PLT			0.535	[0.375; 0.765]	0.625	[0.392; 0.996]			0.629	[0.424; 0.932]
NWR					0.367	[0.094; 1.436]				
Previous toxicities ($high\text{-}MOTox^k$)										
High MOTox ($k = 1$)	4.439	[2.788; 7.070]	1.561	[0.968; 2.516]	1.522	[0.953; 2.430]				
High MOTox ($k = 2$)			4.429	[2.666; 6.772]	1.569	[0.972; 2.532]			1.743	[1.044; 2.910]
High MOTox ($k = 3$)					2.701	[1.696; 4.304]	2.639	[1.664; 4.186]	1.580	[0.938; 2.661]
High MOTox ($k = 4$)							3.718	[2.346; 5.893]	2.542	[1.523; 4.244]
High MOTox ($k = 5$)									3.341	[2.001; 5.580]
Sensitivity	0.681		0.704		0.674		0.699		0.717	
Specificity	0.667		0.661		0.715		0.701		0.766	
AUC [95% CI]	0.733 [0.683; 0.784]		0.743 [0.694; 0.793]		0.728 [0.677; 0.780]		0.756 [0.707; 0.805]		0.787 [0.737; 0.837]	

WBC = white blood count; PLT = platelets; NWR = neutrophils-white blood count ratio; MOTox = overall toxicity.
When not specified, haematological factors were computed before the administration of the course.
WBC and PLT are included in the models as difference between the current logarithmic measure and the logarithmic value measured at randomization.

This work opens doors to many further developments, both in the field of statistical methods and in cancer research. From a clinical point of view, the interest may lie also in distinguishing extremely high and extremely low overall toxicity levels with respect to central areas. Therefore, a possible direction for improvements is the refinement of the problem from a binary (*low/high* MOTox) to a multiclass one. However, identifying thresholds to divide MOTox scores into multiple categories is not a trivial task, and it requires a proper external validation. From a statistical point of view, toxicity levels may be deeper analysed using longitudinal categorical data approaches, such as latent Markov models. In fact, in many applications involving longitudinal data, the interest is focused on the evolution of a latent characteristic of a group of individuals over time, which is measured by occasion-specific response variables (Bartolucci, Farcomeni and Pennoni, 2013,2014). In cancer treatment, this characteristic could be indirectly assessed based on registered toxicity levels and could reflect patient's quality-of-life. The complexity of the problem asks for the developments of new methodologies, aimed at analysing more and more appropriately all the peculiar aspects of chemotherapeutic treatment.

In the end, our approach constitutes a more complete and flexible longitudinal depiction of chemotherapy-induced toxicity than traditional methods, and it can be customised according to the needs of the study. Provided that longitudinal data are available from drug administrations (doses in mg/m^2, biochemical measurements and CTCAE-graded toxicity), the procedure presented here is really flexible and appropriate to analyse chemotherapy treatments in general. This study shows that working in this direction is a difficult but profitable approach. Its possible generalization to many different settings, added to a cooperation with medical staff, could lead to improvements in the definition of useful tools for health care assessment and treatment planning.

Acknowledgements

The authors thank Medical Research Council for sharing the dataset used in this work.

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Appendix

A. OsteoWebApp

The *OsteoWebApp*, available at http://osteowebapp.prod.s3-website.eu-central-1.amazonaws.com/, is a practical support tool developed to help clinicians in their daily practice. It allows for a personalized prediction of high overall toxicity over cycles, starting from the models estimated in Session 4.3. It runs on top of *Amazon Web Services* (https://aws.amazon.com/it/), executing the R code related to the models in Table 6. Thanks to its intuitive interface, the webapp is easy to use, scalable and complete in the information it provides.

An example of the user interface, showing the inputs and results for model related to cycle 2, is reported in Figure 6. The top bar shows the cycle of chemotherapy of interest. The main form asks a series of information, depending on the variables selected for each cycle. The "*Predict Toxicity Index*" button in blue allows to get the results of the prediction, which are provided in terms of probability of develop a high overall toxicity level. Results are shown in 20 seconds. Sensitivity and specificity of each model are also reported. As a practical example, Figure 6 shows that a patient in *Reg-DI* with high-MOTox at cycle 1, a cumulative administrated dose of 350 mg/m^2 (which corresponds to a 100% of achieved dose), WBC values of 7.65 [$\times 10^9$/L] at randomization and of 3.9 [$\times 10^9$/L] at nadir has 73.5% of probability to be in high-MOTox status at the end of cycle 2.

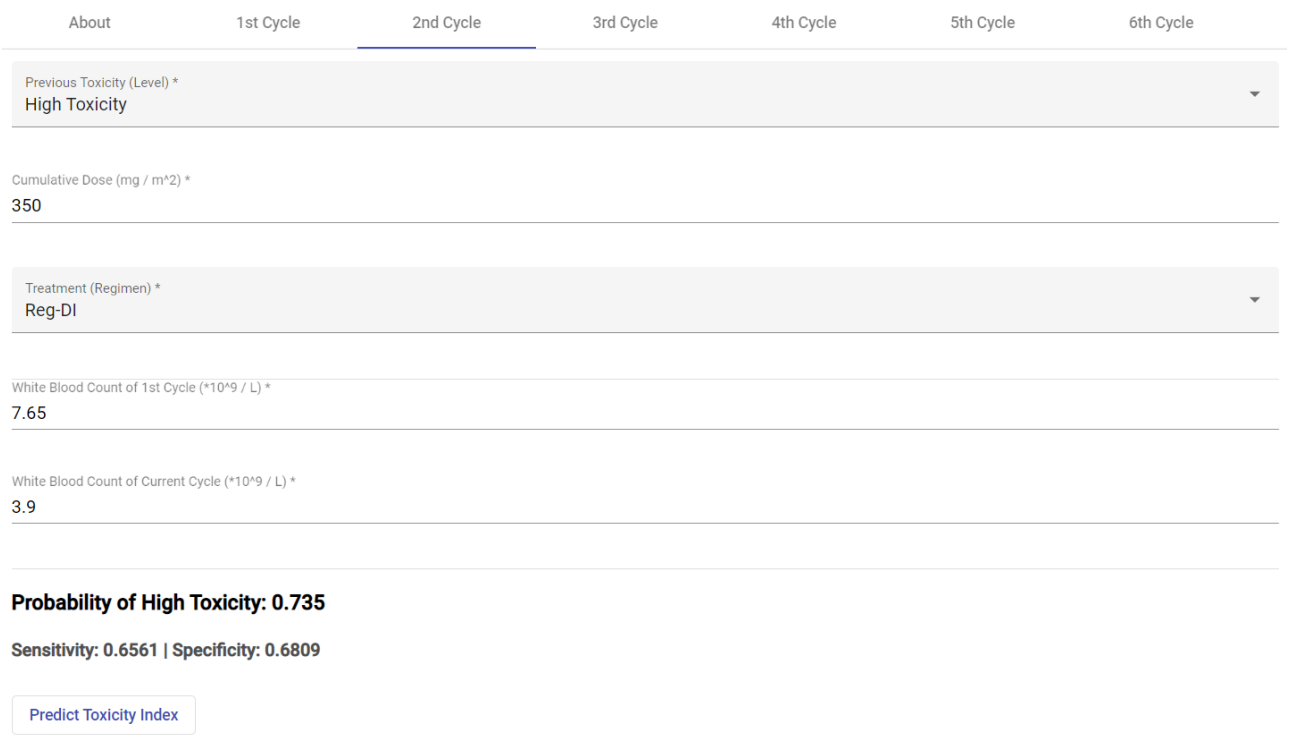

Figure 6. Example of user interface for OsteoWebApp.

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