The importance of jointly analyzing treatment administration and toxicity associated with targeted therapies: a case study of regorafenib in soft tissue sarcoma patients

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ORIGINAL ARTICLE

The importance of jointly analyzing treatment administration and toxicity associated with targeted therapies: a case study of regorafenib in soft tissue sarcoma patients

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Background: Different methods have been proposed to analyze adverse events (AEs) associated with targeted therapies. While these AEs lead to dose adjustments for many patients, conventional reporting methods do not take drug administration into consideration. This paper underlines the importance of jointly reporting AEs and drug administration using prevalence, and proposes a complementary approach to reporting.

Patients and methods: The prevalence method estimates the probability of progression-free patients being in a particular health state (state 1: AEs with full dose; state 2: AEs with reduced dose; state 3: no AEs with reduced dose) at different time points. To take into account the impact of dose adjustments on efficacy, the weighted prevalence method can be used by assigning utility weights to the different health states. The benefit of these methods was illustrated using data from a phase II trial of regorafenib.

Results: Only 4.6% of progression-free patients developed mucositis/stomatitis (grade $\geq$2) at 3 months. The prevalence of patients not experiencing this AE but whose dose was reduced or treatment interrupted was 58.1%. The weighted prevalence of the regorafenib toxicity profile and dose reduction was higher in the control arm.

Conclusion: This case study confirms the importance of jointly analyzing AEs and drug administration. The weighted prevalence approach is an average score that incorporates the dimension of drug administration into AE assessment. This can be helpful for regulatory agencies as well as for clinicians to evaluate the benefit–risk ratio of therapies in their treatment choice.

Clinical trial: NCT01900743.

Key words: targeted therapy, toxicity analysis, prevalence, dose adjustment

Introduction

Over the last decade, the development of oral targeted therapies has modified the evolution of some types of cancer and contributed to the concept of 'cancer as a chronic disease'. Contrary to cytotoxic drug administration for a limited number of cycles, oral targeted therapies may be prescribed daily over months or years in the case of metastatic disease, for example, until progression is observed. Unfortunately, however, as for cytotoxic therapy, target therapies can also induce adverse events (AEs), and dose adjustments and/or drug discontinuation are necessary for many patients.

Incidences of severe AEs and their duration do not always reflect the reasons for discontinuation [1], as discontinuation often occurs in the context of grade 1 and 2 toxicities. Indeed, persistent low-grade toxicities may be less tolerable than episodic higher-grade

AEs. Discontinuation and dose reductions may also lead to decreased efficacy [2, 3] and several authors have suggested incorporating dose intensity in the identification of recommended dose in phase I trials [4]. For tyrosine-kinase inhibitors, different studies have highlighted the correlation between tumor shrinkage and administered dose [5, 6]. Optimal adherence to the recommended dosage is indicated as an important factor in achieving efficacy for tyrosine-kinase inhibitors [7].

To evaluate the benefit–risk ratio associated with oral targeted therapies, it is critical to objectively and accurately report AEs. As the worst-grade method does not accurately characterize AEs for oral targeted therapies, different methods have been proposed to incorporate the dimension of time and the recurrent nature of AEs [8–10]. Recently, a study compared AE reporting in randomized controlled trials and expectations of the EORTC membership [11]. A major weakness identified was the lack of adequate description of AEs leading to withdrawal or dose modifications. Most publications reporting AEs associated with targeted therapies do not jointly consider drug administration and AE analysis. However, two patients with the same AEs who receive different doses of the same agent cannot be considered in the same manner, since the effectiveness of the treatment may differ.

The main objective of this publication is to underline the importance of jointly reporting AEs and drug administration using the prevalence method and complemented by a weighted prevalence (wPrevalence) approach. The use and pertinence of these methods are discussed of a phase II trial of regorafenib in patients with advanced soft-tissue sarcomas.

Patients and methods

The REGOSARC study

REGOSARC was a double-blind placebo-controlled randomized phase II trial conducted in four parallel cohorts (liposarcoma, leiomyosarcoma, synovial sarcoma, and other nonadipocytic sarcomas) aiming to evaluate the activity and safety of regorafenib in doxorubicin-refractory soft-tissue sarcomas (ClinicalTrials.gov: NCT01900743) [12]. The trial showed that regorafenib significantly improved progression-free survival in three cohorts (leiomyosarcoma, synovial sarcoma, and other nonadipocytic sarcomas) but failed to demonstrate activity in the liposarcoma cohort. Ninety-two patients were randomized in the placebo arm. Patients treated in the experimental arm received regorafenib 160 mg orally (3 weeks on and 1 week off). Dose reductions were applied in 40 mg steps, with 80 mg being the lowest recommended daily dose. Among the 89 patients included in the regorafenib arm (safety population), dose reductions were reported in 45 patients and related to toxicity for 41 of them (supplementary Table S1, available at *Annals of Oncology* online). The lowest administered dose after adjustment was 80 mg daily for 17 patients. At least one transient interruption of therapy was reported for 42 patients, due to toxicity in 36 cases. Toxicity was also the reason given for 11 patients among the 55 who permanently discontinued regorafenib (supplementary Table S1, available at *Annals of Oncology* online).

The AE history model

Figure 1A depicts a simple multistate model commonly used for AE analysis with possible paths or transitions for a patient over time (more details in supplementary material, available at *Annals of Oncology* online). In Figure 1B, we proposed in a more suitable multistate model for AE analysis making it possible to deal with dose reductions. From the initial, transient state, we considered four recurrent states that one can leave and re-enter: AEs with full dose, AEs with reduced dose (or treatment discontinuation), no AEs with reduced dose (or treatment discontinuation) and cure from AE with full dose.

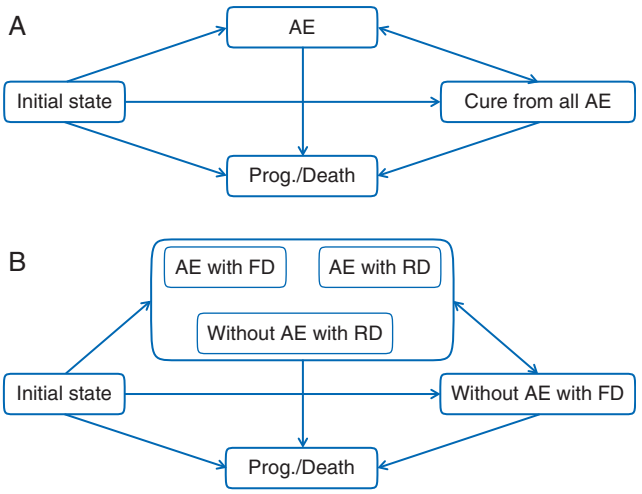

Figure 1. (A) Classical event history model for AE analysis; (B) event history with dose reduction and AE (RD: reduce dose or treatment discontinuation; FD: Full dose).

Toxicity analysis focused on grade ≥2 mucositis/stomatitis having a substantial impact on patients' quality of life (QoL) [13] and on the toxicity profile of regorafenib. This profile was characterized by the following AEs with grade ≥1: diarrhea, mucositis/stomatitis, palmar-plantar erythrodysaesthesia syndrome and skin toxicity.

Prevalence

To explore toxicity associated with targeted therapies, we sought to estimate, at different time points, the prevalence of AE, defined as the proportion of patients presenting AEs conditional to being alive and progression-free [8]. To specifically consider both dose reductions and AEs, we evaluated the prevalence of AEs and/or reduced doses over time. The prevalences, associated with AE and/or dose reductions, were estimated using the Kaplan–Meier method (WKM):

$\widehat{Q_1}(t)$: prevalence of AE with full dose
$\widehat{Q_2}(t)$: prevalence without AE and reduced dose (or treatment discontinuations) (RD)
$\widehat{Q_3}(t)$: prevalence of AE with reduced dose (or treatment discontinuation)

The prevalence of AE and/or RD was defined as the sum of the prevalences estimated above: $\hat{Q}(t) = \sum_{i=1}^{3} \hat{Q}_i(t)$. In this randomized study, a non-parametric weighted WKM statistic was proposed to test differences between prevalence functions [14]. Although this method accounts for duration and the recurrent nature of the event, it does not take into account the fact that dose adjustment can reduce therapeutic efficacy. For this reason, we preferred the wPrevalence approach [15].

The concept of weighted prevalence

Since health states can be categorized, different utility weights can be assigned to the three states associated with AEs and/or dose reductions. It was therefore necessary to rank them, assuming that the worst health state (state 3) corresponded to patients with AEs and dose reduction (or treatment discontinuation). Indeed, for patients presenting AEs, treatment efficacy may be either reduced from dose adjustment, or null in the event of discontinuation. Health state 2, an intermediate level, was defined by an absence of AEs with dose reduction, and state 1, the best

level, as AEs without dose reduction. The order between intermediate and best health state was determined by giving more importance to the therapeutic effect rather than to tolerance, especially in a disease with poor outcome. Utility weights (W_1, W_2, W_3) were associated with best, intermediate and worst states with pre-defined increasing weights ($W_1 < W_2 < W_3$). The average weight of AEs and/or RD evaluated at time t was defined as the weighted sum of the three estimated prevalences:

$$w\widehat{Q}(t) = \sum_{i=1}^{3} W_i \widehat{Q}_i(t).$$

The weights needed to be fixed in advance to avoid any ambiguity. A weight for each state, $W_i = i$ was thus assigned to state i ($i = 1, 2, 3$), assuming that state 'AE and dose reduction' is three times more severe than state 'AE without a dose reduction'. The wPrevalence could be interpreted as an average score over time. For the placebo arm, patients were considered only in the intermediate (without treatment and without AEs) and worst (without treatment and with AEs) health states. An extension of the WKM statistic was proposed to compare wPrevalences between arms [15].

Results

Application to mucositis/stomatitis

Among the 89 patients included in the regorafenib arm, 36 patients suffered mucositis/stomatitis before progression; the worst grade of toxicity was ≥2 for 17 patients. Figure 2A (blue curve) represents the probability of mucositis/stomatitis (grade ≥2) conditional to being alive and progression-free over time. The maximum value of the estimated prevalence was 13.1% at 1.5 months. Among patients not experiencing grade ≥2 mucositis/stomatitis, 45 had either at least one dose reduction or discontinuation before progression, with the lowest dose administered being 80 mg for 13 patients. Figure 2A presents the prevalence of mucositis/stomatitis (grade ≥2) or reduced doses over time (orange: lower than 160 mg, green dot: lower than 120 mg) conditional to being alive and progression-free. During the first 3 months, the prevalence of patients with AEs or RD <160 mg increased to 62.8% and was estimated at 80.0% at 6 months (Figure 2A, orange). Prevalence of AE or RD <120 mg (Figure 2A, green dots) was estimated at 26.9% at 1 month and then ranged between 18.5% (2.0 months) and 46.4% (5.1 months). Individual prevalences are presented in Figure 2C and D. The prevalence of patients without mucositis/stomatitis ≥2 and with dose <160 mg (state 2) increased over time. For a dose of 80 mg or treatment discontinuation, prevalence of AEs and/or RD tended to be stable over time after 3 months. At 3 months, 30.2% of patients alive, progression-free and with no mucositis/stomatitis ≥2 were treated at a dose of 120 mg; 27.9% discontinued treatment or received a dose of 80 mg. To distinguish data from the individual prevalences of the three states, we assigned a different weight to each state, and computed the wPrevalences of mucositis/stomatitis or RD (Figure 2B). Both prevalence of AEs and/or dose reduction (<160 mg), along with wPrevalence, increase over time.

Among patients included in the placebo arm, only three had grade ≥2 mucositis/stomatitis before progression. The prevalence of AEs differed significantly between the two arms ($P < 0.001$). The wPrevalence of AEs in the placebo arm was estimated at approximately two over time and was lower in the regorafenib arm for all dose reductions ($P < 0.001$).

Application to the regorafenib toxicity profile

In the regorafenib arm, 66 patients presented at least one AE (grade ≥1) of the drug toxicity profile before progression. The prevalence of the regorafenib toxicity profile was shown in Figure 3A (blue curve). It increased during the first 3 months and was estimated at 53.5% at that time point. Among patients not presenting the regorafenib toxicity profile, 13 experienced at least one dose reduction or discontinuation before progression. The prevalence of AEs and/or RD increased until 3 months with a maximum of 95.0% at 3.6 months for a dose <160 mg and of 86.0% at 2.5 months for a dose <120 mg (orange and green dot curves in Figure 3A). At 3 months, 18.6% and 30.2% of alive, progression-free patients and with no toxicity profile AEs were treated at a dose, respectively, <120 and 160 mg (Figure 3C and D). The prevalence of the toxicity profile without RD (state 1) increased for 2 months and then decreased over time for dose <160 mg, tending to be constant over time for dose <120 mg. The prevalence of patients with no toxicity profile and with dose reduction (state 2) increased for 3 months for dose <160 mg and was estimated at 16.4% at 2 months for dose < 120 mg. wPrevalences of toxicity profile and/or RD, which characterized the three individual prevalences, are presented in Figure 3B. The wPrevalence for each dose, representing an average score of toxicity and treatment administration, became more constant over time after 3 months compared with individual prevalence.

Among patients included in the placebo arm, 17 presented at least one AE of the regorafenib toxicity profile before progression. The prevalence of the toxicity profile was estimated at 17.6% and 22.2% at, respectively, 3 and 6 months, and was lower compared with the regorafenib arm ($P < 0.001$, Figure 4A). The wPrevalence of the toxicity profile was higher in the placebo arm compared with the regorafenib arm ($P < 0.001$ for both RD <160 mg and RD <120 mg, Figure 4B).

Discussion

Safety and treatment administration data are routinely collected in oncology trials, and are usually reported independently. In this article, we attempted to address the importance of jointly analyzing AEs and dose adjustments. As proof of concept, we analyzed AEs and dose reduction (or treatment discontinuation) from a phase II trial investigating doxorubicin-refractory soft-tissue sarcomas treated by regorafenib. We show that the incidence of severe AEs has probably been underestimated due to dose adjustments and/or drug discontinuation. For example, the prevalence of mucositis/stomatitis (grade ≥2) is 4.6% at 3 months. At that time point the prevalence of patients not experiencing grade ≥2 mucositis/stomatitis and with treatment discontinuation or dose <160 and 120 mg were, respectively, 58.1% and 27.9%. Consequently, the prevalence of grade ≥2 mucositis/stomatitis may actually be higher, since these patients were off treatment or received a reduced dose and did not present grade ≥2 mucositis/stomatitis. We focus here on mucositis/stomatitis which has a substantial impact on patients' QoL [13]. Similar

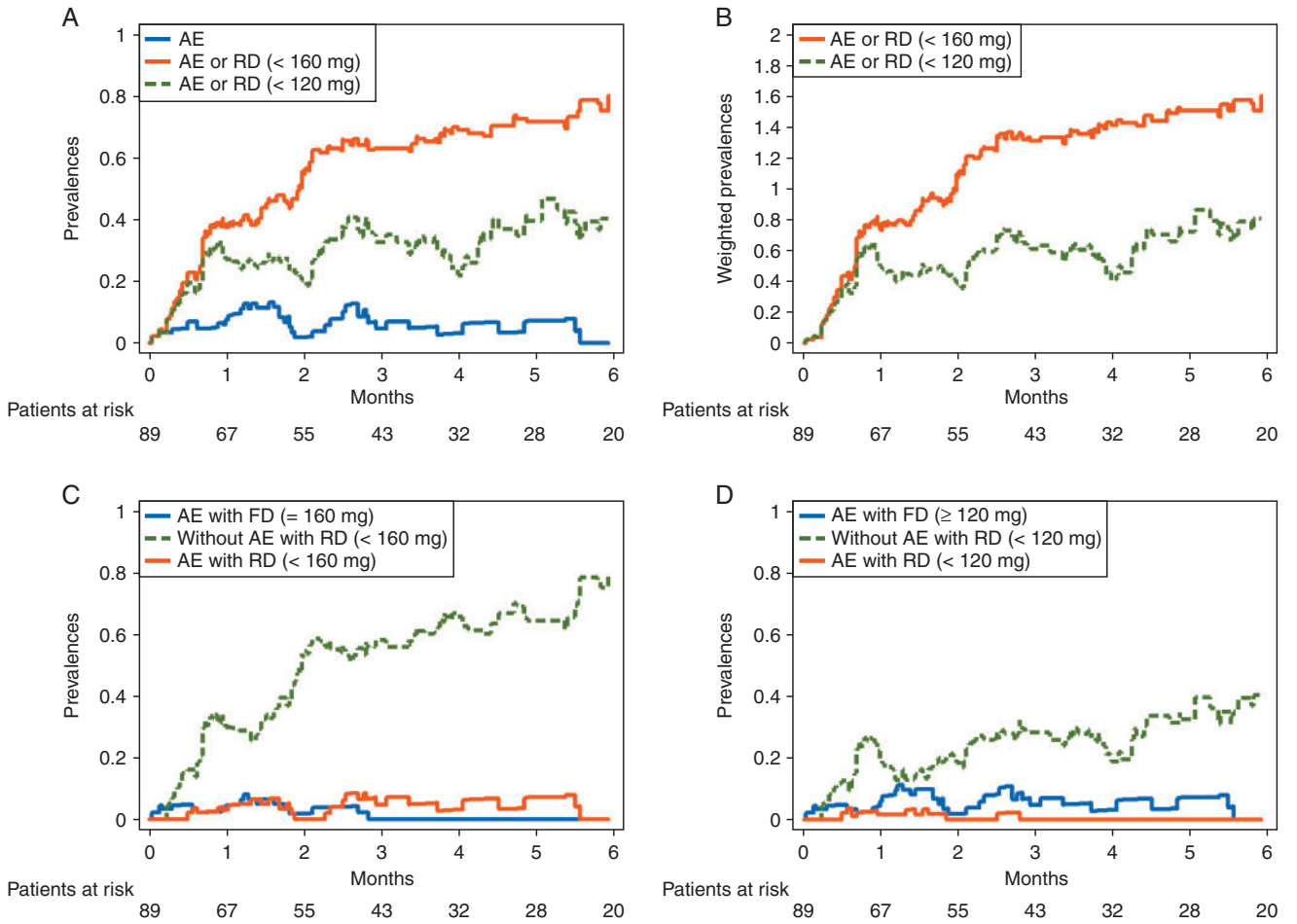

Figure 2. (A) Prevalence of mucositis/stomatitis (blue (online) curve). Prevalences of mucositis/stomatitis or reduced doses (orange (online) curve <160 mg, green (online) dot curve <120 mg). (B) Weighted prevalences of mucositis/stomatitis or reduced doses (orange (online) <160 mg; green (online) dots <120 mg). (C) Individual prevalences of mucositis/stomatitis or reduced doses <160 mg or treatment discontinuations. (D) Individual prevalences of mucositis/stomatitis or reduced doses <120 mg or treatment discontinuations.

methodology can also be used to analyze pertinent AE in an isolate way, such as lower grade fatigue.

Individual and overall prevalence curves make it possible to obtain comprehensive information. As different utility weights may be assigned to each state, we proposed to summarize the information using wPrevalence, i.e. a weighted sum of each individual prevalence. The interpretation of this wPrevalence, however, is more complex than for classical prevalence. This approach was initially developed in the context of complications linked to categories of AE severity [15]. If the categories of severity correspond to grades of toxicity, this information can be interpreted as a mean grade over time. A similar measure, but which does not deal with censored observations, has recently been proposed by Thanarajasingam et al. [10]. We extended this method to deal with dose adjustments and treatment discontinuation. In our context, wPrevalence does not represent a mean grade but rather a mean 'drug' score over time: the higher the score, the less the drug is efficient (i.e. a lower therapeutic effect and/or higher toxicity). Weights were thus defined by giving more importance to the therapeutic effect rather than to tolerance. This may not always be the case, however, as in managing elderly patients where QoL prevails over biological efficacy. Since the average score is dependent on the utility weight assigned to each state, a sensitivity analysis can be carried out by varying the weight for each state across a range of values. In this study, we penalized the placebo arm by considering all patients in intermediate or worst health states. According to this hypothesis, the prevalence of AEs was lower in the placebo arm, but interestingly enough, the wPrevalence was higher. This approach can also be useful to perform analyses by assigning different weights according to treatment effectiveness. Weights can be determined according to the observed difference in the primary outcome rather than from a *P*-value [16] or using the ESMO Magnitude of Clinical Benefit Scale [17]. If the experimental arm shows a clinically meaningful benefit compared with the control arm; it is possible to penalize the control arm in terms of toxicity. On the contrary, if the difference is not clinically relevant, the same weights can be applied to each arm. In the past, maintenance therapies obtained approval with median progression-free survival improvement of only a few weeks. In this setting, where patients are exposed to additional therapies, these approaches will be relevant. This concept would not always make sense in every clinical context, for example in supportive care or palliative chemotherapy trials. In these settings, drugs are given to improve or maintain the patient's comfort and QoL of patients and survival gains are limited.

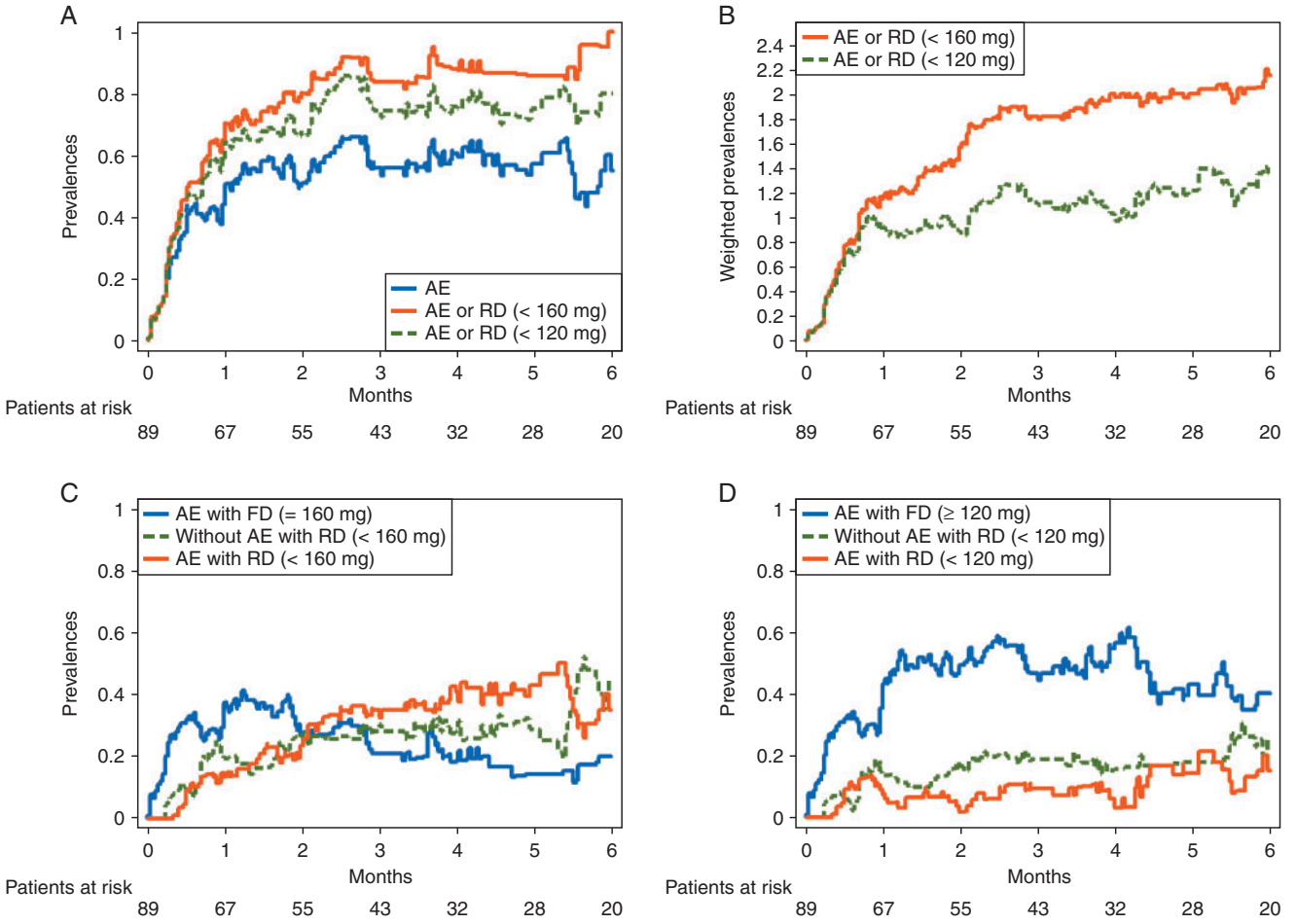

Figure 3. (A) Prevalence of regorafenib toxicity profile (blue (online) curve). Prevalences of regorafenib toxicity profile or reduced doses (orange (online) curve <160 mg, green (online) dot curve <120 mg). (B) Weighted prevalences of regorafenib toxicity profile or reduced doses (orange (online) curve <160 mg, green (online) dots <120 mg). (C) Individual prevalences for reduced doses <160 mg or treatment discontinuations. (D) Individual prevalences for reduced doses <120 mg or treatment discontinuations.

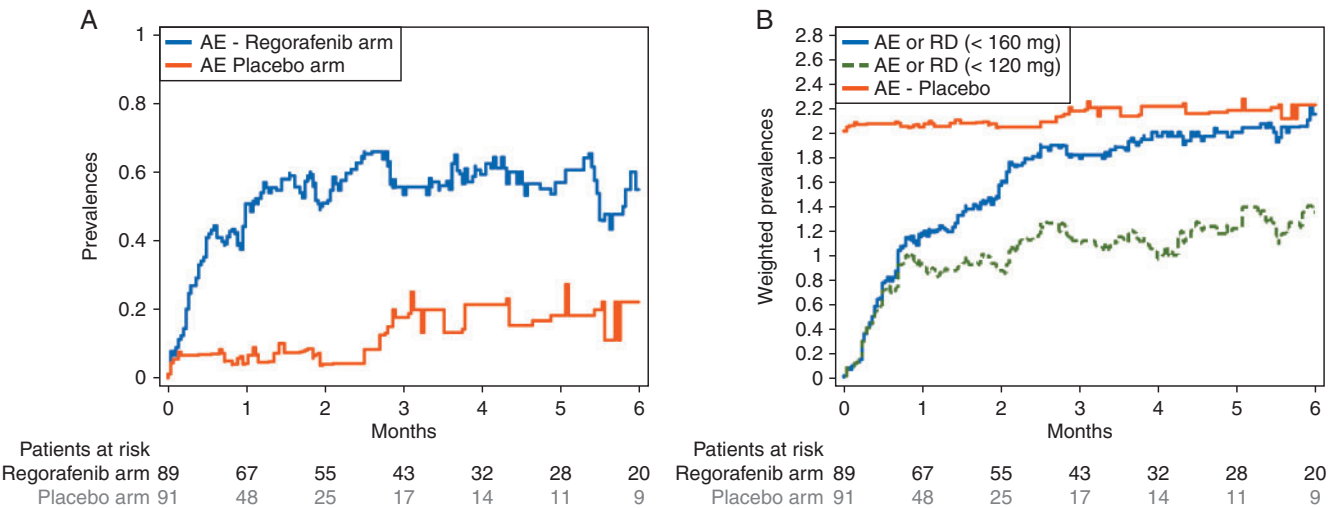

Figure 4. (A) Prevalence of regorafenib toxicity profile (regorafenib arm, blue (online) curve; placebo arm, orange (online) curve). (B) Weighted prevalences of regorafenib toxicity profile or reduced doses (regorafenib arm blue (online) curve <160 mg, green (online) dots <120 mg; placebo orange (online) curve).

In the multistate model presented in Figure 1B, we reduced complexity by summarizing treatment administration using only dose adjustments along with treatment discontinuation. More complex models dealing with other parameters of interest for targeted cancer therapies (adherence and drug exposure) may also be suitable. For oral anticancer therapies, the reported rate of patient adherence varies greatly in the literature (between 20% and 100%) [18]. Non-adherence, which may lead to a decrease of a drug's therapeutic effect and to minimizing the incidence of severe AEs, can be categorized in different health states according to the level of patient compliance [18, 19]. In various cancers, there is evidence that targeted drug exposure correlates with treatment efficacy and toxicity [5, 20, 21]. Overall, health state can be defined according to observed and targeted drug concentrations; this last concept is of particular interest in the case of therapeutic drug monitoring [22].

Our data clearly demonstrate the limitation of the succinct description of AE characteristics and drug administration for therapeutics that are given continuously over protracted periods of time. Prevalence and wPrevalence provide a general framework highlighting the importance of jointly analyzing safety and treatment administration data. With these approaches, both the prevalence of patients receiving a sub-optimal treatment over time and the prevalence of AEs may be evaluated. These methodologies and associated figures permit to obtain a careful balance between toxicity, drug administration and efficacy. Evaluation of this balance is primordial in the development of new anticancer therapies. Further analyses should apply this methodology to previously published randomized clinical trial data. Joint evaluation of drug administration and safety data can help regulatory agencies and clinicians in evaluating the benefit–risk ratio of different therapies in their treatment choice.

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Disclosure

The authors have declared no conflicts of interest.

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