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CCR Translations

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Advantages and Adversities of the Weighted Toxicity Score

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It is imperative to develop a comprehensive toxicity score that will capture, convey, and compare adverse events of agents that are therapeutic options for the same disease state. The weighted toxicity score tool is a valuable aid in the shared decision-making process of therapeutic choice between patients and providers. *Clin Cancer Res; 24(20); 4918–20. ©2018 AACR.*

See related article by Carbini et al., p. 4968

In this issue of *Clinical Cancer Research*, Carbini and colleagues (1) report a weighted toxicity score (WTS) that would serve as a valuable tool for practitioners to use when presenting therapeutic options to patients. Toxicity is frequently the rate-limiting step that restricts the clinical application of cancer therapy. The choice of small-molecule oral tyrosine kinase inhibitors (TKI) is appropriate to develop the score as they tend to have a similar adverse event profile for the class of agents and have a pattern of continuous administration with development of both acute and chronic toxicity. In addition, the choice of studies comparing with placebo gives patients a clear idea of what to expect with each of the therapies as compared with the toxicities induced by the disease state, and seems like a reasonable way to compare different treatments across studies. Dose adjustment was used as an objective measure to quantify the score. This is especially appropriate for oral TKI therapy, as dose reduction is a typical management utilized to ameliorate toxicities. Including dose reduction data also enables focusing on the clinically relevant adverse events. Crystallizing the toxicities to a single numerical score helps comparison across different TKIs and comprehension of the extent of toxicity. Development of the WTS should be applauded as a step in the right direction for advancing risk/benefit discussions with the aid of an innovative and universally applicable metric.

Historically, the initial toxicity system was the one endorsed by the World Health Organization and the broad categories consisted of mild, moderate, severe, and life threatening (2). Gradually, it was recognized that a subjective score is inconsistent and leads to ambiguity. Hence the National Cancer Institute devised the Common Toxicity Criteria for Reporting Adverse Events (CTCAE), which has grown exponentially and evolved into a large repertoire of symptoms that can be now categorized reproducibly, across the globe. The tangible dose modification rates and the toxicity table, which form the basis for the WTS, stem from severe adverse events defined as per CTCAE, and result in some limitations. The pros and cons of WTS are listed in Table 1.

One of the factors that is not included in the current toxicity score is the dimension of "time." Duration of therapy is a critical factor that should be incorporated in toxicity score (3). WTS does not distinctly capture the difference between an acute adverse event that is rapidly reversed by holding the drug and that of a moderate grade toxicity that is sustained for weeks, months, even a lifetime despite discontinuing the offending agent. For example, in metastatic renal cancer, there are two new agents recently approved by the FDA (4); cabozantinib, a receptor TKI, and a combination immunotherapy of the checkpoint inhibitors; ipilimumab and nivolumab, which have a distinct set of toxicities. The incidence rates of severe toxicities appear to be similar with either of these agents; however, the impact of immune-related adverse events is far reaching due to the longer duration of sustained toxicity and the requisite immunosuppressive therapy needed for reversal. The toxicities of TKIs on the other hand tend to be rapidly reversible with the minor intervention of temporarily holding the medication and reducing the dose if the toxicity is severe. Calculation of a WTS at distinct time points will afford the patients a glimpse into the entire range of toxicity.

Multiple reports indicate that there is a tremendous discrepancy between patient-reported outcomes (PRO) and physician assessment of toxicities (5). Patient gravitation toward chat rooms or support groups is a strong testament to the power of PRO. The PRO data reflect a distinct prioritization of the toxicities that are articulated from a patient's perspective. It is also critical to obtain input from cohorts of patients across different age groups, gender, socioeconomic strata, and racial and ethnic backgrounds. PROs from post-marketing surveys are likely to be more valuable in this regard.

Most clinical trials of medications underestimate the toxicity, partly due to lack of follow-up reporting on delayed toxicities. In phase I trials, dose escalation is done only after few weeks of treatment and monitoring, for dose-limiting toxicities. In phase II or III trials of oral TKI, the uncommon and delayed toxicities such as hypothyroidism and cardiac events were noticed and reported later. Providers and patients agree that a chronic grade 1 or 2 neuropathy is likely to be severely disabling and be preserved for a lifetime as compared with grade 3 or 4 nausea and emesis from cisplatin that is rapidly reversed with adequate supportive measures. The chronic toxicities of immunotherapy that have a long-term or lifetime impact on the patient are gradually gaining visibility and absolutely need to be incorporated into toxicity scores.

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Table 1. Pros and cons of the WTS

Pros of WTS	Cons of WTS
Easy to comprehend	Does not include duration of toxicity
Single numerical score	Only applicable for oral TKIs
Patient-reported outcomes incorporated	Chronic toxicities may not be included in score
Incorporating dose reductions as basis of score	Lack of application to therapies without dose reductions
Placebo-controlled trials selected	Limited by study design and data collection

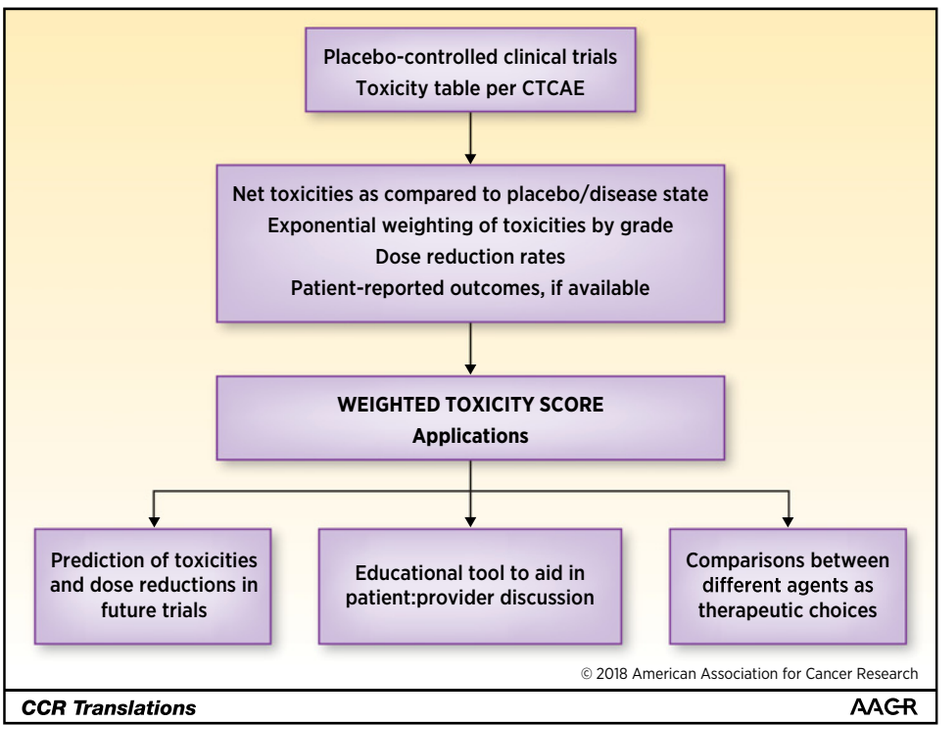

Figure 1.
Design and application of WTS.

The WTS does not transcend across the different mechanisms of action, and between agents utilized in a specific disease, so currently comparison between different agents with distinct mechanisms is not applicable.

The ideal tool should capture, convey, and compare toxicities of multiple agents that are therapeutic options for the same disease state. It needs to be easy to assimilate and communicate for all patients and providers alike. With these goals in mind, it would be useful to incorporate WTS at different timepoints categorizing the toxicity patterns and enhance patient and provider communication (Fig. 1). In future, the vision should be to develop WTS for each therapeutic agent or combination with incorporation of frequency of dose reductions and interruptions. Assigning acute and chronic scores for individual agents could also be considered as a potential method to highlight the time distinction between toxicities.

Informed decision making is the cornerstone of oncology therapeutics. Multiple therapeutic options are now available for the same disease state requiring a complex, shared decision-making process between patient and provider. The information shared and the communication thereof constitute a critical piece of this process. Through decades of drug development, the ideal methods of capturing, comparing, and conveying toxicities have remained elusive. The WTS represents an innovative step in the right direction and should be expanded and updated. Conveying contemporary and comprehensive toxicity information needs to be a critical part of oncology training and should be the commitment from every provider to their patient community.

In summary, the WTS reported by Carbini and colleagues has the potential to convey toxicity data in the form of a condensed numerical score and holds promise for wide clinical application during consideration of TKI therapy in oncology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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