EDITORIAL

Industry and MASCC—an opportunity not to be missed

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Introduction

Toxicities associated with cancer treatment have been recognized since the first patients were treated with cytotoxic therapy and have been redescribed, discussed, categorized, and recategorized for decades. Simultaneously, the limited success and toxicities of many cytotoxic treatment regimens necessitated the introduction of new approaches to cancer treatment which have largely been driven by advances in understanding of cancer biology. Cancer therapies have continuously evolved to include novel radiation delivery technologies, an expanding range of cytotoxic agents, and new targeted drugs and immunotherapies [1–4]. Though the benefits have been extensive, advances also add to the variety and complexity of treatment-associated complications [5, 6]. To further complicate matters, combinations of radiation, medications and combined classes of therapeutics are the norm. Spending for oncology drug development led all other clinical indications last year and this quest for advanced therapeutics will continue, catalyzed by improvement in patient outcomes and the vast commercial potential of successful cancer treatments [7].

Therapy-associated toxicities persist along with these advances—perhaps more troubling, costly, and biologically complex than ever before. The incidence of toxicities has hardly wavered while, disappointingly, clinical options to prevent or mitigate them have barely changed. Publications in the

space are largely dominated by descriptive studies and small clinical trials in which existing treatments are repurposed. While developmental oncology studies have flourished at the biological, translational and clinical levels, research to understand, predict, and lessen toxicities have moved much more slowly and have largely depended upon industry support. Given the clinical importance of oral toxicities, and because, both biologically and clinically, they represent a sentinel complication of cancer treatment, we present a discussion of the challenges and opportunities which will hopefully provoke new thinking and actions.

Where do we stand—the example of oral toxicities

Data from descriptive and epidemiological studies of oral toxicities have largely framed the incidence, course, and impact of standard cytotoxic therapies. Radiation-induced oral mucositis with or without chemotherapy in patients being treated for oral and oropharyngeal cancers is particularly well-characterized. This regimen has provided the primary study population for industry-sponsored clinical trials, which require robust patient numbers, highly defined study cohorts, and sophisticated endpoint of training and regulatory oversight at costs which often exceed academic or NIH budgets [8, 9]. Additionally, many of these studies include biological endpoints such as biomarkers and genomics, which although directed at understanding the study drug, also provide basic pathobiological knowledge.

Though mucositis has been extensively studied, the lack of uniformity in grading across reported treatments has led to confusion, under-reporting, difficulties in comparing the stomatotoxicity of one regimen with another, and inconsistencies in judging the effectiveness of interventions. One only need look at the huge range in the reported incidence of "severe toxicities" associated with the most common cancer treatment regimens. For example, most oncology trials use CTC criteria to report regimen toxicities. This scale is now in its 5th iteration,

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is based upon consensus opinion, and is constantly undergoing amendments. In several instances, grading criteria are ultimately judgmental. Thus, the toxicity profile of a drug tested in 2006, at which time CTCv3 was used, might be different from an assessment of the same drug in 2020 assessed with CTCv5. Likewise, the RTOG scale has evolved continuously with criteria for severe mucositis morphing from one version to the next. While this evolution has resulted in more substantive and accurate tools, the lack of continuity over time has been problematic. The WHO scale has been uniquely favored for OM clinical trials, but the WHO score relies on clinician examination. Unless there is examiner standardization, there is a real risk of inconsistency and inaccuracy in reporting. While the impact of frequency of assessment on mucositis scoring has been studied, there is no uniformity with which it is performed. As a result, disparities are common even in the most fundamental studies of mucositis epidemiology.

While frequently devastating to patients, oral toxicities have, like many others, often been viewed by oncologists as a temporary nuisance that is part of the cost of tumor mitigation. "Mouth sores" may be temporarily painful, but since they are self-resolving, are considered a small price to pay for successful therapy. Salivary dysfunction may necessitate a change in diet or the need for a patient to awaken to rinse and hydrate, and chronic dry mouth following therapy may lead to dental damage, oral infection, and compromised oral function, but none are a direct survival threat. Couched in these terms, oral toxicities seem like an annoyance, rather than a significant consequence of therapy. However, oral toxicities wreak acute and chronic havoc with patients, biologically, symptomatically, functionally, emotionally, and socially. Oral complications are not only drivers of severe pain but may directly threaten compliance with anti-cancer regimens while increasing the direct and indirect burden of disease functionally, psychologically and financially [10].

Recognizing that the oral toxicity landscape suffers from two significant deficits—(1) a consistent and documented understanding of the epidemiology and impact of conventional therapies, and (2) the need to stay current as new drugs and regimens are introduced. We propose an initiative that recognizes that industry, collectively, maintains the most pristine data source for many cytotoxic regimens and advocate for a MASCC-centric initiative that, in collaboration with industry, would create, collate and maintain best care/placebo database in which industry would share toxicity data.

Industry and MASCC—an opportunity not to be missed and a different way of thinking

Like most professional, not-for-profit, medical societies, MASCC has a quixotic relationship with industry primarily driven by an underlying distrust. Not without reason, there is organizational queasiness resulting from a belief that everything that industry does is motivated by the "bottom line." Hence, industry-supported research, meetings, etc. ultimately have the motive of soliciting favor—spinning clinical data, increasing drug sales, and so forth. Yet, MASCC (like other similar societies) openly solicits and welcomes industry's educational support of meetings and other activities while shunning integration into true membership participation. Why is it acceptable for an academic who receives consulting fees from companies to serve on MASCC guideline committees and hold office, but not tolerable for a scientist who is employed by a company to hold a similar position?

It would be naïve to believe that industry's only motive is the goodness of mankind. But why to some assume that profit and altruism are considered to be mutually exclusive? Merck's Mission Statement reads: "To discover, develop and provide innovative products and services that save and improve lives around the world," while Novartis' reads, "Our mission is to discover new ways to improve and extend people's lives." Fluff from the public relations department or truth? Probably both. The fact is that the pharma industry is filled with smart, committed professionals (many recruited from academics) who desire to be part of a process which has the potential of translating discovery science to effective clinical practice.

The reality is that no new drug will ever effectively reach patients if the pharmaceutical industry is not an integral component of the pathway. Furthermore, for MASCC's focuses, there is no richer data source of current and evolving toxicities that will impact supportive cancer care than data obtained during industry-sponsored clinical trials enabling or supporting anti-cancer agents. One in twenty adult cancer patients is enrolled in a clinical trial in the USA, about 88,000 patients [11]. Almost all oncology trials compare the new agent under study against best care regimens, as placebo-controlled trials may not be ethical or realistic. Assuming most oncology studies randomize test vs. best care at a 1:1 ratio (not always the case), data from 44,000 control patients ends up in industry databases in just 1 year. Not only will the control cohort serve as an efficacy control for the drug under study, but it provides a comparator to describe adverse events. From the standpoint of MASCC, a treasure trove of epidemiologic data would be available to describe toxicity incidence, clusters, demographic and comorbidity risk factors, trajectories, and response to interventions. This is certainly a more robust data source than current institutional chart reviews or meta-analyses. Furthermore, the inclusion of biomarkers and biologic end points in some studies, and the ability to include these measures in future trials, may enhance the understanding of mechanisms of underlying toxicity that can accelerate prediction, prevention, and management.

There is no better time for MASCC and industry to actively seek true scientific collaboration in the form of establishing a centralized databank into which control patient data would be

"deposited" and maintained. Conceptually, any company making a deposit, would then be able to make a "withdrawal." From a company's standpoint, this might mean that the number of control patients accrued into a clinical trial could be supplemented by banked data resulting in a reduction in accrual, faster trial completion, and reduced study cost. For MASCC, access to such data provides the basis for the outcomes noted above and a huge incentive for MASCC membership. While the topic of this commentary focuses on oral toxicity, the databank would also stimulate studies assessing toxicity clustering and encourage interdisciplinary collaboration.

The logistics of such an undertaking are not trivial, but certainly possible with commitment and leadership. Integral to effectively using data would be the necessity to develop algorithms which can be used to normalize grading to a single scale. This would enable more accurate and consistent toxicity descriptions and provide a conduit for the melding of study data, regardless of when a study was performed. It is not the purpose of this commentary to discuss the many details that would be required or come up with solutions, but to start a discussion related to appropriate collaboration. It seems to us that such a bold initiative would be a win for all—especially our patients.

Compliance with ethical standards

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