VOLUME 25 · NUMBER 26 · SEPTEMBER 10 2007

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Evaluation of Early and Late Toxicities in Chemoradiation Trials

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Submitted July 6, 2007; accepted July 25, 2007.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/07/2526-4096/$20.00

DOI: 10.1200/JCO.2007.13.3983

A B S T R A C T

Combined chemoradiotherapy is increasingly becoming a standard of care for the nonoperative management of a variety of solid malignancies. A string of randomized controlled phase III trials have shown statistically significant and clinically relevant improvements in outcome, ostensibly without any apparent increase in late toxicity. However, the reliability and the sensitivity of toxicity reporting in most trials are questionable. Audits and phase IV studies suggest that the chemoradiotherapy success comes at a price in terms of late toxicity. This review presents some of the challenges in recording, analyzing, and reporting toxicity data. Methods for summarizing toxicity are reviewed, and a new investigational metric, the TAME reporting system, is discussed. The need for special vigilance in the era of molecular-targeted agents is emphasized because of the possibility that unexpected serious adverse events with a low incidence may occur. Finally, we discuss how progress in molecular pathology and radiation biology may provide novel opportunities for stratifying patients according to risk of adverse effects, interventional targets for reducing or treating adverse effects, and surrogate markers of normal-tissue injury.

J Clin Oncol 25:4096-4103. © 2007 by American Society of Clinical Oncology

BURDEN OF TOXICITY FROM CANCER THERAPY

All cancer therapies developed to date are associated with a spectrum of early and late adverse effects, also known as toxicity, safety, or adverse event profiles. Because of the wide variety and severity of events, toxicity data in oncology are inherently difficult to evaluate. The development of increasingly complex multimodality and multiagent treatment programs creates further challenges. A few trials have been stopped for excessive early or late toxicity, indicating that investigators are exploring the limits of treatment intensity or patient tolerance. One recent analysis[1] noted an almost 500% increase in the number of early toxicity events when comparing aggressive chemoradiotherapy with standard postoperative radiotherapy in head and neck squamous cell cancer (HNSCC) patients treated in the 1990s.

At the same time, at least in part as a result of more effective therapies, the number of cancer survivors in the United States has tripled over the last 30 years; the 2001 estimate was that 9.8 million people, or 3.5% of the population, were alive after a diagnosis of nonskin cancer.[2] The burden of long-term treatment-related adverse effects among cancer survivors is not well documented, but studies have shown that both physical and social functioning are affected in many patients.[3-6] Thus, late adverse effects are increasingly becoming a cancer survivorship issue, and the documentation of the magnitude of the problems, as well as research into strategies for relieving the burden of late effects, are rightly seen as research priorities.

Early effects are expressed during or within a few weeks after the end of therapy, typically in tissues and organs with a hierarchical proliferative structure, such as the hematopoietic system, the mucosal lining of the GI tract, or the skin. Late effects become manifest after latent periods ranging from months to years in humans and include radiation-induced fibrosis, atrophy, vascular damage, neural damage, and a range of endocrine and growth-related effects. The pathogenesis of these effects is varied, but the fibrogenic response pathway[7] plays a major role in many of these effects. Early effects are typically transient (ie, the affected tissue will recover and symptoms and signs will improve), but there are data emerging for a number of tissues supporting the concept that severe early effects may be causally related to subsequent late effects.[8] Also, severe early effects may cause poor compliance to therapy or may even cause the death of the patient. Late effects are often persistent or even progressive in severity and may affect the long-term health-related quality of life of a cancer survivor or compromise the survival benefit from therapy.

Although the conduct and subsequent publication of a trial of a novel cancer therapy without generally accepted clinical end points for assessing

efficacy is unthinkable, it is unfortunately still true that many, if not most, trial reports fail to document toxicity in sufficient detail.[9] Quantification of toxicity is inherently more complex than quantification of efficacy, in part because the set of possible adverse events is virtually unlimited and in part because adverse events vary widely in severity from individual to individual even with the same therapy. Even when studies include toxicity data, the lack of standards for reporting and data analysis means that comparisons between studies are often not possible or lack credibility, and even comparisons within studies (ie, between trial arms) often lack statistical power.[10]

Methods for reporting of adverse events in oncology have substantially evolved over the last 70 or so years of organized clinical cancer research. For additional background on the development of adverse event terminology, grading systems, and reporting guidance by the National Cancer Institute and the US Food and Drug Administration, the reader is referred to an upcoming review.[11] In the present review, we will focus on reporting issues and methods relevant to the use of chemoradiotherapy. We will extensively draw on examples from the treatment of HNSCC, but much of the discussion will apply to other tumor types as well. We will use recent trial outcomes published in the literature as examples to make the discussion more concrete. These trials have been selected mainly on the basis that they report toxicity in sufficient detail to serve this purpose. Thus, they are typically among the better studies in the literature in terms of toxicity reporting.

COMBINING DRUGS AND RADIATION

Biologically, there is a strong case for combining drugs with radiation in a variety of solid malignancies.[12-15] However, the success in terms of improving tumor outcome in numerous sites comes at a price in terms of early and late toxicity. What is even more frustrating is that this price has not been well documented in the pivotal trials that paved the way for a change in clinical practice.

A clinical example is HNSCC, where chemoradiotherapy has been shown consistently in a number of overviews to yield a clinically relevant improvement in locoregional control and overall survival.[16-18] Many early reports concluded that, although early toxicity was more severe, this gain in efficacy was achieved without a significant increase in late toxicity. However, nonrandomized studies after the introduction of combined-modality therapy in the clinic, which are sometimes referred to as phase IV studies, leave little doubt that these treatments are associated with enhanced late adverse effects. For example, swallowing dysfunction and aspiration are seen in a high proportion of patients with HNSCC after combined chemoradiotherapy,[19-22] with prevalence estimates ranging from 30% to 100% depending on the methodology used and the sensitivity of the assay. Studies looking at video fluoroscopy changes from baseline function have high sensitivity to detect changes in a large proportion of all patients. Also, the risk of sensorineural hearing loss,[23] a long-recognized late sequela of head and neck radiation therapy involving a non-negligible dose to the cochlea, seems to be substantially increased after cisplatin combined with radiation.[24-26] It seems relevant to ask the following question[27]: Have we gone so far in our attempts at organ preservation in HNSCC that we have sacrificed organ function in a high proportion of patients?

Among the determinants of normal tissue toxicity are radiation dose distribution and target volume. The wider use of intensity-modulated radiation therapy[28] has created new challenges in terms of recording and reporting dosimetric descriptors that correlate with normal tissue risk. This will become even more of an issue if current research into theragnostic radiation oncology,[29] where the aim is to deliver nonuniform dose distributions to the target volume based on three-dimensional maps from functional or molecular imaging, leads to a wider use of such techniques. However, these novel radiation dose planning and delivery techniques also hold considerable promise for improving treatment tolerance, which in turn may create opportunities for more intensive combined-modality approaches without excessive toxicity.

MOLECULAR-TARGETED AGENTS AND VIGILANCE FOR UNEXPECTED ADVERSE EVENTS

Clinical development of molecular-targeted agents combined with radiation pose further challenges in terms of documenting adverse events. Processing of normal tissue injury involves a large number of different cell types, cytokines, and growth factors[7] that may potentially be affected by molecular targeting. An example is the initially unexpected link between trastuzumab, a monoclonal antibody against the HER-2/neu (erbB2) receptor, and heart failure in a small percentage of patients treated with this drug.[30] A proposed molecular mechanism behind this observation is that anthracycline-related cardiotoxicity may, to some extent, be reduced through activation of erbB2-dependent cardiomyocyte-survival pathways and that these will be blocked by trastuzumab. It seems that the cardiotoxic effects of trastuzumab may be avoided or reduced by administering this agent without agents causing cardiotoxic stress.[31] Also, imatinib mesylate is cardiotoxic[32] and has furthermore been shown to alter bone remodeling.[33] Perhaps it is to be expected that the antiangiogenic agent bevacizumab is associated with an increased risk of bleeding, hypertension, and delayed wound healing,[34,35] which are toxicities that, in some cases, may become life threatening. This seems to be the toxicity profile for several antiangiogenic compounds, and it is hoped that improved understanding of the molecular mechanisms behind these effects will lead to interventions for preventing or treating the effects.[36]

Current enthusiasm for combining targeted agents with radiation is fueled by the large randomized trial by Bonner et al[37] who randomly assigned 420 patients to radiation therapy with or without cetuximab, a recombinant mouse/human chimeric monoclonal antibody against the epidermal growth factor receptor, and found a highly significant 9% improvement in 2-year locoregional control. Interestingly, this improvement was apparently achieved without a significant increase in major toxicities except for acneiform rash and infusion reactions. The reported incidence of grade 3 or greater mucositis was similar in the two arms (52% and 56% for radiation alone and radiation plus cetuximab, respectively; $P = .44$). The investigators collected quite detailed toxicity data, reporting on 30 different items in their article. Although grade 3 or greater toxicity was generally low ($< 10\%$ for 25 of the 30 toxicities), the incidence of any grade of these 30 items was more than 10% in one or both trial arms. For 23 of the 30 items, the incidence in the cetuximab arm exceeded that of the control arm, and this was a statistically significant difference ($P = .005$, sign test). Whether this is an early indication of a clinically meaningful difference

in toxicity between the two trial arms is not clear (see also the discussion later in this article of the weight loss data from this trial). Still, toxicity seemed to be lower than what is typically seen in combinations of cytotoxic drugs with radiation. In an effort to leverage this lower toxicity profile, two current Radiation Therapy Oncology Group (RTOG) studies are combining both targeted and traditional cytotoxic agents.[38,39]

Our quest for recently developed treatments should be tempered with a measure of caution. The cetuximab HNSCC trial represents a single phase III study with modest follow-up. With additional trial experience and wider use of molecular-targeted agents in routine practice, a more complete and possibly different portrait of the safety of these agents may emerge. The potential for interactions or synergistic normal tissue effects will need to be carefully monitored.

IS TOXICITY UNDER-REPORTED?

New therapies are most often tested in specific populations using strict inclusion and exclusion criteria. Exclusion criteria typically comprise various types of comorbidity or lab test values outside a defined range and, in some trials, also the patient's age. All of these factors may potentially affect the generalizability of trial findings to a general patient population.

Wide variations in the methods and completeness of toxicity reporting have been documented, especially in HNSCC studies.[40,41] These observations have caused concerns about under-reporting, raised questions regarding the reliability of toxicity data, and cast doubt on our ability to understand and compare morbidity between studies. Potential sources of reporting variability include existence of multiple terminology and grading systems, the frequency and intensity of protocol-directed toxicity evaluations, limited guidance or standards for safety data reporting, and variations in methods of summarizing and presenting end results.

A few examples related to a single but critical toxicity event in HNSCC trials, mucositis, illustrate how toxicity reporting may vary. Hao et al[15] surveyed the incidence of grade 3 or greater mucositis in eight randomized controlled trials of platinum-based chemoradiotherapy showing a survival benefit from combined modalities. In a total of 10 combined-modality trial arms, the average incidence of grade 3 or greater mucositis was 28%, with only two trial arms recording an incidence exceeding 40% (42% and 49%). These rates are considerably lower than what has been seen in a number of other series. For example, Bieri et al[42] conducted an audit of early normal tissue reactions in 182 patients receiving combined chemoradiotherapy in four Swiss centers and found that, in three of these centers, the grade 3 or greater mucositis incidence exceeded 80%. Lee et al,[43] from the Memorial Sloan-Kettering Cancer Center, reported grade 3 or greater mucositis rate of 66% and 72% in patients treated with chemotherapy and intensity-modulated radiotherapy or conformal radiotherapy, respectively. In mucositis intervention trials, where this end point is more carefully evaluated, rates of mucositis are substantially higher than in therapeutic trials. The rate of high-grade mucositis using conventional fractionation was 25% in the large RTOG fractionation trial but 65% in the iseganan mucositis intervention trial.[44]

Boiling complex toxicity data down to a maximum grade for trial reporting may not present a complete picture of the burden of toxicity. The RTOG[1] recently analyzed high-grade events in more than 2,300 patients in five trials (13 treatment arms) and showed that the maximum-grade summary method excluded 30% to 70% of high-grade toxicity events. The authors also looked at the worst grade over time method (maximum-time). They concluded that both the maximum-grade and maximum-time summary methods make the more intensive treatment programs seem less toxic than they really are.

Paradoxically, although toxicity data are frequently under-reported in the literature, many trials do in fact collect a deluge of normal tissue effect data. For example, the United Kingdom Medical Research Council trial of continuous hyperfractionated accelerated radiotherapy in HNSCC[45] recorded more than 53,000 individual acute toxicity data items.[46] Similarly, Mahoney et al[47] noted that 117,999 adverse event data items had been recorded in 1,016 patients in a single phase III trial, or more than 117 events per patient.

The wide range of therapies and the sheer volume of adverse events generated in cancer therapeutics mean that safety data are difficult to capture, summarize, and compare in a consistent way. Perhaps the more important question is not whether toxicity is under-reported, but rather, given limited resources, whether we are capturing and reporting the most relevant events in a given trial. Bentzen et al[48] suggested distinguishing between routine studies, where the aim is to summarize the whole burden of toxicity, and toxicity-specific studies, where the aim is to investigate the pathobiology underlying these effects and thereby develop strategies for their prevention or amelioration. In the latter case, the emphasis will be on specific end points.

It is not feasible to comprehensively capture and report all the details of all adverse events generated in modern cancer treatment. Reporting of AEs is highly dependent on the screening methods and the rigor used to elicit toxicity information.[49-53] One study uncovered 22 times more adverse events using detailed patient-reported questionnaires compared with unstructured reporting.[49] Thus, there is a need to match data collection and reporting practices to the phase, modalities, treatment intensity, and aims of the study.[11]

METHODS FOR REPORTING LATE EFFECTS

Early reports of trial outcome seem generally to underestimate the risk of late toxicity in long-term survivors.[10] An example of this is provided by the Groupe d'Oncologie Radiothérapie Tête et Cou study of late effects among 5-year survivors in a trial comparing radiation alone with radiation combined with chemotherapy in patients with HNSCC.[54-56] Although the initial trial showed approximately a 10% incidence of grade 3 or greater late effects in both arms of the trial, a subsequent cross-sectional study among the 5-year survivors showed that 47% of patients in the radiation arm and 82% of patients in the combined-modality arm had developed grade 3 or greater toxicity and that this difference was statistically significant in this group of patients.

One reason for this drastic change in toxicity estimates was that the initial Groupe d'Oncologie Radiothérapie Tête et Cou article reported simple ratios of number of patients with grade 3 or greater late effects divided by the total number of patients treated. Alternative and more advanced methods of late effects analysis are available but not consistently used in journal reports. Figure 1 shows two methods of late effects reporting for the RTOG 90-03 fractionation study. (Note: Although this review focuses on chemoradiotherapy, unfortunately there are few examples of formal analysis of long-term outcomes from

chemoradiotherapy trials!) Actuarial estimates, using Kaplan-Meier calculations, of late grade 3 to 4 events are shown in Figure 1A. Actuarial methods are designed to adjust for incomplete follow-up either because the patient was still alive and without the relevant adverse effect when last seen or because the patient died of cancer or unrelated causes (so-called competing risks) without having expressed the adverse effect.[57] Actuarial rates provide an estimate of the cumulative incidence of any late event that ever becomes clinically manifest in long-term survivors. Therefore, it can be argued that this reflects the level of biologic injury caused by the treatment that would be observed if all competing events could be eliminated.

In addition to actuarial estimates of incidence, it is informative to estimate prevalence as a function of time. The reason is that some late events are resolved by medical intervention or spontaneously improve with time. This is captured in annual prevalence rates (Fig 1B), reflecting the toxicity burden for survivors in each year of follow-up. Note that prevalence depends on both the rate of induced toxicity as well as how aggressively this is managed. The latter aspect will become even

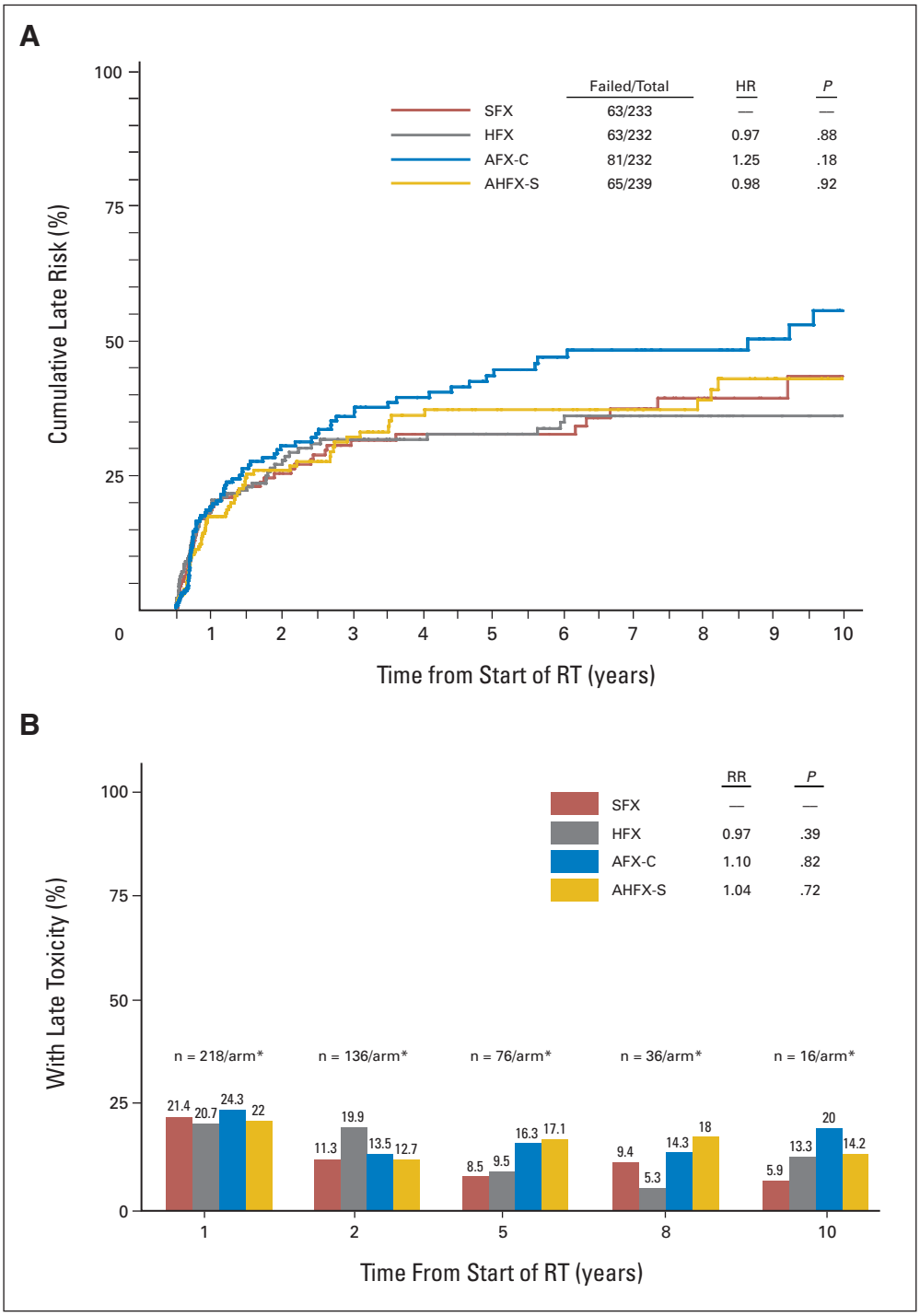

Fig 1. (A) Time to late grade 3 or greater toxicity. (B) Annual prevalence of grade 3 or greater late effects. RT, radiotherapy; HR, hazard ratio; RR, relative risk.

more important with the advent of more effective molecular agents for management of late toxicity.[7] Both actuarial incidence and prevalence estimates are more relevant than crude incidence rates (responders divided by patients), each providing different information on the occurrence of late toxicity and its time evolution.

SURROGATES FOR GLOBAL TOXICITY

Treatment compliance and weight loss may serve as surrogates for tolerance and global toxicity and are often reliably recorded in a trial. Compliance to the planned treatment schedule reflects, in part, early toxicity and, in part, the overall performance of the patient population in a trial. Note, however, that compliance also depends on institutional policies, experience, and supportive care. Khalil et al[58] showed that the actual biologic effective dose delivered in four altered fractionation trials in HNSCC was typically 2 to 6 Gy lower than planned per protocol. However, institutions participating in more than one of the trials tended to do consistently well/poorly in terms of compliance, and furthermore, compliance improved significantly with calendar year of accrual, reflecting an increasing awareness of the importance of keeping the overall treatment time as close as possible to the prescribed time.

Weight loss is an easily measurable objective parameter that has the statistical advantages of producing a continuous scale outcome measure indicating a change from the patient's pretherapy baseline. In the Swiss audit,[42] 30% of the patients receiving combined chemoradiotherapy experienced a weight loss of more than 10% compared with 10% of the patients who were treated with radiation alone.

In the trial by Bonner et al,[37] there was no significant difference in the incidence of grade 3 or greater mucositis in the two arms (52% and 56% for radiation alone and radiation plus cetuximab, respectively; $P = .44$). However, the proportion of patients losing more than 5% of their body weight at baseline went up from 72% to 84% ($P = .005$) when cetuximab was added to radiation. Whether this is a reflection of functional mucositis and dysphagia that was not picked up by the routine scoring of toxicity items required by the trial protocol is not clear. The incidence of grade 3 or greater weight loss was 7% and 11% in the radiation alone and radiation plus cetuximab arms, respectively ($P = .12$). Note that the range for grade 1 to 2 weight loss is rather wide (5% to 20%).

STATISTICAL RESOLUTION VERSUS CLINICAL RELEVANCE

A recurring challenge in the analysis of adverse event data is to summarize mountains of data comprised of dozens of adverse event types, each with 4 grades, and to identify the most important and clinically relevant end points for consideration and formal analysis. Some comparisons may be statistically significant yet cause little clinical concern. Conversely, for some patients with specific health concerns or limitations, even small differences in risk may translate into functionally important differences in outcome.

Although there are clear trial-specific safety considerations, there are also wide variations in data summary and presentation that are primarily caused by a general lack of published guidance or forethought.[41] Nonetheless, the most common practice is to present incidence data for each event type (term) either for all grades or by grouping low grades (grades 1 and 2) versus high grades (grades 3 and 4). Common Toxicity Criteria gradings were designed with generally uniform severity scaling. Close attention was paid to the boundary between grade 2 and grade 3, demarcating a clearly higher level of severity.[11] Thus, grouping grades 1 and 2 versus 3 and 4 can make sense in an overview or broad summary. In addition, grade 3 to 4 events are often used to trigger dose reductions, supportive care interventions, or special reporting in protocol-specific guidance. Whether grade 3 or greater effects are in fact more reliably scored has not been systematically tested. Unexpected grade 3 and 4 events require even higher scrutiny and confirmation, raising confidence in the reliability and completeness of high-grade data capture. However, consolidating all event terms by grade (maximum-grade approach) can be misleading, as noted in the Is Toxicity Under-Reported? section, and may reduce the statistical power of the trial, as discussed in the following section. Also, recording only maximum grade of toxicity or grade 3 or greater toxicity may neglect a considerable burden of lower grade adverse effects.

These issues directly speak to the need to develop a protocol-specific safety plan for each study.[11] In this way, the most important clinical issues will be addressed, and specially selected tools and appropriate data collection methods will be ensured. The use of preplanned safety analyses will also increase confidence in the end results presentation.

RARE EVENTS AND STATISTICAL POWER

Statistically, lower grade adverse effects will have a higher incidence, and this will, generally speaking, increase the statistical power because there will be more events available for analysis. The clinical and biologic question is whether lower grade effects can serve as the canary in the coal mine when testing new therapies.

As an example, two of the four arms in the randomized phase III trial by Buckner et al[59] compared carmustine and standard fractionated radiotherapy with (arm C) or without (arm A) cisplatin in 401 patients with newly diagnosed glioblastoma multiforme. Grade 3 hearing loss occurred in 5% and 3% of the patients in arms C and A, respectively, and this difference was not statistically significant. Looking at any grade of hearing loss, the incidence was 36% and 9% in arms C and A, respectively ($P < .00001$). Because hearing loss is often irreversible, this difference is likely to be considered an important finding. It might also be instructive to carefully analyze audiograms for correlations with platinum dose and radiation dose distribution.

Another way to increase the number of events available for analysis is to pool data from multiple toxicity items. Although this does increase the number of events, it is also associated with a loss of specificity. This can again be illustrated using data from the trial by Buckner et al.[59] Let us say, for the sake of argument, that we pool any grade of hearing loss with any grade of alopecia, the latter seen in 23% and 28% of the patients in arms C and A, respectively. To do the math based on the numbers published in the article, we need to further assume that the chance of alopecia in a patient with hearing loss is the same as in a patient without hearing loss. Now, the incidence of our compound end point is 34% in arm A versus 47% in arm C, and this difference is not statistically significantly different.

IS THERE A BETTER WAY TO SUMMARIZE TOXICITY BURDEN?

In an effort to develop a uniform way to summarize and compare the toxicity burden between cohorts or trials, a novel investigation metric, the TAME summary reporting system, was recently developed.[1] TAME places traditional adverse event data into the following three concise risk domains: short-term toxicity (T), adverse long-term effects (A), and mortality risk (M); these are then calculated for each treatment program to generate an end result (E) summary index. TAME applies new accounting and summary methods to routinely collected adverse event data. In addition to the traditional dimensions of scope and grade, TAME formally includes two new dimensions of risk, namely time and multiplicity. It is intended as a supplement, not a substitute, for traditional detailed toxicity profile reporting.

The authors reanalyzed safety data from five trials by RTOG on patients with HNSCC treated between 1991 and 2000. The trials involved 13 treatment groups and more than 2,300 patients. T-scores (reflecting acute toxicity) were generated by dividing the total number of high-grade events by the number of patients in a given cohort followed in a predefined risk interval (values from multiple risk intervals may be summed in the TAME system). The final value was then converted to a disease-specific relative risk scale. This scale permits overall risk to be understood and compared within the context of a specific disease (advanced head and neck cancer). By analyzing only high-grade events, the TAME system focuses on consolidating clinical events that carry high symptom burden or that might compromise the delivery of treatment.

T-scores in the head and neck trials analyzed showed up to 500% more acute toxicity burden in aggressive chemoradiotherapy regimens versus standard postoperative radiotherapy (Fig 2). The established method (maximum-grade) only detected a 170% difference between those treatments. Limitations were also noted. TAME provides global but nonspecific measures of overall risk. It is best applied to large datasets, and its reliability depends on the consistency of data capture. The late effects domain (A-score) has not been fully developed.

TAME needs further testing by other groups and in additional disease sites. However, it seems to have revealed important toxicity trends in the management of head and neck cancer that had not been previously quantified. It has also highlighted additional sources of potential under-reporting associated with established methods, also discussed in this review.

PREDICTIVE MARKERS, SURROGATE MARKERS, AND SURROGATE END POINTS FOR LATE EFFECTS

The long latent period of late adverse effects has created an interest in early surrogate end point for normal tissue toxicity. It may be useful to make a distinction between a surrogate end point and a predictive marker for late effects.[48] A surrogate end point is an end point that reflects the level of late effects expected from a given therapy in a population of patients without being mechanistically related to the clinical end point of interest. For a surrogate end point to be of value in the conduct of trials, it should provide more statistical power and/or a substantial lead time in terms of expression relative to the true end point. A possible surrogate end point for grade 3 or greater late effects could be grade 2 or greater or grade 1 or greater late effects. Another example is dose-escalation trials in prostate cancer where rectal bleeding has been used as a surrogate end point for late rectal toxicity,[60,61] although rectal bleeding is often treatable and not a true dose-limiting toxicity. However, a surrogate marker is associated with a high probability that a particular patient will go on to develop a clinically overt late effect. This is in contrast to a predictive marker, which is a marker assessable at baseline and associated with an increased risk of developing a specific late toxicity after a given therapy. An example of the two types of markers could be demonstrated by transforming growth factor-β (TGF-β), a potent fibrogenic cytokine.[7] Li et al[62] showed that high levels of circulating TGF-β before the start of radiotherapy are associated with an increased risk of normal-tissue adverse effects after postoperative radiotherapy for breast cancer. In other words, TGF-β concentration before therapy is a predictive marker for these adverse effects. Anscher et al[63] showed that patients with an elevated plasma TGF-β level after 73.6 Gy of thoracic radiotherapy were more likely to develop grade 3 or greater late toxicities, thus making this a candidate surrogate marker for later effects. Currently, there are major research efforts in progress looking at high-throughput assays to identify potential predictive markers for late adverse effects.[7,64,65] Progress in this

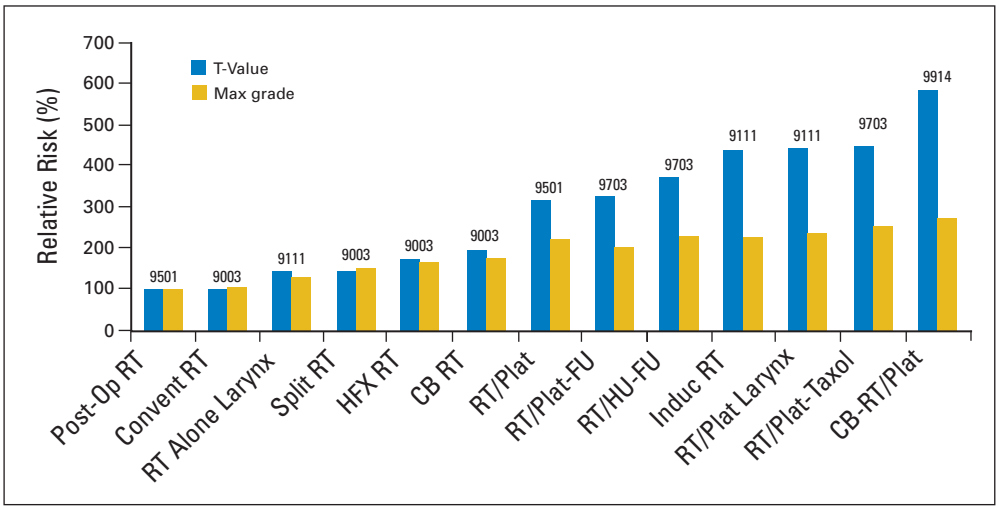

Fig 2. Toxicity burden measures: relative T-values versus relative maximum-grade values. Post-Op, postoperative; RT, radiotherapy; Convent, conventional; Plat, platinum; FU, fluorouracil; Induc, induction.

field will undoubtedly require reliable scoring of specific normal-tissue effects to allow associations with specific pathogenic pathways to be tested.

FUTURE DIRECTIONS

Normal-tissue effects show considerable variability among patients,[66] and studies looking at the correlation between the expression of injury in separately irradiated fields in the same individual suggest that most of this variability is deterministic (ie, caused by some underlying physiologic or genomic factor).[67] Toxicity, in particular high-grade toxicity, seen in a trial or in clinical practice is most likely predominantly expressed in a hypothetical subgroup of sensitive individuals. It seems reasonable to assume that, if we could stratify or stream patients according to risk of normal-tissue effects, treatment intensity could be increased in some patients (perhaps in the majority) with a likely resulting improvement in efficacy. Current attempts aimed at identifying molecular predictive factors for normal tissue sensitivity may also identify interventional targets for reducing the incidence and severity of adverse effects or for treating such effects after they become clinically manifest.[7]

Progress in clinical and translational normal tissue research requires improved means for quantification of adverse effects. At the same time, additional guidance and standards for data collection and reporting are much needed to improve the value of normal tissue outcome data collected in clinical trials as well as in the phase IV setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Manuscript writing: Søren M. Bentzen, Andrea Trotti

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