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SPECIAL ARTICLE

Development of the MASCC/ISOO Clinical Practice Guidelines for Mucositis: considerations underlying the process

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Abstract The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) recently conducted a systematic review to update the MASCC/ISOO clinical practice guidelines for oral and gastrointestinal mucositis. Here, we discuss the details of some considerations underlying the process used.

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Introduction

Evidence-based guidelines have become standard in many medical fields during the last decade. Such guidelines summarize the literature objectively and present it in a manner that is helpful to the practitioners. Since numerous methods can be employed to develop these evidence-based guidelines and those that are used will affect the recommendations in the guidelines, it is important to understand these factors and recognize their meaning.

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) recently conducted a systematic review to update the MASCC/ISOO clinical practice guidelines for oral and gastrointestinal mucositis [1, 2]. The methods used for this guidelines update are described in the preceding methodology paper by Bowen et al. [3] which delineates the methods applied for the 2011 update. Here, we discuss the details of some considerations underlying the process used.

Type of systematic review

The type of systematic review employed is the essence of the methods. Thus, we conducted a preliminary literature search regarding the methods used by well-

recognized medical organizations. We considered two major options for the type of systematic review to use in guidelines development.

1. Guidelines based on a systematic evaluation and weighted rating of all the available evidence.
2. A meta-analysis–a formal statistical (i.e., quantitative) procedure for combining results across comparable studies addressing similar clinical questions.

Each method has advantages and limitations. The first approach allows for all the available evidence to be included. However, it leaves open the possibility of making guidelines based on studies other than randomized controlled trials (RCTs). The meta-analysis approach for a systematic review is statistically very powerful, but it is typically limited to RCTs and may miss other studies which add evidence. A large proportion of the mucositis literature consists of studies other than RCTs. There is also a great clinical need for guidance on what interventions should or should not be used for managing mucositis. A meta-analysis would exclude many interventions for which no RCTs exist to date. Therefore, we decided to continue using the systematic review without the meta-analysis approach. In combination with the guidelines rating scale used (recommendation, suggestion, or no guideline possible), this would allow for a suggestion to be made based on a lower-level but consistent evidence, if there was panel consensus on the interpretation of such evidence.

Databases to be searched

The goal of the literature search was to identify all the relevant literature that met our inclusion and exclusion criteria. In an attempt to be as comprehensive as possible, we initially examined three databases that contain the most health-related literature, namely: Medline/Pubmed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Embase (an online database produced by Elsevier). Each database required its own search strategy due to their different platforms and interfaces. The results from each search were combined and the repetitions were deleted.

The searches for three sections of the review were performed in all three databases. However, we found that there were few additions from the CINAHL and Embase databases, and in most cases they were papers that did not meet our inclusion criteria. It was also determined that a few additional papers identified by these searches were of low-level evidence that would have little impact on the guidelines. Therefore, it was decided that the effort for the triple search was unjustified, and only Medline was searched for the remaining sections.

Period of the review

The previous update of the MASCC/ISOO Clinical Practice Guidelines for Mucositis reviewed all the available literature until May 2005 [1]. We were faced with two options: review only the literature since then or review all the available literature including that was previously reviewed. Since we made some refinements to the methods for this update (see "Criteria for evaluation of scientific evidence" and "Allocating Level of Evidence"), we decided to review all the available literature so that it could all be assessed comparably using our current methodology. Although this decision added significantly to the scope and workload associated with this project, it ensured that our guidelines would be based on a comprehensive and uniform evaluation of all the available evidence.

Criteria for evaluation of scientific evidence

The criteria for evaluation of the scientific evidence allow the quality of the studies to be assessed. We used the criteria published by Hadorn et al. for this purpose (see Bowen et al. [3] for detailed criteria). Hadorn's criteria were originally published by the Agency for Health Care Policy and Research when it sponsored the clinical practice guidelines for the management of patients with heart failure due to left ventricular systolic dysfunction [4]. Hadorn's criteria list possible flaws in the study design and divide them into "major" and "minor" flaws. This list of flaws is a useful and practical tool to evaluate the study design, and thus to weigh the scientific contribution of a single clinical study. We adapted these criteria where necessary for mucositis studies. For example, the panel recognized that it is not feasible for a study of cryotherapy (ice chips in patient's mouth) to be double-blinded. Therefore, it was decided that for RCTs of cryotherapy only, the lack of double-blinding would not be considered a major flaw.

Allocating a level of evidence

The next phase in the review is to integrate the data from all studies regarding a specific intervention into one score. For this purpose we used the criteria from Somerfield et al. [5] originally published for ASCO Health Services Research Committee guidelines on hematopoietic colony stimulating factors. These criteria define five levels of evidence from I to V based on the strength of the underlying evidence (see Bowen et al. [3] for detailed criteria).

The term "well-designed" is used frequently in the Somerfield criteria. In order to achieve calibration between reviewers and minimize subjectivity, we defined a well-

designed study as one with no major flaws per the Hadorn criteria. This represented an improvement to our methods over the previous update and served to further assure that our guidelines would be based on sound evidence.

Our methods also addressed the potential for ambiguity in how the Somerfield criteria could be applied by our reviewers. For example, according to these criteria, a single well-designed RCT constitutes level II evidence, while a non-randomized controlled trial constitutes level III evidence. So there could be some confusion among reviewers as to what level of evidence should be assigned to a single RCT that has one or major flaws (and therefore does not meet the definition of a well-designed study). To address such ambiguities, our "Methods Manual and Instructions to Reviewers" stated that the studies with major flaws were to be downgraded one level of evidence below a study of similar design without any major flaw. In the preceding example, a RCT with one or more major flaws would be allocated as evidence level III (one level below a well-designed RCT with no major flaw).

Categories used to classify guidelines

Medical guidelines are usually presented on a scale representing the quality of the literature that supports each intervention. Two approaches for the classification of guidelines for each agent were considered (see Table 1) [5].

In the three-tier classification, the steps are defined according to clinical implications–whether the intervention can be used with high level of confidence in its effectiveness (recommendation) or used with an intermediate level of confidence in its effectiveness (suggestion) or that there is no sufficient evidence to make any conclusion about the intervention (no guideline possible). This was the system used to develop the previous MASCC/ISOO Clinical Practice Guidelines for Mucositis.

Another commonly used classification system is a four-tier ladder with different steps expressed as letters-A, B, C, and D. The level is assigned based on the support available for that intervention in the scientific literature. However, this system does not clearly direct the practitioner as to whether the intervention should be employed or not. For example, an intervention with very little or no supporting evidence may be assigned level D; however, this can be misconstrued or misrepresented as a low-level "recommendation". Therefore, we chose to continue with the three-tier method since it is simple to understand and can be interpreted in a clinically relevant manner.

Logistics of the review process

The present guidelines update involved almost 100 contributors spread all over the world. Therefore, it was a logistical challenge to conduct the review process across these multiple geographic areas and time zones. We used electronic systems and communications extensively to overcome these logistical challenges. Across all sections, the literature searches initially identified over 8,000 articles. In order to handle this large volume of citations, we used EndNote software. This enabled us to (1) directly upload the output of the search strategy into a library for each section, (2) rapidly view many citations, (3) filter out citations not meeting our criteria, (4) search for overlap between different sections' libraries, and (5) transfer information by email.

Reviewing of each publication generates a large amount of data. In order to manage this data Excel forms were used. We created a standardized form for the review, "Reviewer form" as well as a standardized form for summarizing the reviews for each intervention, the "Section Head form." This form allowed us to combine the data in the following

Table 1 Classification of guidelines

Method	Classification	Tier definition
Three tiers	Recommendation	Guidelines based on level I or II evidence
	Suggestion	Guidelines based on level III, IV, and V evidence, with panel consensus
	No guideline possible	Insufficient evidence on which to base a guideline, either due to paucity of or lack of panel consensus
Four tiers	A	Type I evidence or consistent findings from multiple studies of types II, III, or IV
	B	Type II, III, or IV evidence with generally consistent findings
	C	Type II, III, or IV evidence with inconsistent findings
	D	Little or no systematic empirical evidence

steps: combining the two reviews per paper and then combining multiple publications per agent.

Email, teleconferences, videoconferences, and cloud computing were extensively used to maintain communication, distribute, and collect review materials. Together, these systems allowed us to overcome the logistical challenges posed by this large project.

Conclusions

In this paper, we have described the careful consideration of issues underlying the process of the current mucositis guidelines update. It is our goal that this will lead to increased transparency and understanding of the significant effort put into ensuring that the MASCC/ISOO clinical practice guidelines for mucositis are based on sound methodology and evidence.

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References

1. Keefe DM, Schubert MM, Elting LS et al (2007) Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 109:820–831
2. Rubenstein EB, Peterson DE, Schubert M et al (2004) Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 100:2026–2046
3. Bowen JM, Elad S, Hutchins RD, Lalla RV, For the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) (2012) Methodology for the MASCC/ISOO Mucositis Clinical Practice Guidelines Update. Support Care Cancer. doi:10.1007/s00520-012-1592-7
4. Hadorn DC, Baker D, Hodges JS, Hicks N (1996) Rating the quality of evidence for clinical practice guidelines. J Clin Epidemiol 49:749–754
5. Somerfield M, Padberg J, Pfister D et al (2000) ASCO clinical practice guidelines: process, progress, pitfalls, and prospects. Classic Papers Current Comments 4:881