Pergamon

Oral Oncol, Eur J Cancer, Vol. 31B, No. 4, pp. 258–260, 1995

0964–1955/95 $9.50+0.00

0964–1955(95)00019–4

A Database for Mucositis Induced by Cancer Chemotherapy

S.T. Sonis and K.A. Costello

Ulcerative mucositis has become an increasingly important toxicity of antineoplastic therapy. In an effort to establish mucositis risk prediction for specific cancer chemotherapy regimens, a 25 field database was developed. This paper describes the rationale and methodology for creation of the database and instructions for access to it via the Internet.

Keywords: cancer chemotherapy, mucositis, stomatitis, database, computer access

Oral Oncol, Eur J Cancer, Vol. 31B, No. 4, pp. 258–260, 1995.

INTRODUCTION

ULCERATIVE MUCOSITIS is a common side effect of many forms of cancer chemotherapy [1] and has an overall frequency of approximately 40% [2–6]. Based on the number of patients receiving chemotherapy annually, it can be estimated that approximately one million episodes of the condition occur each year in the United States. Importantly, as other forms of toxicities are more easily controlled, the significance of oral mucositis as a dose-limiting toxicity has increased [7, 8]. In addition to severe pain, mucositis results in the destruction of the oral mucosa as an anatomic barrier hastening the mouth to serve as a systemic portal of entry for its indigenous microbiologic flora [9, 10].

Clinical studies of oral mucositis have been increasing over the past few years. A review of four computerized databases (Medline, Health, AIDSLINE, and Cancerlit) demonstrated only 14 references on the subject between 1980 and 1985. In comparison, 57 citations have appeared in the subsequent 5 years. Forty-five references are already noted since 1991. In spite of the increase of interest in the area, no central database exists for mucositis. Consequently, risk prediction for mucositis for various antineoplastic protocols is associated with individual regimens. Additionally, the lack of a standard mucositis assessment tool has made comparative studies difficult.

The Consensus Statement of the National Institutes of Health Consensus Development Panel on Oral Complications of Cancer Therapies cited a variety of objectives for future research in the area. To attain these goals they suggested that a large, accessible database from which comparative studies regarding oral toxicities and their prevention and treatment can be drawn was desirable. This paper represents our initial effort at establishing an interactive database to define mucositis risk prediction associated with specific antineoplastic protocols.

Correspondence to S.T. Sonis.
S.T. Sonis is at the Division of Oral Medicine and Dentistry, Brigham and Women's Hospital and the Department of Oral Medicine and Diagnostic Sciences, Harvard School of Dental Medicine; and K.A. Costello is at the Division of Oral Medicine and Dentistry, Brigham and Women's Hospital, Boston, Massachusetts, U.S.A.
Received 26 Jan. 1995; provisionally accepted 21 Feb. 1995; revised manuscript received 16 Mar. 1995.

METHODS

An extensive, simultaneous search of Medline, Health, AIDSLINE, and Cancerlit was performed for all literature in which cancer chemotherapy was cited between 1 January 1984 and 9 January 1995. Within those articles, the search was narrowed to include protocols which mentioned or included oral toxicity, specifically mucositis or stomatitis, as a side effect of a particular chemotherapeutic regimen. Specific key words which comprised our search strategy included: cancer, chemo-

Table 1. Fields of the mucositis (stomatitis) database

1	Patient diagnosis
2	Chemotherapeutic agent (single drug therapy)
3	Dosage (single agent)
4	Combined chemotherapeutic agents
5	*n* (number of patients/chemotherapy cycles used in study)
6	Prior chemotherapy
7	Prior radiotherapy
8	Overall percentage of mucositis
9	Toxicity scale
10–15	Individual grades of mucositis (stomatitis) 0–4
16	Duration of mucositis
17	Overall percentage of leukopenia
18	Overall percentage of infection
19	Number of males included in the study
20	Number of females included in the study
21	Mean age of patients included in the study
22	Age range of patients included in the study
23	*n* response to chemotherapy
24	Overall response rate (%) of chemotherapy
25	Number of complete remissions
26	Number of partial remissions
27	Number of patients where the disease progressed during the course of treatment

References for each study or protocol are included in the database.

Table 2. Toxicity scale definitions of specified research groups

	G0	G1	G2	G3	G4
Cancer and Leukemia Group B (CALGB) [11]	None	Painless ulcers, erythema or mild soreness	Painful erythema, edema, or ulcers but can eat	Painful erythema, edema, or ulcers and cannot eat	Requires parenteral or enteral support
Cancer Clinical Trials Common Toxicity Criteria (CCTCTC) [12]		Painless ulcers	Painful ulcers that do not prevent eating	Painful ulcers that do prevent eating	
Eastern Cooperative Oncology Group (ECOG) [13]	None	Soreness	Ulcers, may eat	Ulcers, cannot eat	
European Organization for Research and Treatment of Cancer (EORTC) [14]	Same toxicity criteria as WHO for phase I trials				
National Cancer Institute Common Toxicity Criteria (NCICTC) [15]	None	Diffuse erythema able to eat, pain with spicy foods	Diffuse painful erythema with patchy ulcers, responds to local anaesthetics, may eat	Diffuse painful ulcers, several blistering lesions lasting up to 7 days, partial response to topical drugs, narcotics may be needed to relieve pain	Severe diffuse ulcers, unable to eat, dehydration prostration, requires parenteral support, narcotics needed to relieve pain
Pediatric Oncology Group (POG)					
Southwestern Oncology Group (SWOG) [16]	None	Mild	Moderate	Severe	Life threatening
World Health Organization (WHO) [17]	None	Soreness and erythema	Erythema, ulcers, ability to eat solids	Ulcers, requires liquid diet	Alimentation not possible

Table 3. Toxicity scale definitions of individual research groups

Ref	G0	G1	G2	G3	G4
[18]		None to mild: erythema, able to eat	Moderate: mucositis/ ulcers, able to eat	Severe: i.v. fluids required	
[19]		Minimal dysphagia, thinning but no overt break in mucosal integrity	Significant dysphagia, semi-soft foods only, focal mucosal vesicles or denuded patches	Fluids tolerated only by mouth, obvious large confluent patches of mucosal denudation	Parenteral fluids only, severe confluent mucosal denudation with bleeding
[20]		Minimal: transient no therapy	Moderate: >5 days, requires therapy	Severe: >7 days, <10% weight loss	Life threatening: <10% weight loss, requires hospitalisation
[21]		Erythema, subjective pain and dental indentation	Superficial ulceration without haemorrhage	Haemorrhagic stomatitis and ulceration with an inability to tolerate oral intake	
[22]	None	Mild	Moderate	Severe	
[23]		Mucosal soreness, erythema	Mucosal ulceration of mild degree	Ulcerations which interfered with food intake	
[24]		Mild: transient mucositis that does not prevent eating	Moderate: more pronounced lesions that prevent eating	Severe: denudative mucositis, or lesions that prevent eating	

Table 4. Steps to access mucositis database through the Internet

1	Access "telnet" through the Internet
2	Enter "bustoff.bwh.harvard.edu"
3	At login prompt, type "bulletin"
4	On Gopher main menu, select "BWH Research Databases"
5	Select "Oral Medicine"
6	Select "Sonis mucositis"
7	Select menu choice

therapy, bone marrow transplantation, antineoplastic agents, mucositis, stomatitis and toxicity. Two protocols were excluded in which the rate of observed mucositis was not explicitly defined and in which the demographics of the patient population was not clear.

Eighty-eight regimens met the criteria for inclusion, and were further divided into protocols for the treatment of head and neck cancer and those for the treatment of all other forms of cancer. Twenty-seven papers were limited to protocols for the treatment of the head and neck cancers. The remainder included regimens for the treatment of a variety of solid and haematologic malignancies. A database was organised for each group of studies and comprised of 27 fields (Table 1). The number of fields was established to enable users to have access to data based on a variety of epidemiologic, demographic or therapeutic interests.

DISCUSSION AND COMMENTS

Availability and accessibility to large, shared databases offer important potential assets for the clinician and researcher. For a database to be of value it should meet a number of criteria. Most importantly, the data included must be accurate and standardised. Clearly, the latter is not the case with mucositis. Fourteen different, identifiable scoring systems for mucositis were used in the 88 protocols which comprise this database (Tables 2 and 3). Some are descriptive, and others symptom-based. All have a component of functional compromise as at least part of the criteria for scoring. Such variety hinders comparative studies when trying to differentiate the stomatotoxicity of one protocol compared to another, although the relative toxicity of a particular regimen can still be evaluated. Currently, scoring systems for cancer therapy-induced stomatotoxicity serve two major purposes. First, they are descriptive with respect to the effects of a particular regimen. Second, they are used to evaluate therapy for the prevention and treatment of mucositis. While the needs of the latter are more complex than the former, standardisation of stomatotoxicity should be a priority if accurate comparisons among protocols are to be made and if true assessments of preventive and treatment modalities are to occur.

The significance of mucositis as a toxicity is suggested by the fact that it was specifically noted in the studies cited. These cases vary by patient population, tumour diagnosis and chemotherapies used for treatment. Also noted is the frequency of leukopenia and infection associated with each protocol.

To be of continual value, databases must be current, expansive and accessible. The material presented here will be updated periodically. The last revision was completed in April 1995. The database was expanded at that time to include protocols in which radiation-induced mucositis is mentioned as a toxicity. To ensure accessibility, the database is available on a Gopher Server through the Internet (Table 4). While the database is not currently interactive, we are in the process of developing this capability using the Worldwide Web. A further enhancement, treatment protocols for mucositis, was added in 1995.

1. Sonis ST, Clark J. Prevention and management of oral mucositis induced by antineoplastic therapy. *Oncology* 1991, **5**, 11–16.
2. Caballero BA, Ausman RK, Quebbeman EJ. Long-term, ambulatory, continuous iv infusion of 5-FU for the treatment of advanced adenocarcinomas. *Cancer Treatment Reports* 1985, **69**, 13–15.
3. Balis FM, Savitch JL, Bleyer WA, *et al.* Remission induction of meningeal leukemia with high-dose intravenous methotrexate. *J Clin Oncol* 1985, **3**, 485–489.
4. Roth BJ, Sledge GW, Williams SD, *et al.* Methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic breast cancer. *Cancer* 1991, **68**, 248–252.
5. Magrath IT, Janus C, Edwards BK, *et al.* An effective therapy for both undifferentiated (including Burkitt's) lymphoma and lymphoblastic lymphomas in children and young adults. *Blood* 1984, **63**, 1102–1111.
6. Bishop JF, Joshua DE, Lowenthal RM, *et al.* A phase I-II study of cytosine arabinoside, daunorubicin, and VP16-213 in adult patients with acute non-lymphocytic leukemia. *Aust NZ J Med* 1986, **16**, 48–51.
7. Brincker H, Christensen BE. Acute mucocutaneous toxicity following high-dose hydroxyurea. *Cancer Chemother Pharmacol* 1993, **32**, 496–497.
8. Lokich J, Anderson N, Bern M, *et al.* Dual modulation of 5-fluorouracil using leucovorin and hydroxyurea. *Cancer* 1991, **68**, 744–746.
9. Bergmann OJ. Oral manifestations and fever in immunocompromised patients with haematological malignancies. *Eur J Clin Microbiol Infect Dis* 1989, **8**, 207–213.
10. Donnelly JP, Muus P, Horrevorts AM, *et al.* Failure of clindamycin to influence the course of severe oromucositis associated with streptococcal bacteraemia in allogenic bone marrow transplant recipients. *Scand J Infect Dis* 1993, **25**, 43–50.
11. Brigham and Women's Hospital. CALGB Expanded Common Toxicity Criteria, 1991, 1–9.
12. Ajaini J, Welch S, Raber M. Comprehensive criteria for accessing therapy-related toxicity. *Cancer Invest* 1990, **8**, 141–153.
13. Taylor S, *et al.* PALA in advanced breast cancer. A Phase II pilot study by the ECOG. *Am J Clin Oncol* 1982, **5**(6), 627–629.
14. EORTC New Drug Development Committee. EORTC Guidelines for Phase I Trials with Single Agents in Adults. *Eur J Cancer Clin Oncol* 1985, **21**(9), 1005–1007.
15. Saphner T, Tormey DC, Albertini M. Continuous infusion 5-fluorouracil with escalating doses of intermittent cisplatin and etoposide. *Cancer* 1991, **68**, 2359–2362.
16. Goodwin J, *et al.* Phase II trial of spirogermanium in central nervous system tumors. A Southwest Oncology Group Study. *Cancer Treatment Reports* 1987, **71**(1), 99–100.
17. Miller A, *et al.* Reporting the results of cancer treatment. *Cancer* 1981, **47**, 207–214.
18. Becouran Y, Calabet J, Burnet R. A Phase II study of 5-FU, teniposide, and mitomycin-C combination chemotherapy in advanced colorectal carcinomas. *Tumori* 1987, **74**, 75–77.
19. Byfield JE, *et al.* Phase I and pharmacologic study of 72-hour infused 5-fluorouracil in man. *Am J Clin Oncol* 1985, **8**, 427–440.
20. Lokich J, *et al.* Infusion of floxuridine plus etoposide plus cisplatin in human maligancies. *Eur J Cancer* 1991, **27**(12), 1596.
21. Logothetis CJ, *et al.* Improved survival with cyclic chemotherapy for nonseminomatous germ cell tumors of the testes. *J Clin Oncol* 1985, **3**(3), 326–335.
22. Stewart DJ, *et al.* Combined mitoxantrone plus doxorubicin in the treatment of breast cancer. *Am J Clin Oncol* 1987, **10**(4), 335–339.
23. Jabboury K, Holmes FA, Hortobagyi G. 5-Fluorouracil rechallenge by protracted infusion in refractory breast cancer. *Cancer* 1989, **64**, 793–797.
24. Kuzrock R, *et al.* Phase II evaluation of PALA in patients with refractory metastatic sarcomas. *Am J Clin Oncol* 1984, **7**, 305–307.