CIBMTR™
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Newsletter

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CONTENTS

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Kepivance™: A Breakthrough for Oral Mucositis Associated with Myeloablative Hematopoietic Stem Cell Transplantation

By Ricardo T. Spielberger, MD

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Introduction

Oral mucositis is a frequent side effect of many types of cancer therapies.[1,2] Chemotherapy and radiotherapy target and destroy rapidly-dividing tumor cells, which also results in major damage to the rapidly dividing tissues that comprise the mucosal epithelium of the gastrointestinal tract, particularly the oral and oropharyngeal mucosa.[3] Severe oral mucositis is especially common among patients receiving high-dose chemo- and/or radiotherapy regimens requiring hematopoietic stem cell (HSC) support and in patients receiving radiotherapy for treatment of certain solid tumors such as head and neck cancer.[4,5] Although the incidence of mucositis is lower in patients with malignancies receiving standard-dose therapy, the frequency with which these malignancies occur is high enough to contribute to the overall impact of mucositis in clinical practice.[6]

Pathophysiology of Mucositis

Since introduction of the term oral mucositis by oncologists in the late 1980s, understanding of this condition has greatly increased.[7] Historically, mucositis was thought to arise solely as a direct consequence of epithelial injury by radiation or chemotherapy. It was surmised that nonspecific targeting of the rapidly proliferating cells of the basal epithelium led to atrophy, thinning, and ulceration. Trauma and oral microorganisms were believed to facilitate this process. Although the clinical symptoms of mucositis are largely the result of epithelial injury, the condition itself is the consequence of a dynamic series of biological events involving different cellular and tissue compartments of the oral, oropharyngeal, and gastrointestinal mucosa.

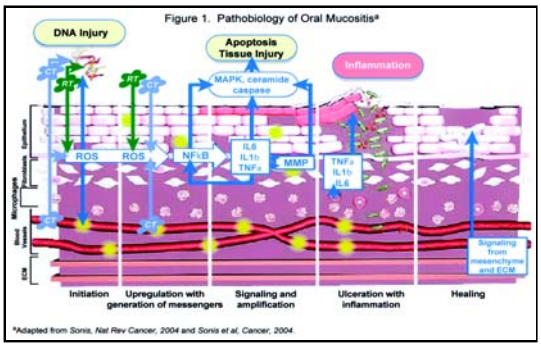


Figure 1. Pathobiology of Oral Mucositis*

*Adapted from Sonis, Nat Rev Cancer, 2004 and Sonis et al, Cancer, 2004.

Mucositis is defined by Sonis et al as a 5 phase biological process: initiation; upregulation with generation of chemical messengers; signaling and amplification; ulceration with inflammation; and healing (Figure 1).[7,8] Despite the linearity of this process, it is common for multiple manifestations of mucositis to occur simultaneously. Symptom progression from the initiation stage until the ulceration stage may take up to 1 week, with the healing process spanning days to weeks, depending on the severity of the insult and resulting ulcerations.

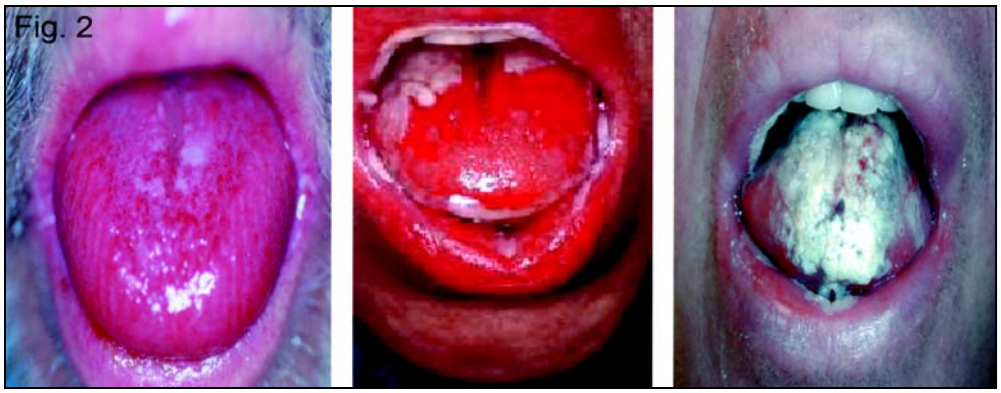
During the initiation phase, there is direct cellular injury of the basal epithelial cells and cells in the underlying tissues.[7,8] Radiation and/or chemotherapy may cause DNA strand breaks within cells, resulting in the disruption of normal cellular function in cells of the mucosal epithelium and underlying mucosa. At the same time, the primary damage response of oral mucositis begins through generation of reactive oxygen species or free radicals, which act as mediators of downstream biological events and can directly damage cells, tissues, and blood vessels. The activation of reactive oxygen species and the subsequent stimulation of transcription factors determine the extent of the acute tissue response. At this stage, the mucosa appears to be normal; however, a cascade of events has been initiated that ultimately results in epithelial destruction.

During the second (upregulation with generation of chemical messengers) and third (signaling and amplification) phases, transcription factors may be activated directly by radiation and/or chemotherapy or indirectly by reactive oxygen species.[7,8] One of these transcription factors, nuclear factor-kappa B (NF-kB), can stimulate production of pro-inflammatory cytokines (including TNF-a, IL-1b, and IL-6) that damage connective tissues and endothelium in addition to initiating a series of events that lead to epithelial cell death. Enzyme activation also leads to apoptosis in the submucosa and basal epithelial cells of the mucosa and destruction of the subepithelial matrix and basement membrane. Some pro-inflammatory cytokines may also provide a positive-feedback loop by further activating NF-kB, thus amplifying the primary damage response. Notably, clinical manifestations are minimal during these stages. Although there may be some mucosal erythema, tissue integrity is present and few symptoms develop.

continued on page 2

Kepivance™: A breakthrough – continued from page 1

The ulcerative phase (fourth phase) of mucositis is the most symptomatic.[7,8] As shown in Figure 2, degradation of the mucosa causes extremely painful lesions. These ulcerations often require secondary supportive care and increases risk of other complications. Breaks in the mucosal barrier provide additional portals through which opportunistic bacteria or other infective agents may attack, leading to increased risks of sepsis and bacteremia that may be life-threatening. These complications can result in delays in the treatment of the primary malignancy.[9]



In the fifth and final phase, the healing phase, signals from the extracellular matrix initiate healing and renewal of epithelial proliferation and differentiation.[7,8] The mucosa returns to a normal appearance, but the patient continues to be at increased risk for future episodes of mucositis with subsequent cancer therapy.[8,10]

Symptoms of oral mucositis may develop as early as 3 days after exposure to chemotherapy.[2,11] Typically, progression from initiation to ulceration occurs between 5 to 8 days after the start of chemotherapy and lasts between 7 and 14 days.[12,13] Radiotherapy-induced oral mucositis depends on the cumulative tissue radiation dose, with initiation commonly occurring at 15 Grays (Gy) to 20 Gy of standard fractionated radiotherapy. Early changes, characterized by erythema and edema, appear 2 weeks after the first radiotherapy treatment, with more severe ulcerative symptoms appearing at doses of 30 Gy or more. Progression from the ulcerative phase to healing and recovery may take days or weeks, depending upon the severity of the episode.

Risk Factors and Impact of Oral Mucositis on Cancer Patients

There are many factors influencing the occurrence and severity of oral mucositis. Younger patients tend to develop oral mucositis more often than older patients. Poor oral health before and during treatment tends to result in higher incidences of oral mucositis. Hypersalivation is a marker of increased risk and severity of oral mucositis.[14-16] The risk and severity of developing oral mucositis are increased when chemotherapy is given at higher doses, at frequent repetitive schedules, in combination with radiotherapy, or as part of a conditioning regimen prior to bone marrow transplantation or hematopoietic stem cell transplantation.[17-19] At least 75% of patients receiving myeloablative conditioning regimens prior to hematopoietic stem cell transplantation, and virtually 100% of patients receiving localized radiotherapy for head and neck cancer suffer from oral mucositis.[15,16,20,21]

Patients describe oral mucositis as the most debilitating side effect of aggressive myeloablative therapy for multiple types of cancers.[5,22] Oral mucositis negatively impacts all aspects of the patient's quality of life, including physical, emotional, social, and functional dimensions.[23] The severe pain can make basic daily activities such as eating, talking, swallowing, and sleeping difficult or impossible. Patients may require narcotic analgesics to alleviate the pain, adding to the treatment burden as well as exposing patients to additional side effects such as drug dependence, mental confusion, gait instability, constipation, and small bowel obstruction.[22,24] Patients may need parenteral feeding, may require longer hospitalization, and may become socially withdrawn or clinically depressed.[1,22-26]

Furthermore, the administration of optimal cancer therapy may be impeded. As many as 50% of patients undergoing standard chemotherapy who experience oral mucositis require dose reductions or delays in their cancer therapies.[15] Treatment delays, dose reductions, or discontinuation of therapy due to oral mucositis may lead to decreased response rates and decreased survival.[27-32]

Current Management of Oral Mucositis

Despite patient reports that oral mucositis is the most debilitating side effect of cancer treatment, most supportive therapies are palliative at best.[5,22] Interventions are primarily supportive and are aimed at trying to control symptoms such as pain, addressing the inability to eat or drink, reducing local trauma, or decreasing the risk of secondary infection.[14,33] The recent evidence-based management guidelines from the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology make several recommendations aimed at lowering occurrences and providing for better patient comfort.[34] Current suggestions include good oral hygiene, careful oral debridement with or without mucolytic agents, oral decontamination with antifungal and antibacterial mouthwashes, and topical and systemic pain management. Numerous agents have been used to treat the symptoms of oral mucositis, including oral cryotherapy (ice chips), anti-oxidants (glutamine); mucosal barriers (sucralfate); mouth rinses (benzydamine); analgesics (morphine); antimicrobial agents (chlorhexidine); anti-inflammatories (prostaglandin E_1 and E_2); and radioprotectants (amifostine).[35-38] To date, none of these has conclusively demonstrated clinically meaningful benefit in preventing or treating oral mucositis.

PALIFERMIN (KEPIVANCE™)

Until recently, there were no approved agents available to prevent oral mucositis. In December 2004, the US Food and Drug Administration (US FDA) approved Kepivance™ (palifermin; recombinant human KGF) to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring HSC support.

Mechanism of Action

Keratinocyte growth factor (KGF) is a 28 kilodalton (kD), heparin-binding protein in the fibroblast growth factor family that binds to the KGF receptor. Initially isolated by Rubin et al in 1989 from pulmonary fibroblasts as a protein with keratinocyte-stimulating activity, binding of KGF to its receptor results in the proliferation, differentiation, and migration of epithelial cells.[39] The KGF receptor, 1 of 4 receptors in the fibroblast growth factor family, is present on epithelial cells in many tissues, including the tongue, buccal mucosa, salivary gland, esophagus, stomach, intestine, lung, liver, pancreas, kidney, bladder, mammary gland, skin (hair follicles and sebaceous gland), and the lens of the eye.[40-56] The KGF receptor is absent on cells of the hematopoietic lineage. Endogenous KGF is produced by mesenchymal cells and is upregulated, possibly as a physiological response, in the setting of epithelial tissue injury.[55]

Palifermin (Kepivance™) is a 140 amino acid protein produced by recombinant DNA technology in Escherichia coli (E. coli). This 16.3 kD, water-soluble protein differs from endogenous human KGF in that the first 23 N-terminal amino acids were deleted, giving the

molecule greater thermal stability but with similar biological activity. Palifermin stimulates growth of epithelial cells from a wide variety of tissues but, due to the restricted expression of the KGF receptor, has no known direct effect on other cell types. In mice and rats, palifermin enhances proliferation of epithelial cells and increases tissue thickness of the tongue, buccal mucosa, and gastrointestinal tract.[57]

Palifermin substantially reduces injury to the oral and gastrointestinal tract mucosa and salivary glands in models of radiation-induced and chemotherapy-induced gastrointestinal injury.[57-59] The protective activity of palifermin is attributable to its mitogenic effect on the mucosal epithelium (which results in both increased epithelial thickness and improved recovery when dosed shortly after myelotoxic therapy), and also to its impact on intercellular junctions and various cytoprotective mechanisms.[55]

Clinical Pharmacology

The pharmacokinetics of palifermin were studied in healthy volunteers after single and multiple injections as well as in patients with hematologic malignancies. After single intravenous (IV) doses of 20 to 250 mcg/kg in healthy subjects and 60 mcg/kg in cancer patients, palifermin concentrations declined rapidly (> 95% decrease in concentration) in the first 30 minutes after administration. A slight increase or plateau in concentration occurred at approximately 1 to 4 hours, followed by a terminal decline phase. Palifermin exhibited linear pharmacokinetics with extravascular distribution, with the volume of distribution at steady state (V_{ss}) greater than the total body water volume.[60] This result is consistent with the KGF receptor's ubiquitous presence on all epithelial cells and the binding of palifermin to this receptor. On average, total body clearance and V_{ss} appeared to be 2- to 4-fold higher and 2-fold higher, respectively, in patients with hematologic malignancies compared with healthy subjects after a single dose at 60 mcg/kg. The elimination half-life ($t_{1/2}$) was similar between healthy subjects and cancer patients, averaging 4.5 hours with a range of 3.3 to 5.7 hours. No accumulation was observed after 3 consecutive daily doses of 20 and 40 mcg/kg in healthy subjects or 60 mcg/kg in cancer patients. There appeared to be no effects of age, weight, sex, and race on palifermin pharmacokinetics.

The pharmacodynamics of palifermin were studied by assessing epithelial cell proliferation using Ki67 immunohistochemical staining in healthy subjects. An increase of at least 3-fold in Ki67 staining was observed in buccal biopsies from healthy subjects (n = 6) who received palifermin IV at 40 mcg/kg/day for 3 consecutive days, when measured 24 hours after the third dose. Notably, at 48 hours after dosing, most of the quantifiable palifermin concentration values were less than twice the lower limit of the assay, indicating that pharmacologic effects persist after active drug levels have dissipated. Dose-dependent epithelial cell proliferation was observed in healthy subjects given single IV doses of 120 to 250 mcg/kg at 48 hours post-dosing.

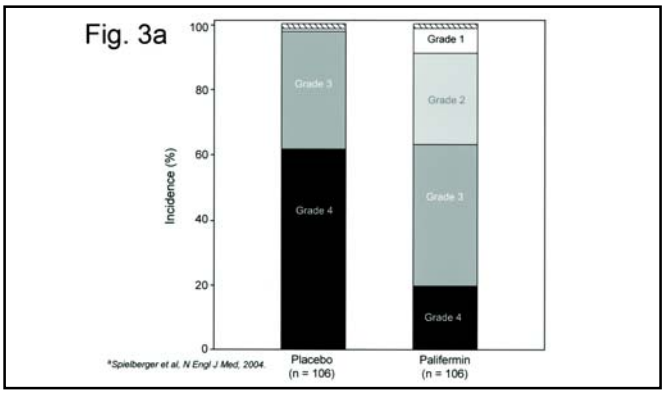
Clinical Efficacy and Safety

The efficacy and safety of palifermin were established in 2 key studies: a pivotal phase 3, randomized, placebo-controlled clinical study of 212 patients and a phase 2, randomized, schedule-ranging, placebo-controlled clinical trial of 169 patients (data on file).[61,62]

Efficacy in Hematologic Cancer Patients

In the phase 3 trial, patients received high-dose cytotoxic therapy consisting of total body irradiation (TBI; 12 Gy total dose), high-dose etoposide (60 mg/kg), and high-dose cyclophosphamide (100 mg/kg) followed by peripheral blood progenitor cell (PBPC) support for the treatment of hematological malignancies (Non-Hodgkin's Lymphoma [NHL], Hodgkin's disease, acute myelogenous leukemia [AML], acute lymphoblastic leukemia [ALL], chronic myelogenous leukemia [CML], chronic lymphocytic leukemia [CLL], or multiple myeloma).[61,63-66] Patients were randomized to receive palifermin (n = 106) or placebo (n = 106), with palifermin administered as a daily IV injection at 60 mcg/kg for 3 consecutive days prior to the initiation of cytotoxic therapy and for 3 consecutive days following infusion of PBPC. The primary efficacy endpoint was the duration of oral mucositis, as measured by the number of days patients experienced severe oral mucositis, grade 3 or 4 by the World Health Organization [WHO] scale.[67,68] (For patients who did not develop oral mucositis, the duration was counted as zero days.) Secondary endpoints included the incidence of oral mucositis of WHO grade 3 or 4, the incidence and duration of WHO grade 4 oral mucositis, the duration of oral mucositis of WHO grade 2 (moderate) or higher, and the use of parenteral or transdermal opioid analgesia.

Results are shown in Figures 3a and 3b and Table 1.[61] Palifermin



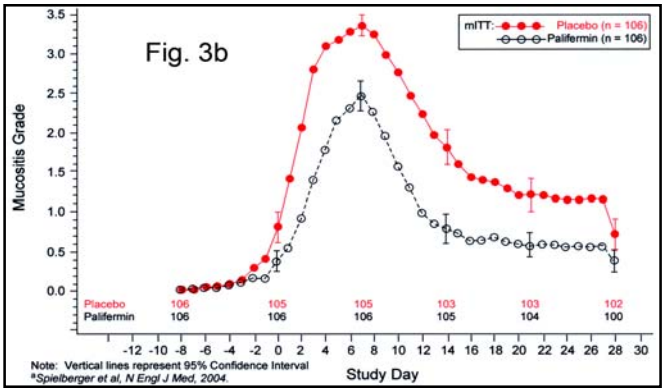


Table 1. Efficacy Outcomes

	Palifermin (Kepivance™) (60 mcg/kg/day) (n = 106)	Placebo (n = 106)
Median[b] (25th, 75th percentile) Days of WHO Grade 3/4 Oral Mucositis[c]	3 (0, 6)	9 (6, 13)
Incidence of WHO Grade 3/4 Oral Mucositis	63% (67/106)	98% (104/106)
Incidence of WHO Grade 4 Oral Mucositis	20% (21/106)	62% (66/106)
Median (25th, 75th percentile) Days of WHO Grade 2/3/4 Oral Mucositis	8 (4, 12)	14 (11, 19)
Opioid Analgesia for Oral Mucositis:		
Median (25th, 75th percentile) Days	7 (1, 10)	11 (8, 14)
Median (25th, 75th percentile) Cumulative Dose (morphine mg equivalents)	212 (3, 558)	535 (269, 1429)

[a] Spielberger et al, N Engl J Med, 2004.

[b] P < 0.001 compared to placebo, using Generalized Cochran-Mantel-Haenszel (CMH) test stratified for study center. P-values presented for primary endpoint only.

[c] WHO Oral Mucositis Scale: Grade 1 = soreness/erythema; Grade 2 = erythema, ulcers, can eat solids; Grade 3 = ulcers, requires liquid diet only; Grade 4 = alimentation not possible.

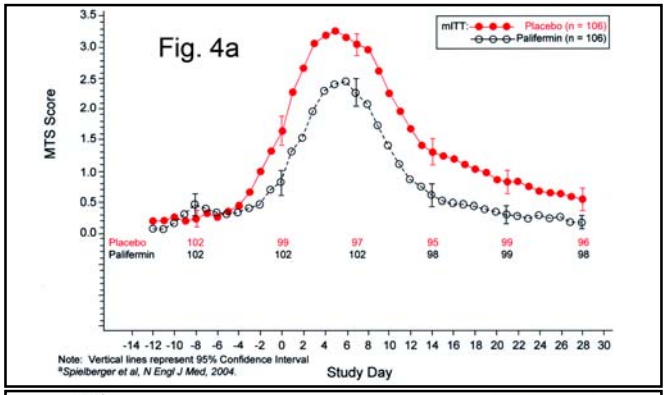
continued on page 4

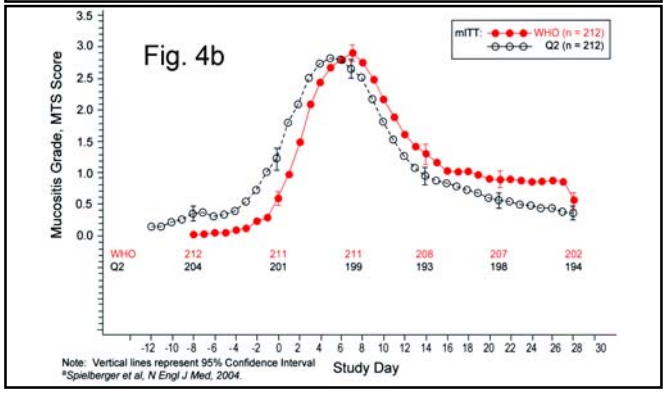
Kepivance™: A breakthrough – continued from page 3

produced a statistically significant and clinically relevant reduction in oral mucositis. The median duration of oral mucositis of WHO grade 3 or 4 was 3 days in the palifermin group compared to 9 days in the placebo group ($p < 0.001$). Fewer patients experienced severe oral mucositis after palifermin versus placebo (63% versus 98%; $p < 0.001$). Among patients with grade 3 or 4 oral mucositis, the median duration was 6 days in the palifermin group and 9 days in the placebo group. These results were consistent across study centers, and type of underlying disease. The incidence and duration of grade 4 oral mucositis was also decreased significantly (20% and 2 days in the palifermin group versus 62% and 6 days in the placebo groups; $p < 0.004$). The distribution of patients by incidence of each WHO grade indicated a shift from higher to lower WHO grades, meaning severe oral mucositis, in patients receiving palifermin. Patients receiving palifermin used fewer opioid analgesics (212 mg morphine equivalents) than those receiving placebos (535 mg morphine equivalents; $p < 0.001$).

A phase 2 randomized, multicenter, placebo-controlled study comparing varying dosing schedules of palifermin was also conducted (data on file).[62] All patients received high-dose cytotoxic therapy consisting of fractionated TBI (12 Gy total dose), high-dose etoposide (60 mcg/kg), and high-dose cyclophosphamide (75-100 mg/kg) followed by PBPC support for the treatment of hematologic malignancies (NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma). Efficacy results in this study were similar to the phase 3 trial (data on file).[62]

The clinical significance of reducing both the incidence and duration of severe oral mucositis was reflected by a parallel improvement in clinical sequelae secondary to severe oral mucositis. Palifermin produced significant and clinically meaningful decreases in mouth and throat soreness, use of opioid analgesics, total parenteral nutrition (TPN), and febrile neutropenic episodes. As shown in Figures 4a and 4b, patients in the phase 3 trial





reliably and consistently reported changes in their ability to perform daily functions of life (eating, drinking, talking, swallowing) prior to their physicians observation of the same effects.[61]

Safety in Hematologic Cancer Patients

Safety data for patients with hematologic malignancies are based on 409 patients who received palifermin and 241 patients who received placebo in 3 randomized, placebo-controlled clinical studies and in 1 pharmacokinetic study (data on file). Palifermin was administered either before, or before and after regimens of myelosuppressive chemotherapy, with or without TBI, followed by PBPC support. The patient population was predominantly male (62%), white (83%), and between 41 and 60 years old (median 48 years). Most had NHL, with Hodgkin's disease, multiple myeloma, and acute leukemia as the next most common disease states. Because these clinical trials were conducted in the high-dose myelotoxic therapy setting, pregnant women were not studied and very few pediatric and geriatric patients participated. To date, palifermin safety and efficacy have not been evaluated in the pediatric population.

The overall adverse event profile was similar between the placebo and palifermin patients and reflected expected outcomes for this population of patients with hematologic cancers receiving high-dose chemoradiotherapy followed by HSC support. Few treatment-related adverse reactions were serious and only 2% of patients discontinued use of the investigational product (either palifermin or placebo) due to adverse reactions. The most common serious adverse reaction attributed to palifermin was skin rash, reported in < 1% of patients. Grade 3 skin rashes occurred in 14 patients (9 receiving palifermin and 5 receiving placebo). Other serious reactions occurred at a similar rate in both patient populations (20% in palifermin patients versus 21% in placebo patients).

The most common adverse reactions attributed to palifermin were skin toxicities (rash, erythema, edema, pruritus), oral toxicities (dysesthesia, tongue discoloration, tongue thickening, alteration of taste), pain arthralgias, and dysesthesia. Most of these cutaneous adverse reactions occurred within 6 days after the first injection and lasted for 5 days. Of note, dysesthesia in palifermin patients was usually localized to the perioral region while in placebo patients this was more likely to occur in the extremities. As shown in Table 2, the most common adverse events (> 5%) in both treatment

Table 2. Most Common Adverse Events (> 5%) in Patients Treated with Palifermin or Placebo[a]

BODY SYSTEM Adverse Event	Kepivance™ (n = 409)	Placebo (n = 241)
BODY AS A WHOLE		
Edema	28%	21%
Pain	16%	11%
Fever	39%	34%
GASTROINTESTINAL		
Mouth/Tongue Thickness or Discoloration	17%	8%
MUSCULOSKELETAL		
Arthralgia	10%	5%
SKIN AND APPENDAGES		
Rash	62%	50%
Pruritus	35%	24%
Erythema	32%	22%
SPECIAL SENSES		
Taste Altered	16%	8%
CNS/PNS		
Dysesthesia – Hyperesthesia / hypoesthesia/ paresthesia	12%	7%
METABOLIC		
Elevated serum lipase (Grade 3/4)	28% (11%)	23% (5%)
Elevated serum amylase (Grade 3/4)	62% (38%)	54% (31%)

[a] Data from 650 patients (409 palifermin; 241 placebo) in 3 randomized, placebo-controlled clinical studies and 1 pharmacokinetic study.

groups included edema, pain, fever, mouth/tongue thickness or discoloration, arthralgia, rash, pruritus, erythema, altered taste,

continued on page 7

CIBMTR Transitional Advisory Committee

Officer Elections

By Paula Watry

Associate Director, Operations, CIBMTR

The CIBMTR Transitional Advisory Committee (which includes previous IBMTR/ABMTR Executive Committee, NMDP Research and Publications and NMDP Histocompatibility Committee members) held its first meeting on October 30, 2004. The organizational structure for the new CIBMTR was approved at that meeting including guidelines for Advisory Committee makeup, committee responsibilities, elections and term durations. A summary of the Organizational Structure is available on the CIBMTR website. The Transitional Advisory Committee will serve through January 1, 2006 before being succeeded by a new Committee elected by CIBMTR members in Fall 2005.

The Transitional Advisory Committee elected several officers at its first meeting:

Chair – Richard E. Champlin, MD
Vice-Chair for North America – Sergio A. Giralt, MD
Vice-Chair for South America – Ricardo Pasquini, MD
Vice-Chair for Europe – Olle Ringdén, MD, PhD
Vice-Chair for Asia/Australia/Africa – Jeffrey Szer, MD

The CIBMTR will have 17 Working Committees that will provide scientific oversight for CIBMTR activities. These committees are headed by 2-4 co-chairs who were nominated by the Advisory Committee at its October meeting. A complete list of WC officers and staff can be found at http://www.ibmtr.org/committees/workinglist.asp.

Perspective from the Chair, CIBMTR Advisory Committee

By Richard E. Champlin, MD

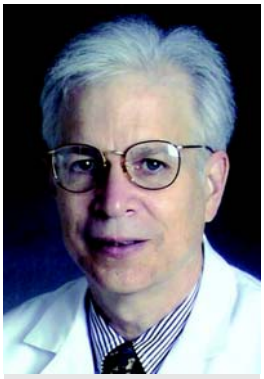
Professor of Medicine, Robert C. Hickey Chair of Clinical Cancer Care, Associate Head, Hematology, Division of Cancer Medicine, Chairman, Department of Blood and Marrow Transplantation, M.D. Anderson Cancer Center, Houston, TX, USA

Welcome to the new Center for International Blood and Marrow Transplant Research, the CIBMTR. This organization is the result of integrating the International Bone Marrow Transplant Registry/ Autologous Blood and Marrow Transplant Registry (IBMTR/ABMTR) and National Marrow Donor Program (NMDP) clinical research operations. The IBMTR/ABMTR and NMDP have cooperated on many levels in recent years, including harmonization of data reporting forms and jointly supporting the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The scientific committees of the two organizations involved many of the same members and the organizations frequently performed similar research studies. The CIBMTR retains the strengths of each organization and effectively merges their research actitivities, which should reduce redundancies and duplicative efforts. The affiliation will ultimately result in unification and simplification of data collection. The new organization retains the Working Committee organization of the IBMTR/ABMTR but expands these to include committees focusing on Immunobiology, including more in-depth analyses of GVHD, histocompatibility and KIR. The number of co-chairs has also been expanded and includes international leaders in many areas of transplantation who are committed to the organization. Additionally, the CIBMTR will address some new areas of research related to Healthcare Policy including socio-economics, epidemiology and healthcare delivery.

The CIBMTR will define key areas for future research in collaboration with leading scientists, physicians and others in the blood and marrow transplant community. The organization will work to secure funding for its research activities through partnerships with government, industry and other private parties. A major planned initiative is the development of a related donor-recipient cell repository to support clinical and translational research studies.

Importantly, the organization remains “International.” As was true for the IBMTR/ABMTR, contributions from members from outside the United States will be vital to our success; the CIBMTR will continue to ensure all members full opportunities for participation and organizational leadership. We also will continue to address research issues related to the international practice of hematopoietic transplantation.

What does this mean to transplant physicians and centers? A major goal is to improve the efficiency of interactions with transplant centers for data collection and reporting. The organization will continue to provide opportunities for physicians and staff from transplant centers to propose and participate in clinical research. The strength of the organization is the talent and energy of its participants, proposing and conducting the clinical research studies in each Committee. It is particularly important to have junior faculty continually coming into the organization, participating in the research and ultimately moving into leadership positions within the organization.



CIBMTR Advisory Committee Chair, Richard E. Champlin, MD, is Professor of Medicine, Robert C. Hickey Chair of Clinical Cancer Care, Associate Head, Hematology, Division of Cancer Medicine, Chairman, Department of Blood and Marrow Transplantation, M.D. Anderson Cancer Center, Houston, TX, USA

I strongly encourage you to attend the Working Committees corresponding to your personal interest at the upcoming Tandem meetings. Please introduce yourself to the Committee chairs, volunteer and actively participate in the clinical studies of the committee. The CIBMTR provides a unique opportunity for junior faculty to bcome involved with major national and international clinical research studies. It’s a great learning experience, and a chance to grow into a leadership position on the working committees. It is also an opportunity to develop formal professional relationships and develop an international reputation in clinical research, which is necessary for an individual’s career development and academic promotion. Many of the current international leaders in hematopoietic transplantation got their professional start within the IBMTR/ABMTR and NMDP.

The 2005 Tandem Meetings is our first annual meeting for the new CIBMTR. It will be an exciting scientific meeting presenting new data and highlighting the major advances within the broad field of hematopoietic transplantation. The program and working committee schedules is available at www.cibmtr.org. It will also be the first opportunity for each Working Committee to meet and set the research agenda for the upcoming year. It is also an opportunity for participants to have a voice in the organization of the new CIBMTR.

I look forward to seeing all of you in Keystone.

How to Propose a Study

By Waleska S Pérez, MPH
Biostatistician, CIBMTR

Anyone may propose a study to the Center for International Blood and Marrow Transplant Research (CIBMTR). This proposal is intended as an overview of the desired project and should include the study objective, primary and if applicable, secondary endpoints and variables required to achieving the study objective. Proposals may be submitted to the administrative office of the CIBMTR (CIBMTR@mcw.edu) or directly to the Statistician for the relevant Working Committee. The working committee statistician will then review the appropriated data collection forms and examine patient numbers, to determine feasibility. If the relevant variables are not captured on existing data collection Forms, a supplementary Form may be required. At this time the decision to proceed with the study is based on the scientific merit of the proposal and will be determined by the Working Committee chair(s) and Scientific Director. The Working Committee Statistician will prepare a table that will include a list of informative variables and number of cases available for the study. This will be presented to the appropriate Working Committee Chair(s) and the Scientific Director for further review. Additionally, all new proposals are discussed at the CIBMTR. Studies deemed feasible and consistent with the CIBMTR's scientific goals are presented at the annual Working Committee meeting for further input and assignment of a priority score. The outline of the proposal is as follows:

- Study title
- Name and institution of person proposing the study
- Objectives: The aims of the study should be stated as concisely and clearly as possible. A person reading the objectives should have a clear idea of the primary issue(s) being examined. The objective is the purpose for which the data will be analyzed.
- Scientific justification: This section should summarize the rationale for the study, citing relevant previous work. The scientific justification should convey the importance of the intended study.
- Study population: It should be as specific as possible, including requirements of age, disease and disease stage, years of transplant, graft and donor type, prior treatment, specific transplant regimens or any other restriction relevant to the study. If the study involves combining CIBMTR data with data from another group, the selection criteria for patients from the other database should also be specified and state how the person proposing the study intends to obtain this data.
- Data collection: If the study requires supplemental data collection, these variables and plans to implement collection of supplemental data should be specified.
- Study design: This section should describe in non-technical terms the approach to achieving each of the objectives of the study. It should include the specific statistical methodology planned, with a discussion of its limitations, if relevant. The Working Committee Statistician along with a PhD statistician will provide the necessary assistance for this section. If necessary, this section may include estimations of power calculations to achieve specified objectives, given anticipated sample size.
- Outcomes: Study outcomes should be defined clearly, including time-points, where relevant. The definition of each outcome may change depending on the disease. In some instance, outcomes may be modified depending the research question
- Variables to be analyzed: Explanatory variables should be listed with suggested categories for analysis. The categories should be based on biological principles and consistent with previous literature. Variables should be available in the CIBMTR database and the format in which the data are collected. For studies combining CIBMTR data with data from other groups, the availability of specific variables in both database and the timing of specific measurements s should be confirmed.
- Table describing population: A table describing the study population will be develop by the Working Committee Statistician with the number of cases evaluable for each variable. For comparative studies, each population will be described separately.

Clinical Research Professional/Data Management Conference 2004

By Diane J Knutson, BS
Senior Research Associate, CIBMTR

Mid September 2004, 130 attendees participated in the Clinical Research Professional/Data Management Conference at Embassy Suites, Brookfield, WI. Friday's sessions included an overview of HSCT, reporting to CIBMTR, and Shelly Carter, Jim Albert and Mary Matty conducted sessions for BMT-CTN participants.

Highlighted topics on Saturday included post HSCT pulmonary complications presented by Dr. Linus Santos Thomas, Medical College of WI; reporting cause of death by Dr. Doug Rizzo; and concurrent Disease Insert sessions, Immune Deficiency by Dr. Stella Davies, Cincinnati Children's Hospital; and Multiple Myeloma by Dr. Chris Bredeson. CIBMTR staff members presented roundtable sessions covering TEDWeb, Error Reports/discrepancy resolution, audits and getting organized.

On Sunday, two outstanding reporting teams gave presentations on how their centers organize data collection for timely submission. The presenters were Theresa Hahn, Roswell Park, Buffalo, and Heliz Regina A. Neves, Federal University, Curitiba, Brazil. Taking a break from Report Form topics, we heard from Kari Whittenberger-Keith, PhD, UW-Milwaukee communications professor, and MCW Assistant Professor of Bioethics, Ryan Spellecy, PhD. regarding communication and consent issues. Dr Fausto Loberiza, CIBMTR, shared transplant center characteristics from a recent survey and Mark Reitz, CIBMTR introduced utilizing MS Access for organizing patient data.

The Mentors Special Interest Group organized activities for participants to meet each other and to become aware of the service provided by their Web site, www.datamanager.blogspot.com.

The BMT Tandem Meetings at Keystone will be held, Wednesday, February 9 through Friday, February 11 for CRP/DM's. Check the Web site for the agenda and registration information. We look forward to seeing you in Keystone 2005!

Kepivance™: A breakthrough – continued from page 4

dysesthesia, and transient elevations of serum lipase and amylase levels. Across all studies, slightly higher levels (not statistically significant) of transient hypertension were noted in palifermin-treated patients than in placebo-treated patients (7% versus 5%). Similarly, proteinuria was detected in 9 palifermin patients and not in placebo patients. For the 9 palifermin patients with proteinuria, underlying medical conditions known to be associated with proteinuria were present at baseline, prior to treatment. A causal relationship between palifermin and proteinuria has not been established.

Since KGF receptors are not present on hematopoietic cells, palifermin administration was not anticipated to have any effect on the incidence of engraftment delays or failure. The overall exposure to filgrastim was similar between the palifermin and placebo patients. Overall, the kinetics of hematopoietic reconstitution between the treatment groups were comparable to what has been previously described for this patient population.[69]

Immunogenicity of biological therapeutics is a well-recognized concern when biologic agents are used. Since palifermin is a modified endogenous protein, the possibility of immunogenicity exists and the production of neutralizing antibodies may occur. An electrochemiluminescence-based binding assay was performed on sera collected after palifermin treatment from 645 patients. Only 2% tested positive for antibodies to palifermin in a preliminary screening test, and none of the samples had evidence of neutralizing activity.

Dosing and Administration of Palifermin (Kepivance™)

Palifermin (Kepivance™) is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring HSC support. The recommended dosage is 60 mcg/kg/day, administered as an IV bolus injection for 3 consecutive days prior to and 3 consecutive days after myelosuppressive therapy, for a total of 6 doses. The first 3 doses should be administered prior to chemo- and/or radiotherapy, with the third dose administered at least 24 to 48 hours prior to the first myeloablative treatment. The final 3 doses should be administered post-infusion, with the first dose administered on the same day as HSC infusion and at least 4 days after the previous administration of Kepivance™.

Palifermin is supplied as a lyophilized powder that should be reconstituted only with Sterile Water for Injection, USP. Palifermin should be reconstituted by slowly injection 1.2 mL of Sterile Water for Injection, USP to yield a final concentration of 5 mg/mL. The contents should be swirled gently during dissolution (~3 minutes) and not shaken vigorously as this may cause protein degradation. Reconstituted palifermin is intended for single use only. This product should be used immediately, but may be stored at 2° to 8°C for up to 24 hours. Prior to injection, palifermin may be allowed to reach room temperature for a maximum of 1 hour. Palifermin should be protected from light at all times.

Palifermin should be administered by IV bolus injection. If heparin is used to maintain an IV line, then saline should be used to rinse the line prior to and after palifermin administration since this product has been shown to bind heparin in vitro.

CONCLUSION

In the setting of high-dose myelotoxic therapy, mucositis is a frequent, extremely painful, and debilitating complication.[70] Patients consistently rate oral mucositis as one of the most debilitating side effects of the transplant procedure.[5,22,23,25,26] Its manifestations negatively impact the quality of life of patients and can have serious economic consequences by prolonging hospitalization, increasing the dependence on narcotic analgesics for pain relief, requiring use of TPN to maintain nutritional needs, and relying on the use of antibiotics to treat opportunistic infections.[22,25,26] Oral mucositis represents a dose-limiting toxicity for many chemoradiotherapy regimens.

Palifermin (Kepivance™) significantly reduces the incidence, duration, and severity of oral mucositis and related clinical sequelae in patients with hematologic malignancies undergoing high-dose myelotoxic therapy followed by HSC support. This first in class drug has demonstrated clinically meaningful benefits to patients, as measured by objective clinical scales such as the WHO, RTOG, and WCCNR scales and also as measured by the patients themselves in daily questionnaires.[61] The safety profile of palifermin is predictable and manageable. Furthermore, it is well tolerated and most of the observable adverse reactions are primarily related to its pharmacologic activity. In conclusion, Kepivance™ is a significant advance in treatment for hematologic cancer patients suffering from oral mucositis from their chemoradiotherapy treatments.

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continued on page 10

CIBMTR Data Management Updates

By Mark Reitz

Programs Director, Data Operations, CIBMTR

This column is dedicated to announcing new tools, forms and frequently asked questions to help those who submit data to the CIBMTR.

Frequently Asked Questions:

What form do I use to register my BMT CTN patients?
The Blood and Marrow Transplant (BMT) Clinical Trials Network (CTN) was established to conduct large multi-institutional clinical trials. Clinical Centers can be either designated as a CIBMTR Registering CTN or Research CTN center. Centers must register all transplant recipients (both on and off protocol) through the CIBMTR Pre-Registration System. Pre-Registration of CTN protocol patients is accomplished via three methods:

1) Paper Pre-registration Form: Place a Green CTN sticker in the upper-right corner and fax to CIBMTR.
2) Ted on the Web: Check the "Yes" radio button for BMT CTN patient.
3) StemSoft (V3.2 or earlier) users: Print a copy of the StemSoft pre-reg form, attach a Green Sticker and fax to CIBMTR.

Sometimes I do not receive Error Reports and/or Reimbursement in the same chronological order that I submitted the forms. Are all data submitted to the Registry evaluated equally?
Data submitted to the Registry are not evaluated equally. We prioritize which Report Forms are entered first based on:

1) Studies
2) Complete Report Forms (no errors)
3) Incomplete Report Forms

Report Forms required for Studies are the first priority. Next priority is complete Report Forms without errors. The third priority is Incomplete Report Forms that contain errors, missing data, discrepancies, etc. Some errors, omissions or discrepancies will not allow the data to be entered into our database until corrected. This delays the normal data entry workflow while we are waiting for clarification or corrections. Teams will not be reimbursed until errors are corrected.

How should backlog be approached for Research Teams?

1) Complete all study request(s)
2) Continue to pre-register ALL your patients and complete all registration Data (MTED/TED-FU)
3) Complete past due Report Forms and Follow-Up Report Forms

Do I need to submit a Follow-Up Report Form for each year the patient is backlogged?
No, if more than 2 years have elapsed without submitting a Follow-Up Report Form/TED-FU, it is only necessary to complete one Follow-Up. Up to the most recent patient contact, provided no new transplant or DCI has been performed.

Which NMDP Forms should be submitted in lieu of IBMTR Forms?
Complete Initial Report Form consists of:

1) A copy of NMDP Form 120-Recipient Baseline and Transplant Data
2) A copy of NMDP Form 120 Disease Specific Insert for appropriate disease
3) A copy of NMDP Form 130-Day 100 Report
4) A completed CIBMTR Graft Insert: ALLOBM, ALLOPB or ALLOCB insert. (Based on tissue transplanted – no corresponding NMDP document available)
5) If the patient died, submit Form 190

Complete Follow-Up Report Form consists of:

1) A copy of NMDP Form 140-6 month to 2 year follow-up
   OR
2) A copy of NMDP Form 150-greater than 2 year follow-up
   Note: For CML patients, also complete 095-CMLFU

Please note:

1) Please DO NOT send copies of NMDP Forms until after they have been accepted as error free by the NMDP.
2) Make any corrections identified by the NMDP or through your own correction process. DO NOT attach the "NMDP correction page(s)."
3) Clearly print your team number & the patient IUBMID number on the top of the page.
4) Remove all Center Identifiers and Protected Health Information, such as names, initials, SSN, Medical Record numbers, etc. as defined by HIPAA.
5) Only NMDP version May 1995 or later will be accepted.

Who is responsible for patients transplanted or followed-up by another institution?
If a patient transplanted at your center has another HSCT or DCI at another center, your responsibility for reporting, both Registration and Research Report Forms, ends one day prior to conditioning for the HSCT or one day prior to infusion for the DCI.
If possible, provide contact information of the new transplant center, so that we may request that they continue reporting where you left off.
If your center is providing follow-up care for a patient transplanted elsewhere, and your team does not provide another HSCT or DCI, you will need to send follow-up data to the team that did the transplant. You are not responsible for reporting directly to the CIBMTR in this case.

What are the current Reimbursement Rates for Research Teams?
Effective for forms received by the CIBMTR on or after July 1, 2003, reimbursement are as follows:

Report Forms = $120.00
(Core Insert + Graft Insert + Disease Specific Insert)

Subsequent Report Forms or DCI Forms = $60.00

Follow-Up Report Forms = $40.00
(Follow-Up Core Insert + Disease Specific FU Insert)

Pre-Registration Forms = $10.00
(Not previously reimbursed. This includes patients Pre-Registered with a transplant date of July 1, 2003 or later.)

The wording for monitoring disease post TX is confusing on the MTED, TED and TEDFU forms. Can you suggest a different wording to make it easier to understand?
Yes, due to various reasons and rewordings, the questions are still poorly worded. The data we are trying to collect is clear, but the question is not. We are not looking for shades of gray (relapse/progression versus persistent disease). Either the recipient has disease post TX or they don't. We suggest using the questions as reworded below and see if the section makes more sense:

1) During this reporting period, did the patient have evidence of

disease (relapse/progression/persistence)? ❑ Yes ❑ No

2) During this reporting period, by what method(s) was the disease monitored? (check all that apply)
3) During this reporting period, was disease detected by any of the methods used? ❑ Yes ❑ No
   If yes, give the date disease was first detected by each method during this reporting period; (the reference to "first detected" never meant THE FIRST, it meant the first date for the reporting period.)
   If no, give the latest date assessed by each method.

When analyzing the data, answer these questions:
Did the TX eradicate the disease or not?
What is your evidence?

Please tell me more about Ted on the Web and what are the benefits?
TED on the Web is an alternative for non-Stemsoft teams to submit Registration data. Pre-reg, MTED, TED and TEDFU can be electronically submitted in lieu of the paper version of these forms. It is recommended that users print a copy of the data before submitting since the data is not accessible once submitted. In other words, similar to paper form data submission, the team does not have a copy of the data in their database unless they do double data entry.

Teams need to apply for a user account to be able to login and submit data online securely. Help for online access is available at tedweb@mcw.edu.
Research, Research CTN and Registering CTN teams can submit:
1) Pre-Registration
2) Modified TED
3) TED Follow-up

Registering teams can submit:
1) TED
2) TED Follow-up

The Ted on the Web instructions state: "Note to Stemsoft users: continue to use BMTbase Ted and BMTbase export to submit data to the CIBMTR." Who exactly is able to use this procedure? Only those centers who currently do not have the StemSoft database?
TED on the Web at first glance may sound like a more efficient process than using the StemSoft software. However, Stemsoft users will find that using the export feature in the application to submit their Registration data will be the most efficient process, since the data will not need to be entered twice.

How do I interpret the TED Discrepancy Report?
TED data submitted electronically is processed weekly on Fridays. A confirmation of the receipt of this data is sent by email after the weekly batch is processed. If you have not received a report within two weeks after submission, please contact us. A Discrepancy Report may be generated with 1 to 4 attachments. The number depends on what type of data was submitted.

1) *TEDImportMainLog.txt*
   You always receive this file. It includes the errors in your report and statistical information for your report.
2) *Reg_new.rtf*
   Lists all new transplants with basic information. Research and CTN teams please note "Report Form Needed" field. If "Yes" please send a Day-100 Report Form. Registering teams should always have this field as "No" unless requested for a study.
3) *Reg_disc.rtf*
   If your data is discrepant from the data existing in our database, you will receive this report.
   • The top line is the data that you sent to us in the TED data file and the bottom line is the data that exists in our database. The discrepancy is noted by a "*" next to the field which needs correcting. Circle the correct information and return it to us.
   • A [R] under the IUBMID field, means the report is rejected.
4) *Reg_detail.rtf*
   • This file provides detailed explanation for some fields in Reg_disc.rtf file such as Dx(Disease), StatusAtTx (disease status at transplant), Donor, etc.

Note that TED on the Web and Stemsoft BMTbase are intended only for submission of new TED data, you should not make corrections this way. Please send the corrections by paper, fax or email to ted_data@mcw.edu

Why doesn't the TED Discrepancy Report go to the same people at my center every week?
Both TED on the Web and Stemsoft allow multiple users to log in. However, the report can only be sent one person every time. The program automatically picks the email address, based on who sent the data first that week. If your team wants a "default person" to receive the report, we have to set all your other senders' email addresses to the default. Also, in the future if there is new person sending the data, they need to use the default address as well.

What is the CIBMTR Audit Program process?
The objective of the Audit program is to ensure accuracy of submitted data and verify registration of all eligible transplants. It also serves a means of positive reinforcement and educational experience for the participating BMT center. An acceptable audit is defined as having accuracy of at least 95% and no more than 3% major errors. A computer randomized Audit schedule has been replaced with a three-year schedule encompassing all Research Teams. Every March or April teams are notified of an Audit for the up coming year. Upon notification your team should meet to:

1) Determine Data Manager and Team Leader or Designee availability
   • Prepare for the following data to be verified
   • Pre Transplant Information
   • Conditioning Regimens
   • Graft and Transplant Information
   • Post Transplant Information
   • Donor Information
   • Source Documentation
2) Prepare for verification of consecutive registration
   • IUBMID Number
   • Date of Transplant
   • Date of Birth
   • Type of Transplant
   • Vital Statistic
   • Date of Last Follow-up
3) Amass Records
   • Medical Records
   • Outpatient Clinic Charts
   • Graft Processing Lab Charts
   • Radiation Oncology Charts
   • Donor Records
   • Research (Shadow) Charts

DATA CONNECTION - A DATA MANAGERS WEB SITE
A source of information for Clinical Research Professionals and Data Managers

Internal Links	***External Links***
Newsletter	CIBMTR, NMDP, EBMT, StemSoft
Mentors	BMT-infonet
News and Information	CTCAE(3.0)
Helping Hand Guide	HIPAA
The Notice Board	HLA Typing
Audits	Chemotherapy Acronyms
Meetings	On-Line Medical Dictionary, Internet Drug Index
Questions and Answers	Social Security Death Index
Organizing the work	Medical, BSA and Day Calculator
Mailing List Signup	NCI Clinical Trials

Visit: www.datamanager.blogspot.com

Kepivance™: A breakthrough – continued from page 7

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