LETTERS TO THE EDITOR

Information About Biafine for Radiation Dermatitis Excluded Important Information

On behalf of Medix Pharmaceuticals Americas, Inc., the U.S. distributor of Biafine®, I am writing to express deep concern over the following review article that appeared in *Oncology Nursing Forum* (Vol. 31, pp. 237–247): "Prevention and Treatment of Acute Radiation Dermatitis: A Literature Review" by Mihkaila Maurine Wickline. The article misrepresents the current state of the scientific literature and does a disservice to oncology healthcare professionals and patients alike. Although my following comments focus primarily on the author's comments and conclusions regarding Biafine, I have no reason to believe that her comments regarding other radiation therapies are valid.

Let me begin by noting the surprising failure on the part of the author to mention that Biafine has been cleared by the U.S. Food and Drug Administration (FDA) specifically for radiation dermatitis, not to mention for use on partial and full thickness wounds, first- and second-degree burns, and dry skin conditions. The FDA has reviewed much of the same literature as the author yet reached a different conclusion.

Although the author may have been unaware of the FDA's clearance of Biafine, she has no excuse for the numerous misinterpretations and misrepresentations of the study results described in the article and the failure to include the positive results observed. For example, on p. 240, in describing the findings of Szumacher et al. (2001), the author stated that "Biafine does not prevent dry or moist desquamation in patients undergoing concomitant radiotherapy and chemotherapy." Simply put, this conclusion may not be drawn from the underlying article. Although the investigators reported that prevention of grade 2 toxicity development was not demonstrated, they presented data demonstrating that the population treated with Biafine experienced significant benefits, including reduction in the quality and quantity of moist desquamation, as well as elimination of therapy interruptions because of skin breakdown.

Furthermore, with regard to Fisher et al. (2000), the author reported that the investigators found no overall difference between best supportive care and Biafine with respect to prevention of radiation-induced dermatitis. The author failed to report, however, that the investigators also found an interventional effect with Biafine and that large-breasted women receiving Biafine were more likely to have no toxicity six weeks after radiation therapy.

The author relied on these and other misinterpretations and misrepresentations of study results to draw the conclusion that Biafine has "not been proven effective and should not be used" (pp. 237, 242). In point of fact, each of the Biafine studies cited in the review article reports a benefit associated with use of the product during radiation therapy. Perhaps even more curious, despite the relative dearth of supportive data concerning the use of aloe vera during radiation therapy, the author concluded that "aloe vera may be beneficial and is not harmful" (p. 237). Although I do not necessarily question the author's conclusion with respect to the use of aloe vera, the logic with which that conclusion was drawn stands in marked contrast to the author's conclusions with respect to Biafine.

Biafine has been studied extensively, with many positive benefits reported and no evidence of any adverse events. Indeed, a continuing education piece on radiation therapy in patients with breast cancer reviewed many of the same studies cited by Wickline and drew completely opposite conclusions (Callahan, 2003). In that article, the author recommended highly the use of Biafine during radiation therapy. Thus, despite the numerous reported benefits of Biafine, Wickline reached an unsupportable—and, quite frankly, irresponsible—conclusion.

Whether because of timing or some other reason, the author failed to consider other data demonstrating the positive effects of Biafine. For example, Boisnic, Branchet-Gumila, Nizri, and Ben Slama (2003) reported Biafine's efficacy in skin subjected to 5 Gy ionizing radiation, with an increase in the mitotic number of cells in the basal layer of the epidermis. The emulsion acted on vascular permeability in the dermis after the first 24 hours. Restoration of CD34 expression after application of Biafine indicated good endothelial cell differentiation, collagen synthesis was increased, and this parameter was restored after Biafine treatment. This may offer an advantage in limiting the occurrence of postradiotherapy fibrosis. Furthermore, the effect of Biafine on interleukin (IL)-1 could be involved in the modulation of collagen synthesis observed. Results concerning IL-6 are consistent with those obtained by Coulomb, Friteau, and Dubertret (1997), who demonstrated that Biafine is chemotactic for macrophages and increases the IL-1/IL-6 ratio, chiefly by reducing IL-6 levels. Controls were treated with petroleum jelly. Biafine outperformed petroleum jelly in all the results mentioned previously, except the collagen assay, where results for both were found to be similar.

Biafine selectively recruits 3–10 times the normal amount of macrophages to a wound site while reducing the number of polymorphonuclear neutrophils recruited, thereby resulting in rapid granulation, epithelialization, and wound closure. Macrophages synthesize human collagenase and collagen and stimulate fibroblast proliferation for granulation tissue replacement. As radiation therapy destroys tissue layers that break down into moist desquamation, Biafine stimulates the body's healing mechanisms to rebuild them.

Finally, for general information, Biafine is soothing and cooling on application and can be refrigerated for additional cooling effect. Most competing products only hydrate the epidermis, but as much as 41% of the demineralized water in Biafine penetrates to the dermal level by osmosis in the first hour of application (Wepierre, 1988). Emollients in Biafine keep skin soft, supple, and elastic and fight maceration of intact periwound skin around moist desquamations. Stearic acid in Biafine's formulation replenishes the skin's natural barrier function against irritants, helping to normalize transepidermal water loss in patients whose skin often is compromised with dryness before radiation therapy starts.

The benefits of Biafine for use in patients undergoing radiation therapy are well documented in the scientific literature and recognized by the FDA. Any recommendation other than continued use of Biafine in this patient population jeopardizes the quality of care that healthcare providers may provide and patients may receive. Biafine should be a staple of the wound care armamentarium in the radiation therapy setting.

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References

Boisnic, S., Branchet-Gumila, M.C., Nizri, D., & Ben Slama, L. (2003). Histochemical and biochemical modifications induced by experimental irradiation of human skin maintained in survival conditions and modulation by application of an emulsion containing trolamine. *International Journal of Tissue Reactions, 25*(1), 9–18.

Callahan, K. (2003). Breast cancer and radiation treatments research studies and resultant observations of a registered radiation therapist. *X-Ray News, 9*(4), 4–14.

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Coulomb, B., Friteau, L., & Dubertret, L. (1997). Biafine applied on human epidermal wounds is chemotactic for macrophages and increases the IL-1/IL 6 ratio. *Skin Pharmacology, 10,* 281–287.

Fisher, J., Scott, C., Stevens, R., Marconi, B., Champion, L., Freedman, G., et al. (2000). Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. *International Journal of Radiation Oncology, Biology, Physics, 48,* 1307–1310.

Szumacher, E., Wighton, A., Fransses, E., Chow, E., Tsao, M., Ackerman, I., et al. (2001). Phase II study assessing the effectiveness of Biafine cream as a prophylactic agent for radiation-induced acute skin toxicity to the breast in women undergoing radiotherapy with concomitant CMF chemotherapy. *International Journal of Radiation Oncology, Biology, Physics, 51,* 81–86.

Wepierre, J. (1988). [Clinical study on the hydrating properties of Biafine® cream applied to normal and damaged skin of hairless rats]. Unpublished raw data.

The Author Responds

I would like to thank you for the opportunity to engage in further discussion about your company's product, Biafine. Like you, I wish for nothing to jeopardize the quality of care that patients with cancer receive. In keeping with the scope and length of a review article, my discussion of Biafine, like the other products reviewed, was brief. My failure to include mention of the historical cohort in the Szumacher et al. (2001) study and the large-breasted subset of patients in the Fisher et al. (2000) study was not an intentional misrepresentation of data. I appreciate this opportunity to clarify my interpretation of the research on Biafine. In the current quest for evidence-based practice, healthcare providers are called on to make patient care decisions that integrate the best scientific evidence with clinician expertise and patient-specific factors and preferences. I would like to respond to the points you raised in your letter using an evidence-based practice model.

In the 2001 article by Szumacher et al., using the National Cancer Institute of Canada Radiation Toxicity Criteria in a single-group phase II trial, the authors concluded that "83% of patients using Biafine cream developed grade 2 and 2% developed grade 3 skin radiation dermatitis during the course of radiotherapy" (p. 84). Although the patients treated in the study reportedly did fare better than a historical cohort (no treatment delays and less moist desquamation), the majority did experience grade 2 radiation dermatitis, defined as consisting of "moderate to brisk erythema, moderate oedema or a small < 1.5-cm patchy moist desquamation, mostly confined to skin folds and creases" (p. 86). The historical cohort simply was described as a "retrospective chart review at the Toronto Sunnybrook Regional Cancer Centre (unpublished data)" (p. 81). Readers were not given any information about the number of charts reviewed; the similarity of reviewed patients to the study population in terms of diagnosis, treatment, dosages of chemotherapy and radiotherapy; or any other factors. My summary of these findings in Table 1 was published as "Biafine does not prevent dry or moist desquamation in patients undergoing concomitant radiotherapy and chemotherapy" (Wickline, 2004, p. 240). My summary was based on the author's report that 83% of patients experienced grade 2 and less than or equal to 15% of patients experienced grade 1 radiation dermatitis, and dry desquamation and patchy moist desquamation are part of the defining characteristics of grade 1 and grade 2 radiation dermatitis. Also, per patient report, when asked whether blistering and breakdown were present, 38% of patients responded "a little" and 13% of patients responded "quite a bit," for a total of 51% subjective positive responses (p. 84). A more accurate summary for the table would have been: Biafine did not prevent dry desquamation and, in many cases, did not prevent patchy moist desquamation in the majority of patients undergoing concomitant radiotherapy and chemotherapy, although no treatment delays were seen. Please accept this correction to the record. Given that this research study had a nonrandomized design, a relatively small sample size, and no description of the historical cohort, its level of evidence would be considered moderately weak in strength (Rutledge et al., 2004). The results would have to be validated and synthesized with other research studies that demonstrate a positive effect with Biafine before translating them into clinical practice.

In the 2000 article by Fisher et al., the authors aimed to determine whether Biafine was effective in preventing radiation-induced skin damage. They concluded that no overall difference existed in the prevention of, time to, or duration of radiation-induced dermatitis in patients receiving Biafine versus patients receiving best supportive care. The authors found a slight statistical benefit for large-breasted women in terms of toxicity. The authors reported, as expected, that larger-breasted women experienced a higher rate of grade 2 or higher skin toxicity with radiation. However, in the subset of the 29 patients stratified into the largest bra-size category, an interventional effect of Biafine was noted: "Large-breasted women receiving Biafine were more likely to have no toxicity 6 weeks post [radiation therapy]" (p. 1307). The authors acknowledged that the trial was designed to find a prevention effect, not an intervention effect and planned to study further the interventional effect of Biafine in patients at greater-than-standard risk for radiation dermatitis in a separate study. Although perhaps not clinically generalizable, this interventional effect was statistically significant, and my review would have been more complete to include it. In the summary of the article, however, the authors concluded that "a method for preventing or minimizing radiation-induced dermatitis in the breast population remains unanswered. There is little scientific or clinical evidence that Biafine is superior to other emollients" (p. 1310). This research study had a larger sample size and was a randomized trial, giving it a stronger level of evidence; however, the overall results for Biafine were no better than standard care options.

Although you stated in your letter that "each of the Biafine studies cited in the review article reports a benefit associated with use of the product during radiation therapy," this is not the case. The two studies discussed previously in this letter may have demonstrated limited benefit to select subjects, but neither study was able to achieve the objectives set forth in the study design. Although unmentioned in your letter, the third article included in my article (Fenig et al., 2001) also was unable to demonstrate a radioprotective effect of Biafine.

Indeed, Callahan (2003) reached very different conclusions in her continuing education article. In reviewing the Szumacher et al. (2001) study, Callahan stated that, "Out of those participating in the study, only one patient had grade 3 toxicity (dry desquamation), and the rest, 50 patients, had grade 2 reaction (moderate erythema) or no reaction at all. This is wonderful news for radiation therapy patients" (p.7). Although it is true that one patient in the study experienced grade 3 toxicity and 50 patients experienced grade 2 toxicity, the definitions of these grades included in the quoted parentheses are grossly inaccurate according to the definitions in the Szumacher et al. article. Grade 2 toxicity, as defined by the study, was "moderate to brisk erythema, patchy moist desquamation less than 1.5 cm mostly confined to skin folds and creases, moderate edema." Grade 3 toxicity, as defined by the study, was "confluent moist desquamation greater than 1.5 cm not confined to skin, pitting edema" (Szumacher et al., p. 81). In reviewing the Fisher et al. (2000) study, Callahan stated, "The findings in this study were phenomenal. There was a 'significant reduction in toxicity post radiation therapy with Biafine® RE'" (p. 8). The term "phenomenal" seems inappropriate and in contradiction to the authors' own conclusion, that no scientific evidence supported the superiority of Biafine over other emollients in preventing radiation dermatitis (Fisher et al., p. 1310). Callahan also failed to point out that this "significant reduction in toxicity" was noted in only a small subset of large-breasted women. Her article highlighted the lack of scientific, peer-reviewed literature available to support the use of Biafine. Of the "Clinical Studies/Expert Reports" listed on the Medix Pharmaceuticals Americas, Inc. (MPA) Web site to support the use of Biafine products for all indications, only 1 of 18 is a published article

indexed in the National Library of Medicine's PubMed database. The majority of the resources is either case studies or opinion papers. Using an evidence-based practice model, these types of resources are the weakest level of evidence. One of the research studies listed as a resource on the MPA Web site is pending publication. The study examined Biafine compared to Radia-care gel™ (Carrington Laboratories, Irving, TX) in patients with cancer of the breast, lung, and head and neck and was closed to patient accrual in August 2002 (MPA, 2004a). Another study pending publication is listed in a brochure for Biafine and completed accrual in April 2002. Results of the study of Biafine use in patients with head and neck cancer are listed as "available Spring 2003" but are yet unpublished, and results of a complete peer review are unknown (MPA, n.d.).

The lack of inclusion of the Boisnic, Branchet-Gumila, Nizri, and Ben Slama (2003) article was due, in part, to timing, as the article was published two months prior to my article submission, but it would not have been included in my review because it was an ex vivo experiment. Although the article reported that the results for Biafine were promising, applying the experimental results of a human skin model exposed to 5 Gy of radiation and maintained in a laboratory for 15 days to real patients undergoing radiation therapy is inappropriate. Interestingly, another article that examined the use of Biafine in the radiation setting has been published since my article submission. The study by Pommier, Gomez, Sunyach, D'Hombres, and Montbaron (2004) compared Biafine with calendula officinalis cream in 254 patients undergoing radiation therapy for breast cancer. The authors were looking at a new product for preventing radiation dermatitis because "no large randomized studies demonstrated the efficacy of any local, nonsteroid topical agents in preventing radiation-induced dermatitis in postoperative breast cancer" (p. 1448). The results of the study demonstrated that calendula had a better outcome than Biafine for nearly every endpoint. Occurrence of grade 2 or higher radiation dermatitis was lower (41% versus 63%). Fewer allergic reactions (0 versus 4), fewer treatment interruptions (1 versus 15), and better patient satisfaction for pain relief (mean maximal pain score of 1.54 versus 2.10 on a visual analog scale) occurred. The only endpoint where Biafine outperformed calendula was "ease of application," with 30% of patients stating that calendula was difficult to apply and 5% of patients stating that Biafine was difficult to apply.

In addition to examining the scientific evidence, clinicians must look at patient factors and preferences when determining best practice. One of these factors is the financial burden of treatment. Biafine is a prescription-only product that is not available in a generic form. Patients can purchase the product directly from their physicians, from pharmacies, or from the MPA Web site. The cost of the product if purchased from the company Web site is $11.75 for a 1.65-ounce tube or $21.75 for a 3.3-ounce tube. Shipping costs range from $7.95 for UPS ground to $29.00 for UPS one-day (Medix Pharmaceuticals Americas, Inc., 2004b). If a patient followed the application instructions in the brochure to "gently massage Biafine into the irradiated area, three times per day, seven days per week" for protection against reactions (MPA, n.d.), a considerable amount of product could be used, depending on the size of the radiation field and the length of the prescribed radiation therapy course. The amount of product used would be even larger if the patient needed to follow the application instructions for management of moist desquamation: "Apply a thick layer (1/4" to 1/2" thick) of Biafine to moistened gauze or any other type of occlusive dressing large enough to cover the entire open wound/moist desquamation area" (MPA, n.d.). If the patient is without prescription drug coverage, the cost of therapy with Biafine may prove to be prohibitive.

Radiation dermatitis is a challenging problem and one of great concern to patients and clinicians alike. No published clinical trials have demonstrated that Biafine can prevent or delay the time to radiation dermatitis. Weak evidence suggests that Biafine can diminish the toxicity of skin reactions in patients undergoing concomitant chemoradiotherapy. Statistically significant evidence in a small and specific population has demonstrated that Biafine can reduce the severity of radiation dermatitis in large-breasted women at six weeks after completion of radiation therapy. Biafine is a costly product that is available only by prescription or purchase from prescribing clinicians. Based on present reported evidence, the cost of therapy with Biafine outweighs the possible benefits of therapy in the majority of patients undergoing radiation therapy. If further research demonstrates true efficacy and benefit of Biafine therapy in patients at risk for radiation dermatitis, its use certainly should be reevaluated.

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References

Boisnic, S., Branchet-Gumila, M.C., Nizri, D., & Ben Slama, L. (2003). Histochemical and biochemical modifications induced by experimental irradiation of human skin maintained in survival conditions and modulation by application of an emulsion containing trolamine. *International Journal of Tissue Reactivity, 25*(1), 9–18.

Callahan, K. (2003). Breast cancer and radiation treatments research studies and resultant observations of a registered radiation therapist. *X-Ray News, 9*(4), 4–14.

Fenig, E., Brenner, B., Katz, A., Sulkes, J., Lapidot, M., Schacter, J., et al. (2001). Topical Biafine and lipiderm for the prevention of radiation dermatitis: A randomized prospective trial. *Oncology Reports, 8,* 305–309.

Fisher, J., Scott, C., Stevens, R., Marconi, B., Champion, L., Freedman, G., et al. (2000). Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. *International Journal of Radiation Oncology, Biology, Physics, 48,* 1307–1310.

Medix Pharmaceuticals Americas, Inc. (2004a). Clinicals. Retrieved June 8, 2004, from http://www.biafine.com/clinicals.html

Medix Pharmaceuticals Americas, Inc. (2004b). Orders. Retrieved June 8, 2004, from http://www.biafine.com/orders.html

Medix Pharmaceuticals Americas, Inc. (n.d.). How Biafine® RE works. Retrieved August 9, 2004, from http://www.biafine.com/brochures/biafine_re_works.pdf

Pommier, P., Gomez, F., Sunyach, M.P, D'Hombres, C., & Montbarbon, X. (2004). Phase III randomized trial of calendula officinalis compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. *Journal of Clinical Oncology, 22*(8), 1447–1453.

Rutledge, D., Cope, D., Haas, M., Hinds, P., Moore, K., Van Gerpen, R., et al. (2004). Critique. *Oncology Nursing Society Evidence Based Practice Resource Center.* Retrieved June 14, 2004, from http://onsopcontent.ons.org/toolkits/ebp/process_model/critique/critique.htm

Szumacher, E., Wighton, A., Fransses, E., Chow, E., Tsao, M., Ackerman, I., et al. (2001). Phase II study assessing the effectiveness of Biafine cream as a prophylactic agent for radiation-induced acute skin toxicity to the breast in women undergoing radiotherapy with concomitant CMF chemotherapy. *International Journal of Radiation Oncology, Biology, Physics, 51,* 81–86.

Wickline, M.M. (2004). Prevention and treatment of acute radiation dermatitis: A literature review. *Oncology Nursing Forum, 31,* 237–244.

Advanced Nursing Certification to Become Role Specific

In April, the Oncology Nursing Certification Corporation (ONCC) Board of Directors approved significant changes to advanced certification in oncology nursing. Beginning in January 2005, ONCC will offer role-specific advanced practice certification examinations: the AOCNP (nurse practitioner) and AOCNS (clinical nurse specialist). The AOCN® examination will be administered for the last time in October 2004.

In considering the recommendations of the AOCN® Task Force, the board carefully weighed several factors before deciding to make changes, the most important of which

were the results of the role delineation study of advanced practice nursing, which was completed in 2003. The study revealed that although oncology nurse practitioners and oncology clinical nurse specialists share a common knowledge base, discernible differences exist in their work responsibilities.

The decisions regarding eligibility criteria for the new advanced examinations were made carefully to ensure that the criteria are rigorous enough to be meaningful yet attainable by most oncology advanced practice nurses. The eligibility criteria for the AOCNP examination are as follows.

- Current, active, unrestricted RN license at the time of application and examination
- Master's or higher degree in nursing from an accredited institution
- Successful completion of an accredited nurse practitioner program
- Minimum of 500 hours of supervised clinical practice as an oncology nurse practitioner. These hours may be obtained in the nurse practitioner program or after graduation from the program.

The eligibility criteria for the AOCNS examination are as follows.

- Current, active, unrestricted RN license at the time of application and examination
- Master's or higher degree in nursing from an accredited institution
- Minimum of 500 hours of supervised practice in an advanced practice role in oncology nursing. These hours may be obtained in the graduate educational program or after graduation from the program.

A faculty member, preceptor, physician, or supervisor must verify the hours of supervised practice.

Nurses who currently are AOCN® certified may renew their credential through the Oncology Nursing Certification Points Renewal Option for as long as they desire to keep the AOCN® credential. Testing will not be an option for renewal of AOCN® certification after 2004. ONCC will work to ensure that employers and other stakeholders understand that the AOCN® credential still is valid, because it was the highest certification in oncology when some advanced practice nurses obtained it.

AOCN® certified nurses who wish to obtain one of the new credentials must meet the eligibility criteria and pass the examination. Those who hold AOCN® certification cannot be "grandfathered" into one of the new credentials because the eligibility criteria and content of the new examinations will differ significantly from the current AOCN® examination. The standards set by certification-accrediting agencies indicate that granting a credential in the absence of evaluating the knowledge and/or skills of an individual is not acceptable. Part of the purpose of certification is to inform the public of the particular specialized experience and knowledge of individuals who hold the credential. Certifying organizations must ensure that individuals have the experience required and that they have demonstrated the knowledge through an objective assessment before granting the credential.

The board did, however, approve a fee discount for all candidates who take the AOCNS or AOCNP examination during the first two computer-based testing administrations in January or April 2005.

Many state boards of nursing require advanced practice nursing certification for the regulation of advanced practice nurses. ONCC is in the process of communicating with all state boards regarding the changes to advanced practice nursing certification in oncology. All advanced practice nurses must understand fully the requirements of their individual state boards of nursing and comply with those requirements. ONCC maintains a list of state boards that recognize the AOCN® certification on the ONCC Web site (www.oncc.org) and will develop a similar list for the new credentials. ONCC also will seek recognition of the new credentials by the Centers for Medicare and Medicaid Services, which currently recognizes the AOCN® credential.

For more information, read the brochure *Options in Advanced Oncology Nursing Certification* at www.oncc.org, or contact ONCC at oncc@ons.org or 877-769-ONCC.

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