Characterization and Management of Dermatologic Adverse Events With the NovoTTF-100A System, a Novel Anti-mitotic Electric Field Device for the Treatment of Recurrent Glioblastoma

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The NovoTTF-100A System (NovoTTF™ Therapy, Novocure Inc.) is a device that delivers alternating electric fields (TTFields) to tumor cells and interferes with mitosis. It is approved for use as monotherapy for the treatment of recurrent glioblastoma (rGB). TTFields are delivered through insulated transducer arrays applied onto the shaved scalp and connected to a battery-operated field generator. The occurrence of dermatologic adverse events (dAEs) is primarily due to the continuous contact between the array-related components and the scalp for periods of 3–4 days (together with other risk factors). These dAEs may include allergic and irritant dermatitis, mechanical lesions, ulcers, and skin infection. The incidence of dAEs in the phase III trial (n = 116) was 16% (2% grade 2, 0% grade 3/4); the post-marketing surveillance program (n = 570) revealed 156 (21.8%) dAEs with some patients reporting more than one event. Prophylactic strategies for dAEs include proper shaving and cleansing of the scalp and array relocation. Treatment-based strategies are AE-specific and include topical or oral antibiotics, topical corticosteroids, and isolation of affected skin areas from adhesives and pressure. The addition of skin care strategies to the NovoTTF-100A System use will maximize adherence to therapy while maintaining quality of life, all of which contribute to the therapeutic benefit of NovoTTF Therapy in rGB.
Semin Oncol 41:S1-S14

INTRODUCTION AND BACKGROUND

Glioblastoma

Malignant gliomas are a group of primary brain tumors that are heterogeneous, highly invasive, and aggressive.[1,2] Glioblastoma (GB) is classified by the World Health Organization as a grade IV tumor with a median survival of only 15 months and a 5-year survival rate of less than 10%.[3–6] Despite advances in imaging techniques and multimodal treatment approaches, the overall prognosis of patients with GB is still poor.[7] In patients with

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Conflicts of Interest: Mario E. Lacouture, MD, has been a consultant for Novocure. Mary Elizabeth Davis, RN, MSN, AOCNS, has served on an advisory board for Novocure. Grace Elzinga, RN, has no disclosures to declare. Nicholas Butowski, MD, has served on an advisory board for Novocure. David Tran, MD, PhD, has been a member of a speakers bureau and has served on an advisory board for Novocure. John L. Villano, MD, PhD, has been a member of a speakers bureau and has served on an advisory board for Novocure. Eric T. Wong, MD, FANA, has received a research grant from Novocure. Lucianna DiMeglio, MSN, ANP-BC, AOCN, is a Novocure employee. Angela M. Davies, MD, FRCPC, is a Novocure employee.

The NovoTTF-100A System is approved for the treatment of patients with recurrent GBM. Please refer to the Instructions for Use (IFU) for full prescribing information. Novocure provided financial support to Elsevier with respect to this supplement.

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0093-7754/ - see front matter

http://dx.doi.org/10.1053/j.seminoncol.2014.03.011

recurrent glioblastoma (rGB), response rates to systemic therapies are typically less than 10%, and the progression-free survival (PFS) at 6 and 12 months are 15% and 6%, respectively.[8] The median overall survival (OS) of these patients with salvage chemotherapy is 5.8 months with a 1-year survival rate of just 21%.[8] rGB patients who are surgical candidates have a median OS of only 4.6 months if left untreated.[9] Furthermore, although treatment with the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, results in a high radiographic response rate and prolonged PFS, there are no randomized data that demonstrate an increase in OS.[10,11] In fact, recent data have shown that in newly diagnosed GB patients, bevacizumab does not increase OS. Thus, there is a clear need for new and innovative approaches for the treatment of rGB.

The NovoTTF-100A System

The NovoTTF-100A System (Novocure Inc., Portsmouth, NH) is a novel anti-mitotic device that delivers alternating electric fields (tumor-treating fields, TTFields), and is approved by the US Food and Drug Administration (FDA) and has a European Conformity (CE) mark in Europe for use as monotherapy for the treatment of rGB.[12] The basis of the approvals was a phase III study (EF-11) comparing NovoTTF Therapy to active standard chemotherapy in rGB patients.[13] The NovoTTF-100A System has been commercially available by prescription since 2011 in the United States.

The NovoTTF-100A System consists of four transducer arrays, a connector cable, a field-generating device, and a power source (battery or electrical outlet). Treatment parameters are preset (200 kHz and a minimal field intensity of 0.7 V/cm in the brain); thus, there are no electrical adjustments made by the patient or healthcare provider. TTFields are delivered through non-invasive insulated transducer arrays that are applied to the shaved scalp (Figure 1). The location of the arrays on the scalp is calculated using a simulation software (NovoTAL™, Novocure Inc.) that optimizes the field intensity within a patient's tumor based on head size and tumor location.

Transducer arrays are supplied to patients in individual sterile packages to minimize the risk of infection, although the application of the arrays to the scalp is not a sterile procedure. The arrays are composed of insulated ceramic discs (nine per array). The ceramic discs (with a high dielectric constant) are biocompatible and are soldered to a flexible circuit board (Figure 2). The ceramic discs do not come into direct contact with the skin as they are separated from the skin by a layer of conductive hydrogel (similar to that found on electrocardiogram pads). There is no direct electron transfer to the skin; ion concentration changes in cells do not occur, nor does electrolysis.[14] The ceramic discs, hydrogel, and circuitry are all attached to a hypoallergenic medical adhesive bandage to keep the arrays in place on the scalp and in continuous direct contact with the skin. A single plastic-coated wire

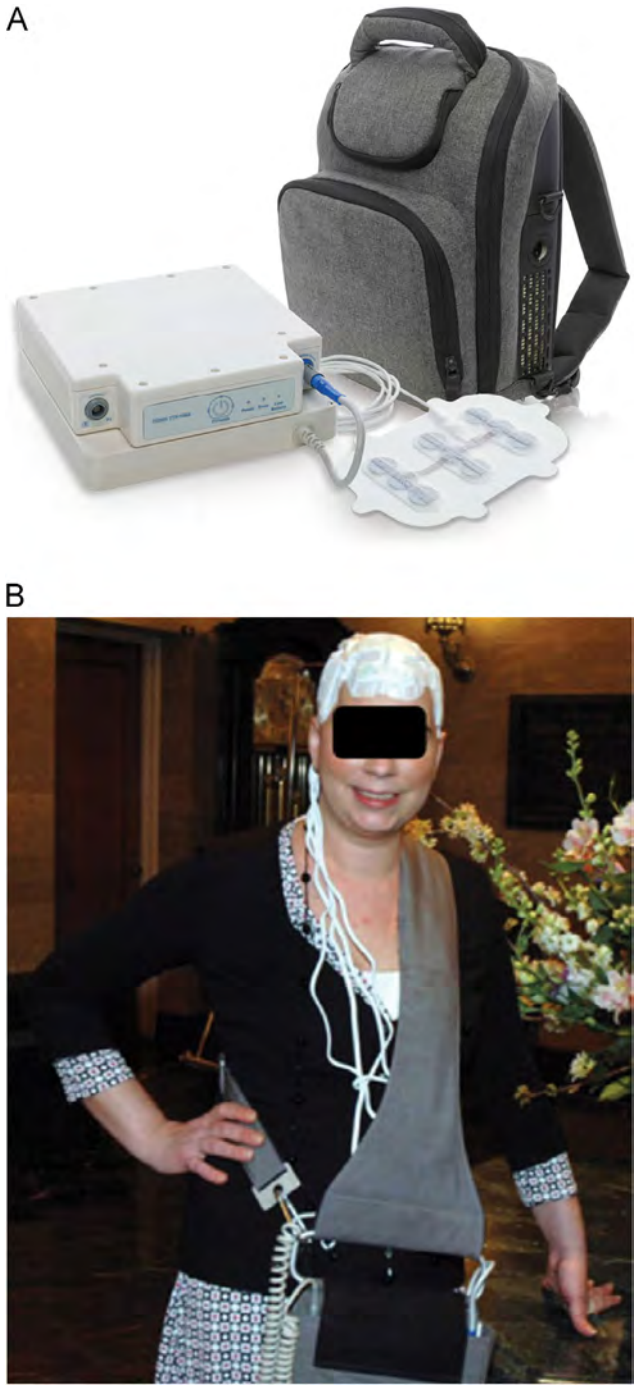

Figure 1. The NovoTTF-100A System. (A) NovoTTF-100A System with battery-operated field-generating device, connected transducer array (patient wears 4 arrays), and included backpack for portability. (B) The NovoTTF-100A System as worn during therapy.

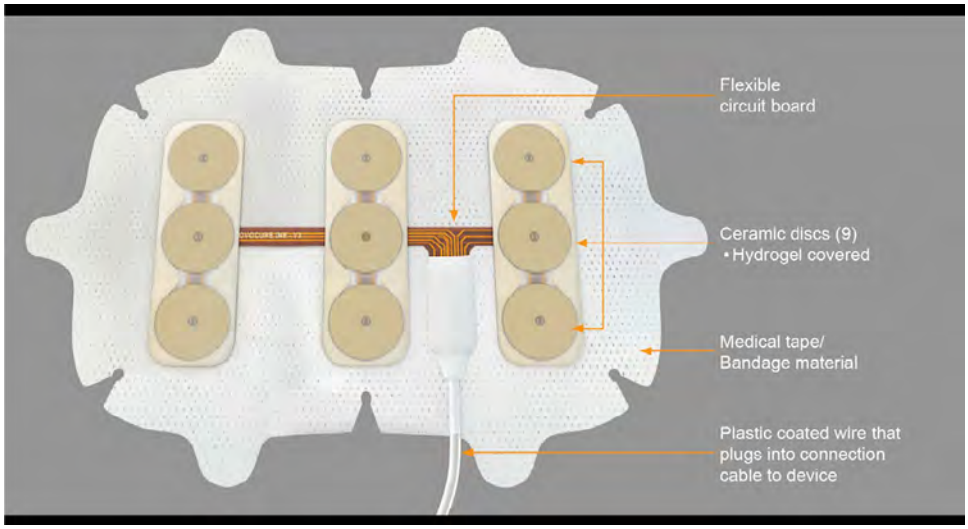

Figure 2. The NovoTTF-100A System Transducer Array.

from each array then plugs into the connection cable, which is attached to the field-generating portion of the device. Although patients have described a "warm sensation" during normal operation of the device, each array has eight temperature sensors (thermistors) that continuously monitor temperature. If the array temperature exceeds 41°C (105.8°F), which is below the threshold for a thermal skin burn,[15] the device will shut off and sound an alarm. The NovoTTF-100A System meets all FDA medical electrical equipment and biocompatibility standards.[16]

NovoTTF-100A Therapy is administered by affixing two pairs of orthogonally positioned transducer arrays to the shaved scalp. Adequate shaving of the scalp is required for optimum array-to-skin contact. The arrays are worn continuously for 3–4 days before removal for hygienic care of the scalp, re-shaving of hair, and reapplication with new sets of arrays.

Mechanism of Action of the NovoTTF-100A System

While electric fields (at differing frequencies and intensities) have been used in medicine for many decades, it is only within the past decade that the biological effect of alternating electric fields at intermediate frequencies (100–300 kHz), and low intensity (1–3 V/cm), has been realized. Evaluation of these intermediate-frequency, alternating electric fields in multiple cancer cell lines has demonstrated an antimitotic effect that is both frequency-specific and intensity-specific in cancer cells, with no effect on non-mitotically active cells.[14,17] TTFields interfere with cancer cell division during three phases of mitosis: (1) metaphase, with inhibition of microtubule spindle assembly; (2) anaphase, with cytoplasmic blebbing and asymmetric chromosomal segregation; and (3) telophase, with a dielectrophoretic effect, resulting in an inability of the organelles and macromolecules to segregate within the daughter cells due to the formation of a nonuniform field gradient.[18–21] TTFields do not cause cell membrane depolarization and thus do not stimulate nerves or muscles, nor do they cause thermal heating of tissues.[22] The current FDA-approved frequency and intensity settings for the NovoTTF-100A System are optimized for the treatment of rGB.

Pivotal Phase III Study (EF-11)

A phase III randomized trial (EF-11) was conducted based on encouraging evidence of TTFields activity in glioma animal models and subsequent pilot data in patients with newly diagnosed and recurrent glioblastoma demonstrating safety, feasibility, and promising efficacy.[13,14] This trial compared NovoTTF Therapy to active chemotherapy (based on physicians choice) in patients with rGB.[13] Patient characteristics were well balanced between the treatment arms of the trial, median age was 54 years, 19% of patients had previously been treated with bevacizumab, and 90% were at their second or later recurrence. Patients were randomized to NovoTTF Therapy alone (n = 120) or chemotherapy (n = 117), with patients in the active chemotherapy treatment arm receiving either a single agent or a combination containing bevacizumab (31%), irinotecan (31%), nitrosoureas (25%), carboplatin (13%), temozolomide (11%), or other agents (5%).

The primary endpoint of the trial was OS. NovoTTF Therapy demonstrated comparable OS to active chemotherapy, with a median OS of 6.6 versus 6.0 months, respectively (hazard ratio = 0.86 [95% confidence interval [CI], 0.66–1.12]; $P = .27$). The PFS6 (PFS rate at 6 months) was 21.4% versus 15.1%

(hazard ratio 0.81 [95% CI, 0.60-1.09]; $P = .13$), and the overall response rate was 14.0% versus 9.6% ($P = 0.19$) for NovoTTF Therapy compared to active chemotherapy, respectively. The safety analyses favored NovoTTF Therapy, with severe adverse events occurring in 6% and 16% ($P = .022$) of patients treated with NovoTTF Therapy and active chemotherapy, respectively.[13]

In the phase III trial, the median adherence to NovoTTF Therapy was 86% (range, 41%–98%) of the time (n = 116), measured by a log file in the device that records time on therapy. This translated into a mean use of 20.6 hours per day. In the NovoTTF Therapy group, 93 (78%) patients completed 4 weeks of therapy (one cycle), with 27 (23%) discontinuing treatment within cycle 1, due to non-adherence or inability to handle the device.[13] Adherence with NovoTTF Therapy was the main predictor of improved OS in this trial, with patients who used the device for more than 18 hours a day living significantly longer than those who used it for less than 18 hours a day (7.8 months *v* 4.5 months, $P < .05$, respectively).[12] The most common device-related adverse events were grade 1 and 2 dermatologic adverse events (dAEs) of the scalp beneath the arrays, occurring in 18 patients or 16% (all grades; 2% grade 2) and no grade 3 or 4 dAEs. Skin ulceration was observed in one patient (<1%). All dAEs were reversible and did not result in discontinuation of patients from study. Other device-related AEs included headache (3%), malaise (2%), muscle twitching (1%), and fall (1%). Systemic toxicities including grade 3/4 hematologic (17%), gastrointestinal (17%), and infections (8% of patients) were significantly more frequent in chemotherapy-treated patients, compared to 3%, 4%, and 4%, respectively, for patients receiving NovoTTF Therapy ($P < .05$; Fisher exact test).[13]

Quality-of-life was analyzed in patients who remained on therapy for >3 months and for whom quality-of-life data were available (n = 63, 27%). Whereas no differences in global health and social functioning between NovoTTF Therapy and active chemotherapy were observed, cognitive, social, role, and emotional functioning were all higher in the NovoTTF Therapy-treated group, while their physical functioning was slightly worse when compared to the chemotherapy treatment group. Symptoms that were reported by patients to be more severe with chemotherapy than with NovoTTF Therapy included appetite loss, diarrhea, constipation, nausea/vomiting, pain, and fatigue.[13]

Because the dAEs observed with NovoTTF Therapy are unique to this novel oncologic treatment modality, and treatment continuity is critical for better response to therapy, there is a need for improved nomenclature, preventive and management strategies, and the identification of risk factors. In addition, the current Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading criteria for the skin and subcutaneous tissue disorders; injury, poisoning and procedural complications; and infections and infestations system organ classes do not adequately describe or characterize the dAEs seen with NovoTTF Therapy.[23–25] Efforts to improve the nosology will help communication between healthcare providers and will also improve the description and grading of these dAEs in current and future clinical trials. Similarly, the development of management strategies for dAEs will help maintain patient quality-of-life and adherence to NovoTTF Therapy.

BASIC PATHOPHYSIOLOGY OF SKIN AND HAIR

In order to understand pathogenic mechanisms underlying dAEs and to develop effective interventions, it is important to recognize that the skin is a complex, mitotically active, multi-layered organ composed of multiple cell types with various functions.[26] Structurally, the skin is composed of three layers: (1) the epidermis, which functions as a permeability and protective barrier and as an organ for immune surveillance; (2) the dermis, which provides the structural support to the skin and contains an extensive lymphatic and neurovascular network; and (3) the hypodermis and the associated subcutaneous fat, both of which provide insulation and contain blood vessels and nerves (Figure 3). All three of these layers function together to form a physical permeability barrier that protects the body from pathogenic microbes and ultraviolet radiation, regulates temperature, allows for the transduction of sensations, repairs wounds, and contributes to an individual's physical appearance and sense of self.[27] Although the epidermis and its outer stratum corneum provide the initial physical barrier to the environment, the structural integrity of skin as a whole is supported primarily by the dermis and hypodermis.[28]

The epidermis is the outermost layer of the skin. It is the only skin layer in direct contact with the hydrogel covering the ceramic discs and the adhesive tape of the bandage holding the transducer arrays in position. The epidermis is a continually renewing structure that gives rise to appendages such as pilosebaceous units (hair follicles), nails, and sweat glands. Epidermal appendages also provide special protective or sensory functions. The epidermis ranges in thickness from 50 μm to 1.5 mm, as compared with the 1.5- to 4.0-mm thickness of the dermis.[29] More than 80% of cells in the epidermis are keratinocytes.

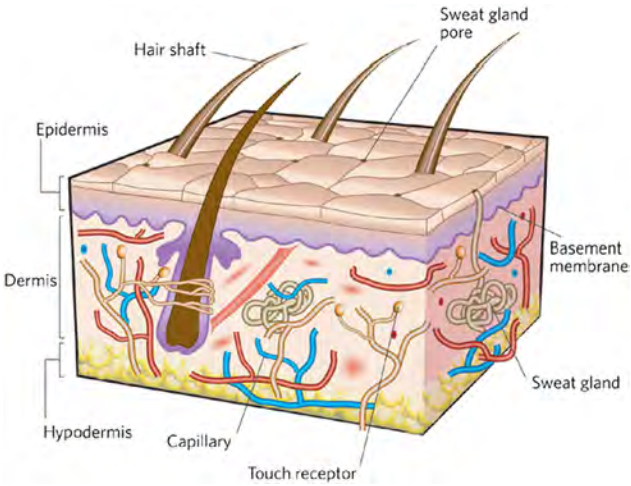

Figure 3. Schematic representation of human skin structure and cell population. The skin comprises three main layers: the epidermis, dermis, and hypodermis. The resident cell populations and various structures present throughout the skin allow for maintenance of an efficient barrier against water loss and protection against threats such as ultraviolet radiation (UVR) and microbial pathogens. The blood and lymph vessels allow for the migration of immune cells in and out of the skin, so that the cell population of the skin is constantly in a state of flux, in response to the demands of the cutaneous inflammatory and immune systems. Reprinted by permission from Macmillan Publishers Ltd: Nature (MacNeil S. Progress and opportunities for tissue-engineered skin. Nature. 2007;445:874-80), copyright 2007.

In humans, the normal doubling time for keratinocytes is 24 hours, and the transit time for a keratinocyte in the basal layer, from the time it loses contact with the basal layer to the time it enters the stratum corneum (outermost layer in the epidermis), is at least 14 days.[30] Transit through the stratum corneum and subsequent desquamation require another 14 days.[30] Intercalated among the keratinocytes at different levels are other cells—melanocytes, Langerhans cells, and Merkel cells. Additional cells, including lymphocytes, are temporary residents of the epidermis and are rare in normal skin. The innate immune system of the skin, which comprises antigen-presenting cells and circulating immune cells, provides additional antimicrobial functions.

Pathologic changes in the skin exposed to NovoTTF Therapy can occur or become exacerbated as a result of a number of different stimuli. These include repetitive mechanical trauma (as in the application and removal of the arrays[31] or shaving[32]) resulting in erosions, inflammation (from the hydrogel covering the ceramic discs or adhesive[33] or moisture from ecrine sweat or ambient humidity[34]), infection (as in bacterial folliculitis or impetigo[35]), wound healing (surgical scars or delayed healing associated with the use of bevacizumab[36,37]), and ultraviolet (UV) radiation damage resulting in atrophy and actinic keratoses.[38]

Erosions are moist, circumscribed, depressed lesions that result from loss of a portion or all of the viable epidermis, with mild bleeding and associated with pain or burning.[39] Erosions may result from trauma related to the repeated removal of the arrays or shaving, inflammation and maceration from sweat-derived moisture, rupture of vesicles or bullae from infection, or epidermal necrosis from altered perfusion due to pressure of the arrays. In general, erosions do not result in a scar unless they become secondarily infected.

Dermatitis is a nonspecific term denoting skin inflammation, presenting with edema and erythema, followed by scaling. With NovoTTF Therapy, two types of dermatitis may develop. The first, representing approximately 20% of new cases of contact dermatitis, is allergic contact dermatitis (ACD), a cutaneous inflammatory reaction caused by contact with a specific exogenous allergen to which a person has been sensitized.[40] The second is irritant contact dermatitis (ICD), a nonspecific inflammation of the skin in response to direct chemical damage to epidermal cells and the release of inflammatory chemokines. These two types of dermatitis have unique clinical and pathophysiological characteristics. In ACD, following contact with an allergen (more than 3,700 chemicals have been identified as culprits of ACD[41]), the skin reacts with inflammation and the severity of the dermatitis can range from mild and temporary to severe and persistent. In the latter case, the dermatitis may not resolve unless treated, even if the offending allergen has been withdrawn. When ACD is suspected, allergen identification through epicutaneous patch testing has been demonstrated to improve quality-of-life,[42] as it allows for identification of the condition and avoidance of the causal allergen. In oncology patients, patch testing may not always be feasible due to the frequency of visits necessary (usually four) and concomitant medications that hinder the interpretation of patch testing (ie, corticosteroids, immunosuppressants). In these cases, a provocative use test (PUT) may identify the culprit in some cases.[43]

In ACD, the symptoms will not resolve unless the offending agent is removed and the area is treated with a topical corticosteroid, while ICD will resolve a few days after the culprit is removed. As noted above, ICD is a nonspecific inflammation of the skin manifested by erythema, edema, pruritus or burning, and scaling as a response to direct chemical damage.[44] Thus, in ICD, removal of the culprit is the only treatment necessary.

A more severe dAE is an ulcer, a lesion in which the epidermis and the dermis have been destroyed. Ulcers are usually round and their borders are well

defined. The base of an ulcer may be clean or necrotic and may contain granulation tissue. A discharge is usually indicative of infection and may be purulent, granular, or malodorous. Surrounding skin may be altered. During healing, the ulcer will form a crust composed of dried serum, blood, or exudate. The color of the crust is important: yellow-brown from a dried serous secretion; yellowish-green from a purulent secretion; and reddish-black from a hemorrhagic secretion. Ulcers may result in scarring.

Infections are common in skin and soft tissues given the abundance of microbes present in these structures.[45] A pustule is a circumscribed, raised lesion in the epidermis containing pus. Pus is composed of leukocytes and cellular debris (yellow color) and may contain bacteria (greenish-yellow color) or be sterile (white color). Pustules may contain a hair at the center, may vary in size, and may coalesce to form plaques of pus. Pustules may be confused with vesicles and bullae, which are fluid-filled lesions that are not always infected. Friction vesicles or bullae with clear contents may occur with shear forces on the epidermis or initially with viral infections, whereas those resulting from bacterial infections or late-stage viral infections will have yellow-greenish contents. In cases of bacterial infections resulting in bullae, the term "bullous impetigo" is used.

Scars arise from fibrous tissue proliferations that replace previously normal skin after a wound or ulceration disrupts the integrity of the skin. Surgical scars may retain a deeper pink or red color for months after a surgical procedure, and hairs are usually absent. The blood flow in scars is altered due to excess fibrous tissue deposition, making them susceptible to dAEs with NovoTTF Therapy use when the ceramic discs are placed immediately over them. Similarly, skin scarring, in the form of atrophy and absence of hair follicles, may develop after radiation therapy and may place these areas at higher risk for dAEs.

The use of NovoTTF Therapy involves placement of the transducer arrays directly onto the scalp for at least 18 hours a day. The arrays are left in place for 3–4 days before they are replaced with new arrays that are relocated on the scalp, the latter practice serves to minimize direct contact over the same areas of skin. Prolonged contact with the arrays poses unique chemical, mechanical, moisture, and thermal-related stresses on skin which may account for the development of dAEs. Consequently, continuous application of the transducer arrays without timely exchanges may cause the development of distinct dAEs on the scalp characterized by inflammation and, in some cases, associated with erosions, ulcers, and secondary infections.

The quality of the array-to-scalp contact is negatively affected by hair growth. The scalp contains approximately 100,000 hair follicles. These hair follicles are part of pilosebaecous units, which contain hair shaft-forming cells, sebaceous glands, and arrector pili muscles. During hair growth, the preceding hair shaft is pushed up and out by a new shaft and results in shedding (normally, approximately 100 strands of hair are shed from the scalp every day).[46] Hair grows approximately 5–12.5 mm every month or 0.2–0.5 mm per day, which results in outward pressure on the adhered transducer arrays and requires repeated shaving at every array replacement (every 3–4 days). This is because an increased distance between the arrays and skin will allow an air gap to form, with air being an insulator for electric fields, and will affect the delivery of TTFields.

CHARACTERIZATION OF DERMATOLOGIC ADVERSE EVENTS

In order to characterize the dAEs, data from patients using NovoTTF Therapy were analyzed with a focus on skin-related AEs (including photographs of the scalp reviewed by a dermatologist) from the completed phase III trial (EF-11) of NovoTTF Therapy (n = 116 patients),[13] as well as from those patients with AEs submitted in the post-marketing surveillance program (n = 570 patients). The ongoing phase IV post-approval study in rGB (EF-19; NCT01756729) has not had sufficient enrollment at present to further define dAEs adequately.

Types of dermatologic adverse events were characterized, and associated patient data (if available) were reviewed, including time to development of dAE, clinical presentation, risk factors, and management strategies employed.

In the phase III trial (EF-11) 16% of patients (18 of 116 patients) had grade 1 or 2 dAEs and there was a 1% incidence of skin ulcer (1 of 116 patients). There were no grade 3 or 4 dAEs. Time to dAE onset was 2–6 weeks. These events were graded according the CTCAE version 3.0. However, this version of the CTCAE did not allow for adequate characterization of the dAEs seen with NovoTTF Therapy. As a result, all dAEs were grouped into the same category.

Although the information available from the post-marketing surveillance program does not allow for detailed grading, 21.8% of patients (156 of 570 patients) had non-serious dAEs, with some patients reporting more than one event. There was a 0.7% incidence of skin ulcer (4 of 570 patients). The median time to dAE onset was 32.5 days (range of 2–520 days). Patients in this setting have reported the need for treatment interruptions or discontinuation of NovoTTF Therapy due to dAEs, but the exact percentage is not known because the post-marketing program is a "self report" program. This latter issue highlights the need for dermatologic management guidelines when NovoTTF Therapy is utilized in

Table 1. Types and Potential Causes of Dermatologic Adverse Events

Adverse Event	Potential Cause
Irritant contact dermatitis	Chemical irritation from hydrogel, moisture, and/or alcohol
Allergic contact dermatitis	Allergy to tape and/or hydrogel
Erosion	Mechanical trauma from shaving and/or array pressure/removal
Ulcer	Decreased perfusion from array pressure (especially in areas overlying scars/ hardware/prior radiation)
Skin infection/ pustules	Secondary bacterial infection

clinical practice outside of the carefully managed setting of a clinical trial.

A review of scalp photographs from patients on the EF-11 trial and from the post-marketing program (when available) by a dermatologist (M.E.L) allowed for the characterization of these dAEs. The clinical presentation of dAEs associated with NovoTTF Therapy can be divided into four major categories: dermatitis (allergic or irritant), erosion, infection, and ulcer (Table 1 and Figures 4–7).

In addition to the above findings, a review of patient data identified the following risk factors that may be associated with NovoTTF Therapy dAEs: (1) placement of ceramic disc(s) from the transducer arrays on the scalp overlying scars or craniotomy hardware; (2) history of contact dermatitis to materials used in the composition of array skin contact materials (ie, tape adhesive or hydrogel); (3) hyperhidrosis (excessive sweating) from hot, humid weather, fever, or occlusive wigs; (4) previous skin exposure to UV or ionizing radiation; (5) high doses or recent change in systemic corticosteroids; or (6) concurrent administration of systemic anticancer agent (eg, chemotherapeutics, biologics, or targeted therapeutics).

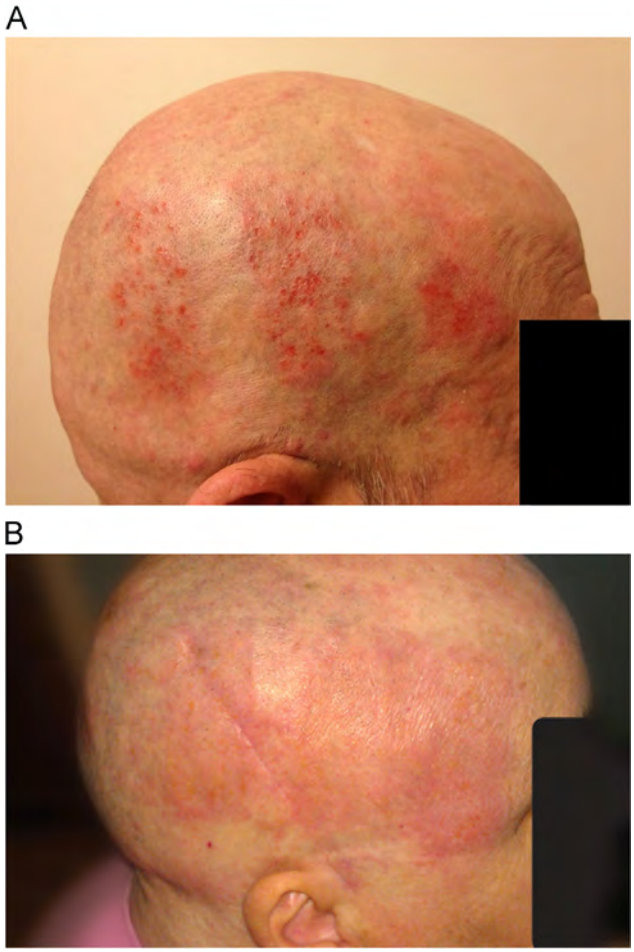

Figure 4. Contact dermatitis (may or may not be symptomatic). (A) Erythema from scalp irritation that was caused by the adhesive tapes or hydrogel. The allergic dermatitis resolved with the application of a topical corticosteroid. (60-year-old man who had been on temozolomide and NovoTTF Therapy for 7 months). (B) Irritant reaction on the right side of scalp with erythema corresponding to the three strips of hydrogel on the transducer arrays. This adverse event occurred during the hottest days in the summer and was a result of a combination of high ambient temperature, increased humidity, excessive sweating, and patient sleeping on the right side of her head. Treatment required 1-2 weeks of device interruption and use of a topical corticosteroid (65-year-old woman who had been on NovoTTF Therapy for 2 months).

MANAGEMENT OF DERMATOLOGIC ADVERSE EVENTS

The management of the dAEs associated with NovoTTF Therapy can be divided into prophylactic and treatment interventions.

Prophylactic Interventions

Based on the clinical trial and post-marketing experience to date with NovoTTF Therapy, prophylactic interventions that decrease the risk of dAEs are divided into five categories: (1) patient and caregiver education, (2) scalp preparation, (3) infection prevention, (4) avoidance of scars and craniotomy hardware, and (5) array relocation. Table 2 provides a summary of these practices for use by the patient or caregiver.

Patient and Caregiver Education

Scalp preparation. This basic step is critical to ensure good array-to-scalp contact, which will lower the risk of skin irritation and optimize delivery of the TTFields. Factors that are known to affect array-to-scalp contact include hair length (determined by proper and

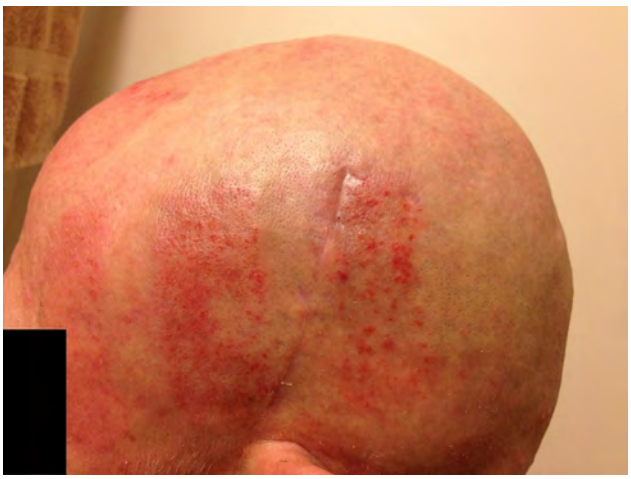

Figure 5. Dermatologic erosions and skin infection (folliculitis) in a 60-year-old man who had been on temozolomide and NovoTTF Therapy for 3 months.

timely shaving), moisture from sweat (determined by eccrine sweating on the scalp), the presence of sebum or the degree of "oiliness" of the scalp (determined by individual patient skin characteristics and removal prior to array placement), and the duration of skin contact with the same set of arrays.

For removing hair from the scalp, an electric razor is recommended because it offers a smaller risk of cuts as compared to a straight blade razor. However, in some patients, the use of an electric razor may actually lead to an increase in folliculitis due to the pulling and tension exerted on the hair while it is being cut. If this is the case, patients may use a straight blade razor while great care is taken to avoid skin cuts. The closeness of the shave can be tested by running a piece of gauze or a cotton ball, wet with 70% isopropyl alcohol, across the shaved scalp. If there is detectable friction or resistance, a closer shave is required.

After shaving, washing the scalp with a mild, fragrance-free shampoo (eg, baby shampoo) will remove some of the sebum of the skin that can interfere with array-to-scalp contact. Dandruff shampoos (which contain pyrithione zinc) also can be used and may offer additional benefit because they have antimicrobial properties. Finally, wiping the skin with 70% isopropyl alcohol will help to remove the naturally occurring scalp sebum, resulting in better contact of the arrays to the scalp. When using alcohol, it is important to avoid contact with areas of dermatitis, erosions, or ulcers, as the alcohol may further irritate the skin.

On subsequent applications of the arrays, use of mineral oil before shaving is recommended because the oil can remove adhesive residues from the prior set of arrays. This will allow for adequate cleansing of the scalp and prevent the accumulation of bacteria and scaly skin.

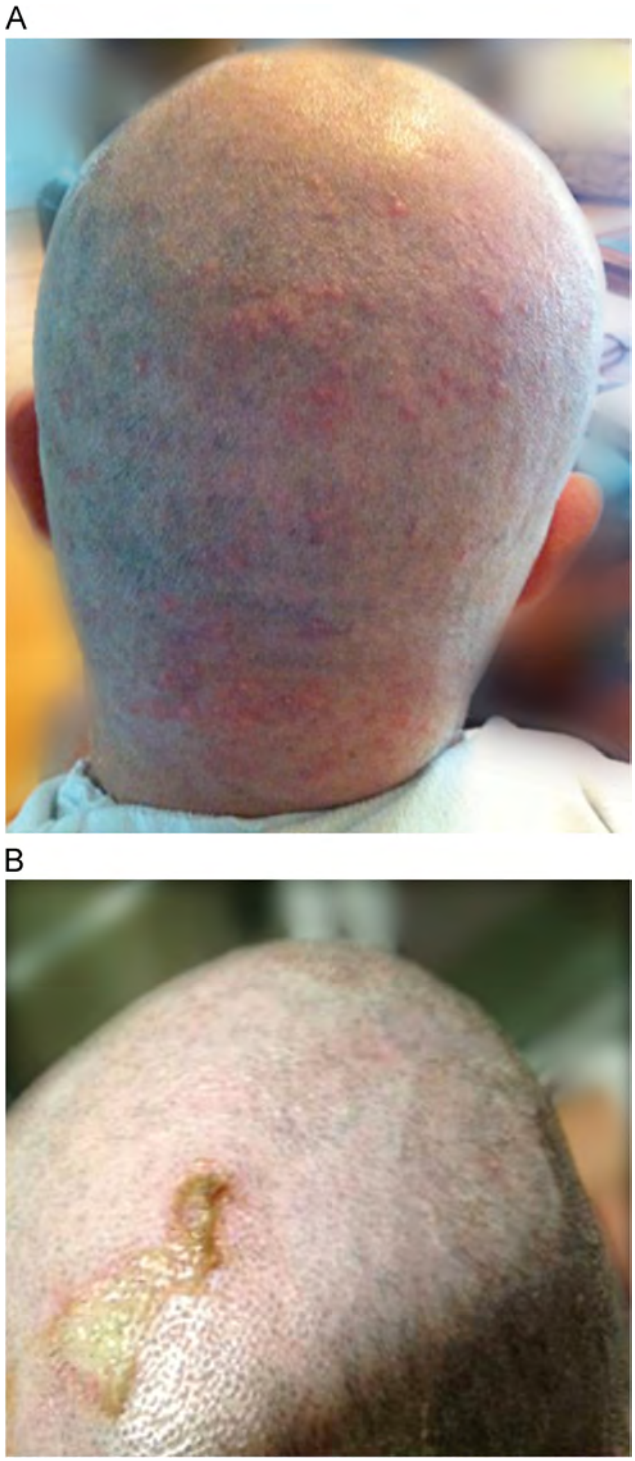

Figure 6. Skin infection/folliculitis. (A) Folliculitis (62-year-old man after receiving NovoTTF Therapy for 4 weeks). (B) Skin infection (41-year-old woman after receiving NovoTTF Therapy for 3.5 weeks).

Infection prevention. The arrays are provided in individual sterile packages to minimize infection risk. Patients and their caregivers are advised to wash their hands prior to application and removal of the transducer arrays. The scalp should be washed with shampoo between array exchanges. The electric

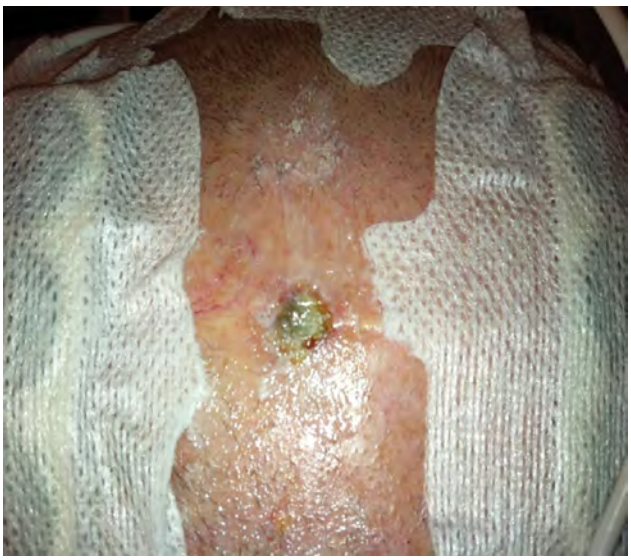

Figure 7. Skin ulceration. Note how the arrays are arranged around the site of the ulcer (61-year-old man after receiving NovoTTF Therapy for 2 weeks).

razor should be cleaned (following manufacturer instructions for cleaning) on a regular basis and should not be shared with others.

Transducer array application. Arrays are placed on the scalp according to the transducer array layout plan, which is based on head size measurements, tumor size, and tumor location. The ceramic discs of the arrays should not be placed directly over implanted craniotomy closure hardware or surgical scars. Placement of the ceramic disc over a screw or plate may lead to subsequent skin breakdown, erosion, or ulceration.

Every time a set of arrays is changed (approximately every 3–4 days) the position of the arrays should be shifted approximately 0.75 inches from the last location, so that the hydrogel layer is between the prior contact sites. The ceramic discs will leave a slight indentation on the surface of the scalp, allowing patients and caregivers to readily see where to position the new set of arrays. On the next transducer array exchange, arrays should be shifted back to the

Table 2. Preventive Strategies for Dermatologic Adverse Events

Category	Guideline for Patient/Caregiver
Shaving and preparation of the scalp	• Proper hand washing prior to preparing the scalp for array application • Take time shaving the scalp using gentle but firm circular motions • Ensure a close shave prior to applying the arrays • Cleaning the electric razor *after* every shave is important to lessen the risk of skin infection • Wash scalp with fragrance-free, mild shampoo (eg, baby shampoo); seborrheic dermatitis shampoo can also be used as it has antibacterial properties (eg, pyrithione zinc 2%, ciclopirox 1%, ketoconazole 2%). • Ensure scalp is completely dry before applying a new set of arrays
Use of isopropyl (70%) alcohol	• Use of first aid antiseptic rubbing alcohol (70% isopropyl alcohol) prior to array application is a necessary step to remove naturally occurring scalp oils, resulting in better adherence of the arrays to the scalp • After shaving and before placing the arrays, wipe the scalp with a gauze or cotton ball soaked in first aid antiseptic rubbing alcohol (70% isopropyl alcohol) • Avoid areas of skin irritation, as the first aid antiseptic rubbing alcohol (70% isopropyl alcohol) may further irritate the skin
Transducer array exchanges	• Change arrays on a regular basis (at least every 3-4 days) • When removing the arrays, avoid “pulling” on the skin and take approximately 60 seconds to remove each array • Using mineral (baby) oil on the edges of the array may make the removal of the adhesive tape easier and less irritating to the skin • To remove leftover array adhesive, use gauze or cotton ball soaked in mineral (baby) oil or pour into hands and gently rub scalp in areas of remaining adhesive • Pay close attention to the scalp at each array exchange and notify the doctor/nurse if there are signs of skin irritation or open areas, in order to receive information on how to treat the affected area(s). Taking a picture of the affected area(s) on the scalp and sharing with doctor/nurse is advised

Figure 8. Preventive measures. Illustration of shifting transducer arrays at each array exchange.

previous position. Shifting the arrays every time they are changed will minimize continuous exposure of the same portion of the scalp to the hydrogel that may lead to subsequent dAEs (Figure 8).

Transducer array removal. Each set of arrays should be exchanged at least every 3–4 days. More frequent array exchanges may be required in some patients. Careful removal of arrays (taking approximately 60 seconds to remove each array) will lessen irritation to the skin. When removing the arrays from the scalp, excessive force should be avoided. In addition, applying mineral oil to the edges of the arrays may make removal easier and less irritating to the skin. The use of mineral oil (applied via a soaked gauze or cotton ball or directly to the scalp by hand) will help to ensure complete removal of array adhesive and minimize damage to the skin. Forceful rubbing of the scalp to remove array adhesive should be avoided.

Examination of the scalp at each array exchange by patients and/or caregivers will allow for identification of asymptomatic dAEs and early intervention after consultation with the health care provider. Taking photographs of the affected area(s) on the scalp to review with the physician or nurse in subsequent office visits, or for more urgent consultation and intervention, is recommended.

Additional considerations. Because the array hydrogel is hydrophilic, it may become partially liquified (glutinous) during warmer weather or after intense physical activity because the hydrogel will absorb sweat. This may necessitate more frequent changes of the arrays (eg, every 1–2 days). Some medications such as corticosteroids (after prolonged use), systemic chemotherapies, and certain targeted therapies (ie, vascular endothelial growth factor [VEGF] inhibitors such as bevacizumab) may increase the risk of skin reaction or affect wound healing. Ongoing clinical trials evaluating NovoTTF Therapy in combination with other systemic therapies will better define the safety of NovoTTF Therapy with concurrent therapies. A recent presentation of data from a cohort of 20 patients treated with combined NovoTTF Therapy and bevacizumab did not suggest any concern regarding adverse events in general and dAEs specifically.[47]

Treatment Interventions—Pharmacologic and Treatment Interruption

The NovoTTF-100A System treatment parameters (frequency and intensity), based on preclinical studies, are preset into the device; therefore, no "dose modifications" can be made for the management of adverse events. Thus, in addition to prophylactic interventions, the primary options for treatment of dAEs are based on the type of dAEs and include topical therapies, relocation of arrays, and avoidance of affected skin whenever possible. Although array shifting to different scalp locations is a recommended prophylactic measure, this can also be used if there are existing sites of dAEs by shifting the arrays around the existing injury sites (Figures 7 and 8). If the area of skin irritation is such that shifting of the arrays is not feasible, the area(s) of skin irritation can be protected with sterile nonadherent dressing pads (Figure 9), while avoiding placement of the ceramic discs directly over these areas. Infrequently, oral antibiotics are required along with treatment interruption for intolerable grade 2 or grade 3 dAEs.

Pharmacologic Treatment

The primary treatments for NovoTTF Therapy-related dAEs are topical corticosteroids and topical antibiotics (Figure 10). If there are signs of dermatitis (Table 1), a topical corticosteroid is recommended. However, when the epidermal barrier is compromised (erosions) or when there are signs of infection (Table 3), topical antibiotics are recommended. Obtaining bacterial skin cultures prior to initiating antibiotic therapy is helpful to identify the causative microorganism(s) and to ensure appropriate antimicrobial coverage.

Topical therapies may be applied only at the time of transducer array exchanges (approximately every

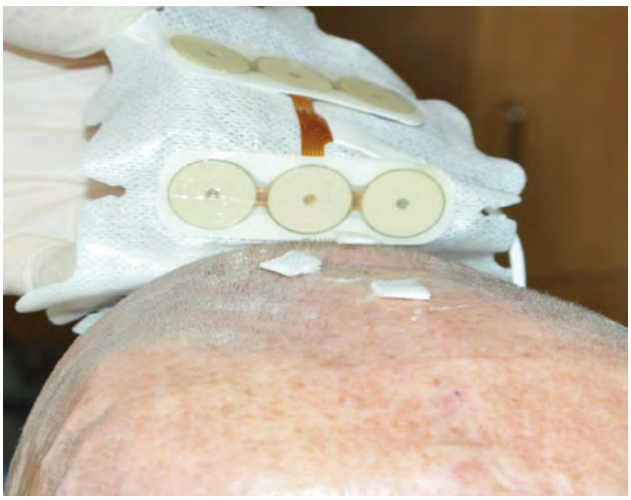

Figure 9. Example of protection of sites of dermatologic adverse events with small sterile nonstick gauze barriers. (Note: gauze should not be directly beneath any of the array ceramic disks.)

3–4 days); therefore, high-potency corticosteroid ointments (eg, clobetasol 0.05%, betamethasone 0.05%) are recommended to maximize skin absorption and pharmacological action. Because creams and ointments contain lipid ingredients, it is important that any topical residue left on the skin be removed with scalp washing or 70% isopropyl alcohol as this residue will interfere with the adherence of the arrays to the scalp and hence may affect transmission of the TTFields. The use of topical or oral antibiotics should be selected based on the spectrum of activity for the skin flora on the scalp (eg, mupirocin or polymyxin B/bacitracin for topical preparations). Use of neomycin-containing topical antibiotics is discouraged because of the relatively high incidence of contact dermatitis in the general population. It is recommended that topical therapies are applied and left on the scalp for a minimum of 15–30 minutes before removing any residual cream/ointment with 70% isopropyl alcohol or re-washing of the scalp and reapplication and relocation of the arrays.

Treatment Interruptions

For intolerable grade 2 and grade 3 dAEs, treatment interruption in conjunction with topical therapies is recommended. It should be noted that reapplication and relocation of the arrays is possible after treatment interruptions due to intolerable grade 2 or grade 3 events. Anecdotal data suggest that interruption for 2–7 days is frequently sufficient for resolution of the dAEs. This is consistent with the turnover rate of cells in the epidermis as described previously. Patients with prior dAEs may be more likely to have a recurrence of

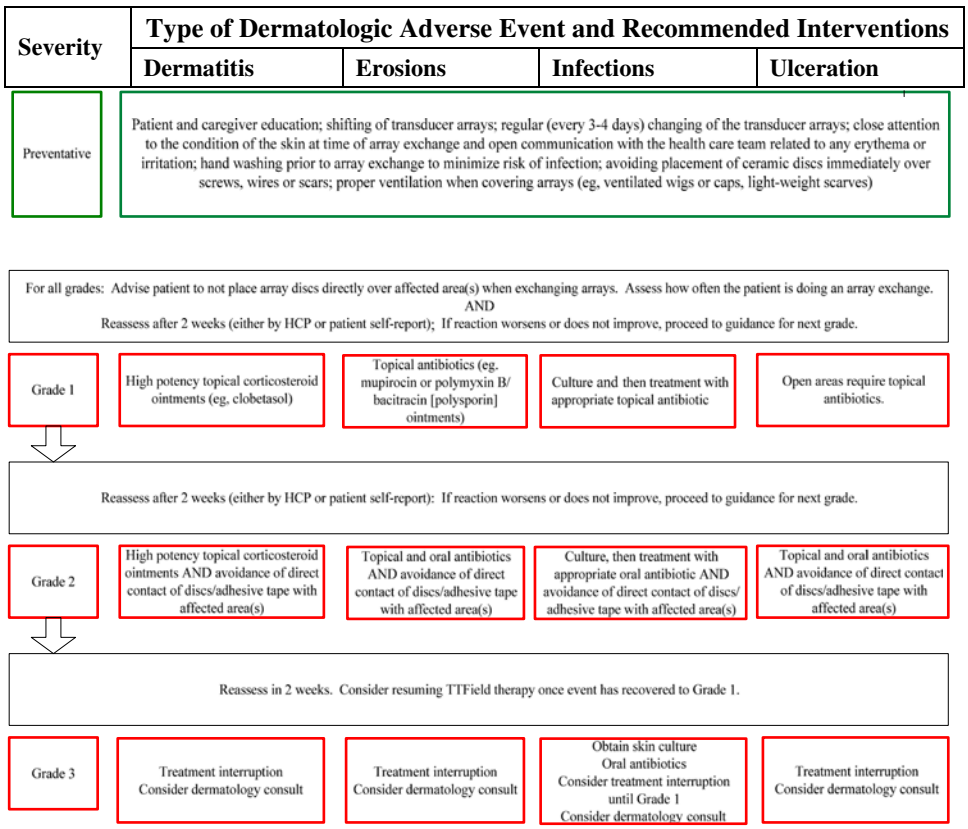

Figure 10. Treatment algorithm for dermatologic adverse events associated with the use of NovoTTF Therapy.

Table 3. Signs of Skin Events Based on Underlying Pathogenesis

Dermatitis	Skin Infection	Mechanical	Ischemia
Erythema	Erythema	Erosions	Ulcers
Scaling	Discharge	Abrasions	Pain
Erosions	Pustules	Lacerations	
Edema	Pain	Pain/burning	
Pruritus	Yellow/green crusting		

dAEs once the arrays are reapplied, so patient education and use of prophylactic measures upon rechallenge are recommended.

Duration of treatment interruptions should be minimized, as treatment adherence is correlated with NovoTTF Therapy efficacy. A post hoc, subset analysis from the phase III trial (EF-11) demonstrated a higher OS in patients that were treated for 75% or more of the time (approximately 18 hours per day on average over the course of a month) compared to those patients treated for less than 75% of the time on average (OS 7.8 months *v* 4.5 months, respectively, $P = .04$).[12]

DISCUSSION AND CONCLUSIONS

NovoTTF Therapy represents a treatment modality for rGB that produces effects on multiple phases of the cell cycle through the use of alternating electric fields (TTFields). It has undergone clinical comparison with systemic chemotherapies in a phase III trial in which NovoTTF Therapy demonstrated a comparable survival benefit, but with improved patient function in cognitive, social, role, and emotional measures, along with decreased systemic adverse events such as anorexia, fatigue, nausea, vomiting.[13] A higher OS was seen in patients that were treated for 75% or more of the time (approximately 18 hours per day on average over the course of a month).[12] Due to its unique mechanism of action and the epicutaneous delivery system with transducer arrays applied on the scalp, dAEs are the most common adverse events seen with this therapy. As with any AE, these dAEs can impact the patients' quality-of-life, adherence to therapy, and medical costs.

A standardized system for clinical description and grading of dAEs related to NovoTTF Therapy is critical in order to ensure proper communication between healthcare providers and to identify appropriate interventions. Characterization of the dAEs observed with NovoTTF Therapy revealed that there are four types of events that differ clinically and that require distinct preventive and active management strategies. These are: (1) irritant contact dermatitis caused by chemical irritation from sweat, hydrogel, and/or alcohol; (2) allergic (immunologic) contact dermatitis resulting from a delayed type hypersensitivity to tape and/or hydrogel; (3) mechanical erosions from cuts induced by shaving and stripping injury from array removal; (4) ulcers from decreased perfusion where the ceramic discs compress the skin, especially over scars or hardware; and (5) skin infections that are bacterial in origin. Taken as a whole, the pathogenic mechanisms underlying dAEs with NovoTTF Therapy are probably related to the occlusive nature of the adhesive tape of the bandages and hydrogel-covered ceramic discs, rather than to the TTFields generated by the device.

Similar dAEs, including allergic and irritant dermatitis, ulcers, and skin infections, have been described with other devices that are directly applied onto skin, such as abdominal appliances for stomas and ileal conduits.[48,49] To date, there are no randomized controlled trials for the prevention or management of dAEs from the use of abdominal appliances, yet there are abundant anecdotal and empirical data. Indeed, more than 30% of colostomy patients and more than 70% of urostomy and ileostomy patients develop dAEs; however, this unusually high incidence is likely related in part to the enzymatic activity produced by bacteria in the urine and stool. Approximately 30% of visits to stoma nurses are related to skin complications, underscoring the importance of dAEs with epicutaneous devices.[50] Consequently, a similar rationale for the treatment of NovoTTF Therapy-related dAEs has been devised here.

Correct identification of AEs will dictate specific therapies towards their treatment and prevention of recurrence. While most dAEs may be managed with topical interventions and relocation of the arrays, preventive strategies are critical in minimizing recurrent and additional dAEs. For bacterial infections, a swab culture along with topical or oral antibiotics are needed. For erosions or abrasions care should be taken to avoid mechanical trauma and to isolate the lesion from further injury. For ulcers, it is important to remove arrays from the site of the ulcer since they may decreases blood perfusion and interfere with proper wound care. Due to the relatively protracted processes of skin proliferation and wound healing, improvement and resolution of dAEs usually takes at least 7–14 days. Thus, at a minimum, interventions to treat dAEs must continue during this time frame. One notable

Table 4. Proposed Grading for Device-Related Dermatologic Adverse Events

Grade	Description*
1	Asymptomatic or mild symptoms; topical therapy indicated (eg, antibiotic, corticosteroid).
2	Moderate symptoms AND topical and systemic therapy indicated (eg, antibiotic, corticosteroid); device application interruption; temporary relocation of device to avoid affected skin areas; or isolation by dressings of affected areas indicated.
3	Severe or medically significant but not immediately life-threatening AND topical and systemic therapy indicated (eg, antibiotic, corticosteroid); operative intervention indicated; hospitalization or prolongation of existing hospitalization indicated; device application interruption indicated.
4	Life-threatening consequences: urgent intervention indicated; device discontinuation indicated.

* A cutaneous device-related dermatologic event is defined as a disorder characterized by dermatitis, skin infection, erosion, or ulcer related to the noninvasive use of a medical device.

exception is the development of ulcerations. Ulcerations involve the dermis and may require surgical intervention and may demand a longer time to heal even with appropriate wound care.

Treatment interventions will depend on the type and the severity of AE. The severity of AEs is defined by the National Cancer Institute's CTCAE. At the time the phase III NovoTTF Therapy trial was conducted, the CTCAE version 3.0 was used to describe dAEs. Current and previous iterations of the CTCAE (versions 3.0 and 4.0) do not adequately capture the clinical characteristics and management of NovoTTF Therapy-induced dAE.[13] A proposed grading system based on the CTCAE has been described here that includes specific terms related to NovoTTF Therapy-related dAEs (Table 4), including the need for device application interruption or relocation, application of dressings over the affected skin, and indications for topical or systemic therapies. This system may allow for more consistent grading in forthcoming trials investigating the efficacy of NovoTTF Therapy, supportive care interventions and daily clinical care.

Most dAEs can be prevented or managed with the skin care recommendations set forth in this manuscript. With the increasing adoption of NovoTTF Therapy for rGB, proper prevention and timely management of dAEs is crucial to maintain patient quality-of-life, to ensure consistent use of the device, and to maximize the clinical benefit of NovoTTF Therapy for patients with rGB.

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