Necrotizing Fasciitis: Low-Dose Radiotherapy as a Potential Adjunct Treatment

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Abstract

Necrotizing fasciitis (NF) is a rapidly spreading bacterial infection causing extensive tissue necrosis and destruction. Despite appropriate therapy, the disease results in significant morbidity/mortality and substantial treatment costs. Several studies published in the early 1900s demonstrated the effective use of low-dose X-ray radiotherapy (RT) for the treatment of many diverse inflammatory conditions and diseases (eg, gas gangrene, sinus infections, arthritis, tendonitis, and serious inflammatory lung conditions). The mechanism by which therapeutic RT doses produce positive patient outcomes is related at least in part to its capacity to induce tissue-based anti-inflammatory responses. This action is due to the polarization of macrophages to an anti-inflammatory or M2 phenotype via optimized low-dose RT. Low-dose RT has the potential to significantly reduce debilitating surgeries and aggressive treatments required for NF, providing a 3-prong benefit in terms of patient mortality, length of hospitalization stays, and cost of health care (both short term and long term). Low cost and easy availability of low-dose RT makes it a potentially useful option for patients of every age-group. In addition, low-dose RT may be a particularly useful option in countries treating many patients who are unable to afford surgeries, antibiotics, and hyperbaric oxygen.

Keywords

low-dose radiotherapy, necrotizing fasciitis, macrophage polarization, hormesis, anti-inflammatory phenotype

Introduction

Necrotizing fasciitis (NF) is a rapidly spreading bacterial infection that may extend from the epidermis to the deep musculature causing extensive tissue necrosis and destruction.[1] Clinical features of NF include severe regional cellulitis with ill-defined margins, soft tissue edema with grayish brown discharge, severe pain, systemic toxicity, skin necrosis with bullae formation (blisters containing serous fluid), crepitus (grating sound), and sloughing of the skin followed by numbness of the involved region due to destruction of nerves in the fascial planes. Once the bacteria are locally seeded, the bacterial toxins spread through skin extremely rapidly. Any failure in early diagnosis and appropriate treatment often results in widespread devastating consequences such as loss of limb or mortality.[2] The bacteria can also result in ischemia of the involved region due to thrombosis of blood vessels which eventually results in gangrene. Limbs are the most common site involved in this life-threatening disease, followed by perineum and trunk.[3]

Epidemiology

True incidence of NF is unknown but has been extrapolated using the incidence for group A streptococcal (GAS) NF which has been studied extensively epidemiologically. Young

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estimated that nearly 7000 to 14,000 cases of all types of NF occur in the United States each year.[4] Although NF can affect all age groups, it is predominant in adult males and with an overall mortality rate of nearly 30% that increases at extremes of age.[5-8]

Although considered to be a rare fatal dermatological condition, it entails a significant mortality rate reported at nearly 4.8 per 1,000,000 person-years.[9] Time is critical in the treatment of NF, as the mortality rate increases from nearly 6% to 30% depending upon the timing of surgery (within 12 hours of the onset of symptoms vs 24 hours).[5-8]

First-line treatment currently available for NF includes rapid surgical debridement and use of broad-spectrum antibiotics. Despite appropriate optimal therapy, the disease carries significant morbidity and mortality risk.[10,11]

History of NF

Although NF has been a known clinical entity for centuries, the term was first used by Wilson[12] in 1952 to describe "fascial necrosis." A fulminant and fatal case of erysipelas has also been documented by Hippocrates.[13] Many different names have been used for NF with physicians in Europe coining terms such as "necrotizing/gangrenous erysipelas," "phagedena gangrenosa," "synergistic necrotizing cellulitis," "nonclostridial gas gangrene," and so on.[14] In the United States, the term "hospital gangrene" was first reported by Jones to describe necrotizing skin infections in 1871.[15] In 1924, Meleney emphasized the need for an early diagnosis and immediate surgical treatment to reduce mortality.[16]

The GAS NF became a known clinical entity when in 1989 Stevens and colleagues described unique clinical characteristics and streptococcal toxic shock syndrome that was often associated with NF.[17] Several outbreaks of the "flesh-eating" disease were reported in mid-1990s by the British tabloid press.[18]

Pathology

Necrotizing fasciitis can progress in 2 ways: (1) penetrant mode, where organisms or the spores get inoculated via a break in the integrity of skin or mucosa, and (2) nonpenetrant mode, where a deep tissue injury in individuals with transient bacteremia leads to an influx of organisms that gain access via deep tissue vessels to the surrounding tissues. In both modes of entrance, microbes once inoculated release exotoxins altering host repair mechanisms leading to leucocyte–platelet aggregation resulting in widespread tissue damage, occlusion of vessels causing tissue necrosis, and exaggerated inflammatory responses.[2] The GAS is the most commonly recognized causative agent for NF. The role of exotoxins released by these organisms had been well explained in the literature; however, the mechanisms that occur at molecular level, especially the role of inflammatory cytokines and macrophages, have been poorly studied. Invasion of these microbes is recognized by the host immune system leading to widespread influx of acute inflammatory cells with an aim to kill these pathogens.[19] A cascade of host immune responses is initiated during which cytokine tumor necrosis factor α (TNF-α) controls the influx of leukocytes such as macrophages and polymorphonuclear neutrophils (PMNs). The role of PMNs has been well recognized in preventing rapid dissemination of infection; however, the role of macrophages in host defense mechanisms remains poorly defined.[8,20-26]

Mishalian et al[20] used murine models to explore the potential role of macrophages in controlling disseminated GAS infections such as NF. The authors showed that a murine model that was systemically deficient in TNF-α was highly susceptible to soft tissue infections with GAS due to impaired macrophage recruitment, while the recruitment of PMNs was not affected. The 2 murine models used in this study were wild-type (WT) and TNF knockout mice (TNF-αKO). After intraperitoneal injection with heat-killed GAS, the number of PMNs found in the peritoneum of both WT and TNF-αKO mice was same; however, the TNF-αKO mice had significantly lower macrophages in the peritoneum. In addition, the authors demonstrated that systemic depletion of macrophages led to substantial increases in bacterial load without interrupting the role of PMNs. A technique of Clo-Lipo treatment on mice systemically depleted the monocytes from the blood and spleen without interfering with the numbers of PMNs. When inoculated with GAS, the monocyte-depleted mice showed larger increases in bacterial load systemically as well as in soft tissues, suggesting that the absence of monocytes can lead to widespread and disseminated infection by GAS.

Macrophages are heterogenous immune cells that play an important role in inflammatory responses at the infection site primarily acting as responders to foreign pathogens. There are 2 main phenotypes of macrophages that have been identified: M1 (pro-inflammatory) and M2 (anti-inflammatory). Various physical, chemical, and pharmacological agents polarize macrophages to M1 and/or M2 phenotypes. The M1 macrophages have antimicrobial and anticancer properties, whereas M2 macrophages have been recognized to have further subtypes M2a, M2b, and M2c with properties that enhance tissue repair, angiogenesis, phagocytosis, and immune cell recruitment.[27]

Cost of Treatment

In their study of 216 patients with NF in Florida, Mulla et al reported that the median total patient charges were US$54,533 and cumulative charges for all 216 patients were nearly US$20 million.[28] A similar study conducted in Melbourne, Australia, on 92 patients with NF reported an estimated inpatient total cost of A$5,935,545 with an average cost per patient of A$64,517.[29] Current costs are likely going to be much higher when inflation over the last 12 to 15 years is taken into account.

The costs associated with long-term care of these patients has not been studied as the focus has always remained on hospital-associated costs. What remains unassessed are costs

associated with posthospital sequelae of NF that include postdischarge physical therapy and rehabilitation of these patients and indirect costs accrued by the community (loss of a productive workforce), which includes number of workdays lost by the patient and family. These indirect costs add a significant societal economic burden.

Low-Dose RT: A Potential Adjunct Alternative

During the first half of the 20th century, tens of thousands of patients with more than a dozen of serious inflammatory and infectious ailments (eg, gas gangrene, bronchial asthma, pneumonia, pertussis, sinus infections, ear infections, tendonitis, bursitis, arthritis, carbuncles, and so on)[30-38] were successfully and safely treated with low doses of ionizing radiation. Radiotherapy was reported to be frequently effective after only a single treatment, with a rapid (within 24 hours) and often long-lasting (from months to years) relief from symptoms.[39]

According to the historical evaluation by Calabrese and Dhawan,[31] X-ray treatment of gas gangrene (a variant of NF) was a well-established practice in the United States during the 1930s to the early 1940s. In 1940, the use of X-rays for prophylactic and therapeutic approaches in the treatment of patients with gas gangrene was effectively used by the US Army medical staff at Fort Sam. In 1940, Bowen mentioned that the "successful use of x-ray therapy in gas gangrene suggests to the military surgeon that possibility of such therapy in war casualties . . . Mobile x-ray therapy should be part of the Medical Department's armamentarium in any fatal campaign."[40(p111)]

According to Cantril and Buschke,[41(p345)]

> The civilian surgeon, faced with a single case of traumatic gas bacillus infection, or the military surgeon with a ward full of its victims, is confronted by a menace to the life and future welfare of his patients. Well directed roentgen therapy has proved its efficacy in saving both lives and limbs. The thoughtful and diligent combination of surgery and x-ray therapy can produce results not heretofore obtained by any approach to this most severe complication of traumatic wounds.

Similarly, Kelly[42(p43)] stated that:

> If one may be permitted to draw conclusions from such a small series of cases, it seems to be definitely certain that x-ray treatment is indicated in gas gangrene, both in extremity and in trunk cases; that the treatment should be started as soon as the disease is suspected and be given throughout its course, twice each day for at least three days.

Calabrese and Dhawan[31] provide extensive historical documentation and evaluation of research in 1930s to 1940s illustrating how low-dose X-ray was employed to treat patients with gas gangrene.

Proposed Mechanism of Action for Low-Dose RT in the Treatment of NF

A recent study has elaborated on a possible mechanism of action for the beneficial effects by low-dose radiation. Calabrese et al have investigated various stimuli that display activation of macrophages via biphasic hormetic dose responses.[27] Considerable research has demonstrated the role of low-dose ionizing X-rays in enhancing immune response and treating various inflammatory conditions.[30-38] Genard et al[43] used a range of mammalian models and cell types to demonstrate that low-dose ionizing radiation polarizes macrophages toward anti-inflammatory (M2 phenotype) macrophages, while higher doses polarizes macrophages toward the pro-inflammatory phenotype (M1). The study also suggested a triphasic dose response where a low dose of roughly <1.0 Gy induced the M2 phenotype, a moderately higher dose induced the M1 phenotype, while a dose of >5 Gy directed the macrophages back toward the M2 phenotype. In contrast to these animal model studies, historical assessment of several human inflammatory conditions and/or infectious diseases have shown successful treatment with RT doses between 1 and 6 Gy, indicative of M2 polarization at radiation doses of >1 Gy. On the other hand, successful use of RT for the treatment of leukemia/lymphoma at doses <1 Gy is indicative of M1 polarization.[27] Low-dose RT induces an anti-inflammatory phenotype by affecting various pathways: decreasing inducible nitric oxide synthetase and TNF-α, increasing TNF-β, activation of several transcription factors such as nuclear factor KB and activating protein-1, as well as decreasing adhesion of leukocytes and PMNs to endothelial cells, decreasing reactive oxygen species, and increasing heme oxygenase.[43-45]

Optimal Dose of Low-Dose RT

Calabrese et al[39] have recently proposed a dose range of optimal human therapeutic effectiveness for RT across a spectrum of clinical conditions studied over several decades. Ionizing radiation can be effective over a broad dosage range, generally extending from as low as 20 roentgen (r) (eg, approximate upper limit of common single computed tomography scans) to 200 r (about 2 Gy), approximately a 10-fold range. This supports a dose range that could encompass both M1 and M2 phenotypes. In this situation, the RT might be effective either by enhancing the destruction of the microbe or by enhancing repair, depending on the dose. There was a possibility that the efficacy of treatment may be enhanced even further at lower doses.

Long-Term Cancer Risk With Low-Dose RT

In a 2006 publication, Trott and Kampard[46] stated that the methodology used by International Commission of Radiation Protection to estimate the risk of cancer from low-dose radiation exposure (occupational or environmental) to the general population cannot be accurately extrapolated for estimating the

risk of cancer by the use of RT for malignant or nonmalignant diseases. This was based on results indicating that the types of cancers caused by low-dose total body irradiation as reported for Japanese Atomic bomb survivors are different. The researchers stated that cancer risks due to the RT of benign (noncancerous) diseases therefore should be based on data from epidemiological studies of patients who have received RT for such benign/nonmalignant diseases. The authors additionally reported that the linear nonthreshold (LNT) model may overestimate the true cancer risks by one order of magnitude and thus claimed that RT-induced tumors do not follow the LNT model as used in radiation protection risk assessment.

Similarly, Sautter-Bihl et al[47] evaluated cancer risk based on LNT approach when RT was used for the treatment of inflammatory joint conditions. The whole-body dose was determined using a standard whole-body conversion formula based on the assumption that exposure was 6×1 Gy dose for joint treatments. They adjusted for multiple factors, including differential distances to the irradiated areas. Based on their results and using the LNT approach, the authors estimated an additional 20 to 40 malignancies per million people over a lifetime. Since the average age of patients was 54 years, the authors argued that based on the expected long latency of tumor development, the risks of inducing cancer when using the conservative LNT approach were not of any practical relevance. The findings of Sautter-Bihl et al[47] were generally supported by Tubiana et al[48] who found no enhanced carcinoma and sarcoma cancer risk in patients receiving RT at doses <5 Gy, with an apparent hormetic effect for both carcinoma and sarcoma below 0.5 Gy.

Several long-term studies[49-56] were conducted on patients irradiated with nasopharyngeal radium to treat ear dysfunctions and inflamed adenoids. None of these studies found a definitive link between nasopharyngeal irradiation and any disease, including cancer. Consistent with this perspective, a recent paper by Cuttler[57] also suggested a relatively high threshold (500 mSv) for ionizing radiation-induced leukemia in humans.

Current Use of Low-Dose RT in Humans

A search of clinicaltrial.gov web site with the keyword, "low dose-radiation" with and without a filter "actively recruiting," yielded 36 and 140 human clinical trials, respectively, reflecting the growing interest in the possible clinical utility of this treatment modality. Several case studies and phase 1 clinical trials are currently exploring the use of low-dose RT for the treatment of degenerative neurological diseases with major inflammatory aspects such as Alzheimer and Parkinson disease.[58-63]

Other studies have found positive outcomes with the use of low-dose RT for the treatment of indolent non-Hodgkin lymphoma,[64,65] cutaneous B-cell and T-cell lymphomas,[66-68] marginal zone lymphoma,[69-71] prostate cancer, ulcerative colitis, diabetes, rheumatoid arthritis, and so on.[72,73] In Germany, low-dose RT is currently used for the treatment of a host of benign, nonmalignant diseases.[74,75]

Conclusions

- Despite current medical advances, the fatality rates for NF have remained high.
- Several past studies on the use of low-dose RT to treat various inflammatory and infectious diseases, especially gas gangrene, validated the potential beneficial effects of low-dose RT with a rapidly favorable response.
- Treatment of NF involves a multidisciplinary approach, and thus, we recommend evaluation of low-dose RT as an adjunct therapy for the treatment of suspected cases of NF.

Authors' Note

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