Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome): Updated Review of Minimally Invasive Treatments

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An updated review of management of nevoid basal cell carcinoma syndrome (NBCCS) is presented. An ideal treatment of NBCCS does not exist, and surgical intervention has been the most commonly used treatment, as it provides excellent cure rates. However, patients with NBCCS typically present with a large number of basal cell carcinomas (BCCs) with repeated occurrence throughout life. Surgical intervention, although efficient, may be too painful and discomforting, especially if it has to be frequently performed. Additionally, depending on the location and extent of the tumor, the risk for cosmetic or functional defects exists. This article investigates and compares current alternative, minimally invasive treatment modalities and their potential benefits and success rates.

Cutis. 2008;81:53-60.

Nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, is a rare autosomal dominant disorder with complete penetrance and variable expressivity affecting multiple systems.[1] The major characteristics of the disorder include multiple nevoid basal cell carcinomas (BCCs), odontogenic keratocysts, palmar and/or plantar pits, skeletal abnormalities, and ectopic calcifications.[1]

Accepted for publication October 10, 2006.
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An ideal treatment for NBCCS does not exist. Traditionally, the treatment has been surgical (ie, curettage, electrodesiccation, wide excision, Mohs micrographic surgery) because the most common findings involve tumors. Studies have been implemented to assess the efficacy of alternative, less invasive treatment modalities for this condition. This article is a review of current English language literature and discusses possible minimally invasive management options.

Cryosurgery

Cryosurgery is widely used to treat solitary and multiple BCCs. Studies report cure rates up to 99%.[2,3] Its advantages include simplicity of use, treatment of multiple lesions in one session, few complications, minimal bleeding, low cost, and good functional and cosmetic outcome.[4,5] However, satisfactory results are more consistently reported with cryotherapy treatment of low-risk, nonaggressive, superficial BCCs—the type commonly seen in patients with NBCCS.[5] In general, cryosurgery should be excluded in cases of high-risk BCCs. To achieve high cure rates, it is important to emphasize the careful selection of appropriate lesions with nonaggressive histology that are away from critical facial sites.[6] However, Buschmann[7] advocates cryosurgery instead of traditional excision for treatment of BCCs and squamous cell carcinomas in the eyelid region. In a clinical trial (N=221), he found that cryosurgery provided a lower-cost option, better preservation of eyelid structures, and better rates of tumor recurrence (5.1% after a single treatment and 0.6% after a second cryosurgery treatment) than traditional surgery in patients followed up for 5 years or longer.[7]

Mallon and Dawber[3] assessed the efficacy of 1 and 2 freeze-thaw cycles and found that a single

freeze-thaw cycle for superficial truncal BCCs resulted in a 95.5% cure rate. When facial BCCs were treated with liquid nitrogen, the cure rates were 79.4% and 95.3% after 1 and 2 freeze-thaw cycles, respectively.[3]

For more aggressive, difficult-to-treat BCCs (because of size, location, or patient condition), 2 separate studies reported high cure rates with cryotherapy following curettage.[8,9]

In addition, cryosurgery may be a safe efficient alternative therapeutic modality for patients who refuse surgery and elderly high-risk surgical patients, such as patients with a pacemaker or coagulopathy.

Retinoids (Topical, Systemic)

Treatment of BCCs with oral isotretinoin and etretinate has been tested with some degree of success. Peck et al[10] reported that high-dose isotretinoin can cause complete clinical and histologic regression in approximately 10% of BCCs. Because of the small percentage of complete therapeutic response and the increased rate of toxicity, high-dose oral isotretinoin (mean daily dosage, 3.1 mg/kg daily) as chemotherapy for patients with NBCCS is not recommended. Lower doses of isotretinoin were ineffective as chemotherapy for existing BCCs but demonstrated varying degrees of efficacy in the prevention of new BCCs.[10] However, the chemopreventive effect of isotretinoin was more complete in patients with arsenical and sunlight-induced BCCs than in patients with NBCCS. Withdrawal of treatment was associated with recurrence of tumors, suggesting the need for long-term, if not lifetime, maintenance therapy.[10,11]

In a case report by Sanchez-Conejo-Mir and Camacho,[12] complete regression of tumors less than 1 cm in diameter was seen in patients treated with oral etretinate (1 mg/kg daily) for 3 months. Approximately 70% of the larger tumors (>3 cm in diameter) showed some regression but not complete resolution. However, the most important feature the researchers observed with oral etretinate was the inhibition of the development of new tumors.[12] This observation also was reported in 2 other clinical studies.[11,13]

Sankowski et al[14] reported that treatment of 50 patients with topical isotretinoin resulted in diminution of BCCs on the face. Complete regression was observed in 4 patients. Histologic examination revealed necrosis of cancer cells and mononuclear infiltration into the treated tumors.[14] In a similar trial of 15 patients, treatment of solitary BCCs on the face with isotretinoin 0.6 mg/kg daily for 21 days resulted in complete regression in 2 patients, partial regression in 5 patients (>50% reduction in tumor size), and minimal response in 8 patients (<42% reduction in tumor size). Prolongation of treatment did not show any improvement in the regression rate of the tumors.[15]

Topical tazarotene also has been tested and revealed dramatic inhibition in the formation of BCCs induced with either UV or ionizing radiation in mice.[16] The ability of tazarotene to inhibit BCC formation in this mouse model provides encouragement for the use of tazarotene in skin cancer chemoprevention trials in humans.

The efficacy of topical and systemic retinoids for the treatment of BCCs is not comparable to other modalities and should mainly be used as an adjunct to other therapies, such as surgery or topical 5-fluorouracil (5-FU).[13] Oral etretinate can reduce the size of existing tumors, and therefore, enormously facilitate postsurgical treatment of BCCs, causing less damaging effects to the patient.[12] In addition, systemic administration of retinoids has demonstrated inhibition in the development of new tumors and may be useful as chemopreventive agents in patients with NBCCS.[10-13] It is essential, however, that the lowest effective dose be determined for each patient to minimize systemic toxicity from long-term therapy that appears necessary for maintaining the chemopreventive effect.[10]

Immune Response Modifiers

The efficacy of immune response modifiers, such as imiquimod cream, has been tested in the treatment of BCCs with promising results. Researchers have demonstrated that imiquimod cream 5% is an effective therapeutic option for both superficial and nodular BCCs in patients with NBCCS, though a higher number of applications and longer treatment periods are required for nodular BCCs.[17]

In a study, the composite (combined clinical and histologic assessment) clearance rates of superficial BCCs after a 5 times weekly and 7 times weekly treatment with imiquimod cream 5% were 75% and 73%, respectively.[18] Histologically, the clearance rates were 82% and 79%, respectively. Treatment was implemented for 6 weeks and the treated tumor sites were clinically and histologically evaluated after 12 weeks.[18] Furthermore, Kagy and Amonette[19] reported effective eradication of nonfacial superficial BCCs after an 18-week treatment course with imiquimod cream 5% in a patient with NBCCS. Similarly, other studies reported histologic and clinical resolution of BCCs in patients with NBCCS treated with an immune response modifier for periods

ranging from 6 to 14 weeks, with no tumor recurrence for at least one year.[20,21]

In all the studies, the most notable adverse reaction was skin irritation at the site of application.[19-21] The inflammation at the treated site was severe enough to compromise compliance in some patients, which is a problem in individuals with multiple BCCs, such as patients with NBCCS who cannot tolerate treatment with an immune response modifier. However, Geisse et al[18] pointed out a substantial correlation between degree of inflammation and tumor clearance rate—as the severity of the adverse skin reaction increases, so does the clearance rate. The local inflammatory response at the treatment site appears to be a manifestation of cytokine induction in the involved skin.[22]

The exact mechanism of action of imiquimod is not known. It has been suggested that the antitumorigenic effect of imiquimod is mediated by up-regulation of cytokines, especially interferon α (IFN-α), through production of interferon β (IFN-β), interferon γ (IFN-γ), and tumor necrosis factor (TNF)–α2.[22] Further research has proposed that imiquimod induces an antitumor immune response mediated by lymphocytes and macrophages, a reduced BCL-2 expression, and an increase in the apoptotic index of BCC by IFN-α–induced expression of Fas receptor.[23]

The use of immune response modifiers for the treatment of BCCs is very promising and exciting. Tolerability issues may be overcome with further research and the development of other less irritating immune response modifiers. A more practical approach would be to reduce the frequency of application of imiquimod cream to 3 or 4 times weekly and compare adverse reaction and tumor clearance rates with the higher frequency regimen.

Topical 5-FU

5-FU is used as a topical treatment of actinic keratosis, superficial BCC, and Bowen disease. Topical 5-FU has been shown to play a prophylactic role in the management of NBCCS. Strange and Lang[24] reported a child with NBCCS successfully treated for a decade with topical 5-FU and tretinoin for BCCs. The prophylactic and suppressive effect of 5-FU was implied when new BCCs occurred after a 6-month cessation of therapy. Many patients are unable to tolerate prolonged treatment with 5-FU due to the adverse side effects at the sites of application.[24] It should be noted that the successful management of the patients with NBCCS was only evident when 5-FU and tretinoin were used in combination. The results of the use of topical 5-FU and tretinoin alone, even with occlusion, were disappointing.[24] Similar disappointing results were reported with the prolonged treatment of a patient with NBCCS with topical 5-FU.[25]

It is suggested that the synergism of topical 5-FU and tretinoin is in the keratolytic effect of the retinoid, which likely enhances the penetration of 5-FU.[24] A synergistic effect also was demonstrated in a patient with NBCCS who was treated with cryosurgery and 5-FU. The results suggested that cryotherapy followed by 5-FU was more effective in treating BCC than either treatment modality alone.[26]

The effect of a specially formulated 5-FU therapeutic implant or MPI 5003, a new preparation for intralesional sustained-release chemotherapy for BCC, was assessed by Orenberg et al.[27] The potential of intralesional 5-FU for targeted local chemotherapy was demonstrated as 8 of 10 patients showed histologically confirmed elimination of their tumors. This study, however, excluded patients with NBCCS.[27] In a randomized controlled study by Miller et al,[28] a histologically confirmed 91% cure rate (106/116) of BCCs was demonstrated with 3 to 4 weeks of treatment of the tumors with 5-FU after 3 months' follow-up. But, again, no patients with NBCCS were included in this study.

Intralesional Interferon

Interferons possess an inhibitory effect on cellular growth and modulate cellular function. IFN-α specifically has been shown to have activity against a variety of tumors.[29] Greenway et al[30] used intralesional recombinant alpha-2 interferon 3 times weekly to treat BCCs in 8 patients. Complete resolution of the tumors was observed in all patients 2 months after the completion of therapy.[30] In a similar study (N=172), the researchers reported cure of BCC lesions in 86% of interferon-treated patients compared with only 29% of placebo-treated patients. Approximately 81% of interferon recipients remained tumor free one year after initiation of treatment.[31] Noduloulcerative and superficial lesions were equally responsive to treatment with interferon.[31,32] However, efficacy of treatment at the doses used was reduced for the more aggressive BCCs, such as deeply infiltrating, morpheatype lesions and recurrent tumors.[32]

Wickramasinghe et al[29] reported a variable response of skin tumors to intralesional interferon. There was clearance of all treated squamous cell carcinomas, actinic keratoses, and a single treated

keratoacanthoma, but they failed to obtain regression of any treated BCCs. Similarly, Sollitto and DiGiovanna[33] reported failure in the complete resolution of BCCs in a patient with NBCCS who was treated with intralesional IFN-α in combination with oral isotretinoin.

IFN-γ has theoretic advantages over IFN-α in the treatment of BCCs.[34] Furthermore, IFN-γ has been shown in some skin tumor systems to have more antiproliferative activity than IFN-α.[33] In a trial of patients with BCC, treatment efficacy with 2 different doses of intralesional IFN-γ was assessed. A 12-week therapy resulted in complete histologic tumor clearance in 7% (1/15) and 50% (7/14) of the patients injected with a low dose and a higher dose of IFN-γ, respectively.[34] More studies investigating the effect of higher intralesional doses of IFN-γ and even the combination of IFN-α and IFN-γ on patients with BCCs and NBCCS could provide interesting results.

There seem to be discrepancies among studies regarding the efficacy of intralesional interferon in the treatment of BCC. The number of injections and duration of treatment seem to be as important as the total dose. A dose response effect seems to exist because lower doses of interferon in fewer injections produced lower cure rates.[31] Additionally, recurrence rates have not always been clearly defined, and studies citing the highest effectiveness have only assessed clearance for one year or less after treatment.

X-ray Therapy

X-ray therapy (XRT) currently is used to treat BCCs less frequently than in the past. When used in some patients with NBCCS, it may lead to the rapid development of new BCCs.[35] The new tumors are particularly aggressive and infiltrative.[6] This drastic adverse effect renders this modality unfavorable for treating patients with NBCCS.

Photodynamic Therapy

Photodynamic therapy (PDT) is a nonionizing radiation treatment modality still in the investigational stages for the management of BCC. The main principle of PDT is use of the interaction between visible light and tumor sensitizing agents to cause cell death. In a trial where delta-aminolevulinic acid and blue light PDT were used to treat BCCs in 2 patients with NBCCS, researchers reported complete clinical response of 89% (8/9) and 67% (18/27) of superficial BCCs on the face and extremities, respectively.[36] The clearance rate of nodular BCCs on the face was lower at 31% (5/16). Additionally, resolution of the lesions was accompanied by excellent cosmetic outcomes and no recurrence during the 8-month follow-up period.[36]

In a different report, hematoporphyrin derivative photoradiation therapy was used to treat BCCs in 3 patients with NBCCS.[37] Clinically, all treated lesions disappeared. Histologically, 82.5% (33/40) of the lesions revealed complete clearance, whereas the rest showed residual tumor cells. The recurrence in the 1-year follow-up period was 10.8%.[37] Additionally, Rifkin et al[38] presented a case report of a patient with NBCCS who was successfully treated with PDT using tin ethyl etiopurpurin and showed no evidence of recurrence of BCC in a 6-month follow-up period.

In a clinical trial, PDT was compared to cryosurgery for treatment of BCCs.[39] In terms of efficacy, PDT was comparable to cryosurgery, though repeat treatments were more often required with PDT than with cryosurgery. However, the healing time was considerably shorter and the cosmetic outcomes were substantially better with PDT. Pain and discomfort during the treatment session and in the following week were low and were equivalent in both treatment modalities.[39]

The use of PDT, though still in its infancy, seems promising, especially for management of superficial BCCs. Larger studies are needed to confirm the efficacy of this method and its benefits in patients with NBCCS.

Electrochemotherapy

Electrochemotherapy (ECT) is a novel treatment involving exposure of cancerous tissues to short pulses of electricity during conventional chemotherapy. The locally applied electric field temporarily destabilizes cell membranes in the presence of a drug and allows increased uptake of the agent into the cytosol.[40] The greatest antitumor effect has been observed with bleomycin sulfate, but cyclophosphamide, cisplatin, mitomycin C, and peplomycin also have been used.[41]

Preliminary clinical studies have produced promising results in treating BCCs with this modality. Heller et al[42] treated patients (N=20) with intralesional bleomycin sulfate–mediated ECT. A total of 54 primary BCC tumors were treated resulting in a clearance rate of 98% (53/54). In the majority of these tumors (51/54), complete response was observed after a single treatment.[42] In another trial, ECT was shown to be effective in the treatment of cutaneous malignancies with good healthy tissue sparing and minimal scarring.[43] Furthermore, the antitumor effect of ECT with cisplatin was demonstrated in another study.[44]

Summary of Randomized Controlled Studies on BCC Treatment[3,18,28,31,34,39,45-51]

Treatment Modality	Randomized Controlled Studies	Comments
Cryosurgery	93 patients[45] (with low-risk BCC lesions) 88 patients[39] (with histologically verified BCCs) 84 patients[3] (tumors not histologically confirmed) 96 patients[46] (with histologically verified BCCs of head and neck)	Highest cure rates (>90%), with low-risk, nonaggressive, superfi cial BCCs. Two freeze-thaw cycles associated with higher cure rates compared with one cycle.[3] Few complications, low cost, may treat multiple lesions in one session, good cosmetic results
Retinoids	N/A	Efficacy of topical and systemic retinoids is not comparable to other treatment modalities; should mainly be used as adjunct to other treatment options
Immune response modifiers (ie, imiquimod cream 5%)	128 patients[18] (tumor clearance assessed clinically and histologically) 35 patients[47] (tumor clearance assessed histologically) 99 patients[48] (with biopsy-verified BCCs) 92 patients[48] (with biopsy-verified BCCs) 99 patients[49] (tumor clearance assessed histologically	Clearance rates ranging from 70%–100%. Higher dosage frequencies revealed trend toward fewer early treatment failures. Occlusion does not appear to make a difference in response. Lower skin irritation is an adverse effect in all trials
Topical 5-fluorouracil	122 patients[28] (tumor clearance assessed histologically) 13 patients[50] (with biopsy-proven, moderate-thickness BCCs)	Cure rates approximately 90%.[28,50] Assessed multiple regimens (dose, schedule, and vehicle). Safe and effective alternative without the inconvenience, risk, and expense of surgery. Main adverse effect is local tissue reaction[28,50]
Intralesional interferon	162 patients[31] (with biopsy-proven BCCS) 65 patients[34] (tumor clearance assessed histologically)	Dose-effect relationship in all studies. Higher dose associated with higher cure rate. Main adverse effect is pain at injection site and flulike symptoms[31,34]

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Table. (continued)

Treatment Modality	Randomized Controlled Studies	Comments
X-ray therapy	N/A	No longer frequently used. Not recommended for patients with nevoid BCC syndrome
Photodynamic therapy	88 patients[39] (tumor response assessed histologically) 83 patients[51]	Promising results, but use still in infancy. Larger studies needed to confirm efficacy
Electrochemotherapy	N/A	Promising results, but use still in infancy. Larger studies needed to confirm efficacy

Abbreviations: BCC, basal cell carcinoma; N/A, not available.

On the other hand, a study by Glass et al[40] demonstrated only minimal antitumor response of bleomycin sulfate–mediated ECT in patients with NBCCS. The reason for the disappointing outcomes may have been that researchers chose to administer the bleomycin systemically rather than intralesionally. Certainly, more studies involving patients with NBCCS need to be conducted, as the potential of ECT in the management of patients with NBCCS should be further explored.

Comment

Unfortunately, no large studies on the treatment of NBCCS exist. Most evidence would be considered grade B or C derived from case reports and clinical trials including small populations. Nevertheless, several randomized controlled studies exploring different modalities for treatment of BCC were found and are summarized in the Table. It should be noted, however, that these studies did not exclusively focus on patients with NBCCS. One may question the quality of the evidence presented by these studies, as several limitations in the methodologies used do exist. Some studies used histologic evidence to either diagnose or confirm resolution of lesions.[10,14,18,20,21,27,28,34,37,39,47,49] The majority of studies established tumor diagnosis and treatment outcome clinically.[3,7-9,11-13,15,19,29,30,33,39,40,42,43] In terms of follow-up, only 1 trial measured tumor recurrence in 4 years[7]; the remaining studies had a follow-up period of several months to a year. This follow-up time does not permit objective judgment of recurrence rates, as the majority of tumors do not reoccur until several years posttreatment. Additionally, the type, location, size, and aggressiveness of tumors also need to be considered. Only a small number of studies included patients with high-risk lesions (ie, large size, located on face or neck.)[3,7-9,12,14,36] The remaining studies focused on patients with low-risk primary BCCs (ie, small size, located on trunk and extremities). Consequently, the findings of these studies may not be applicable to high-risk lesions.

In general, curettage and cautery, cryotherapy, and Mohs micrographic surgery appear to be the most accepted treatment modalities for BCC, including patients with NBCCS. More recently, topical imiquimod and PDT have emerged as promising alternatives.

The focus of treatment should be on not only the successful management of existing BCCs but also the prevention of new lesions. An ideal treatment would be one with a high cure rate, maximum preservation of surrounding normal skin tissue, minimal scarring, short healing time, and minimal side effects. It is important that the patient's idiosyncrasies and tolerability to the different treatment regimens, as well as the patient's financial situation, be taken into consideration. Every physician wants to provide the best possible care for his/her patients. Given the multitude of research available, it may not always be possible to keep abreast of all current developments or to translate them into clinical practice. In the era of evidence-based medicine, physicians should integrate the best research evidence with their own clinical expertise and their patient's values to determine the optimal way for managing their patient's condition.

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