Combination vismodegib and photodynamic therapy for multiple basal cell carcinomas

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ABSTRACT

Background: Oral vismodegib therapy and photodynamic therapy (PDT) are non-invasive treatments for basal cell carcinoma (BCC) with overlapping utility in widespread BCCs and patients who are poor surgical candidates. There is no published study to date investigating the combination use of PDT with vismodegib to optimize individual response rates.

Objective: To evaluate the combination of red light PDT and vismodegib therapy in patients with multiple nodular BCCs. The primary objective was to determine the safety of this combination therapy. Secondary outcomes included evaluation of the overall response rate, treatment-related pain, and cosmesis.

Methods: An open label pilot study of immunocompetent patients with multiple BCCs treated with 3 months of continuous vismodegib therapy (150 mg daily) and 3 consecutive ALA PDT sessions. Outcomes were assessed following each PDT session and 30 days post-treatment.

Results: Four patients with multiple nodular BCC (median = 5) were enrolled in the trial between January and August of 2016. Three patients completed the full intervention phase trial and a total of 19 lesions were treated. One patient completed 2 months of vismodegib and 2 PDT sessions. One PDT session was sufficient for small lesions, whereas larger lesions required all 3 sessions. The fifteen evaluable lesions at the end of the 3 PDT sessions showed complete responses. At 30-day follow-up, one of the treated lesions was noted to have clinical evidence of disease. Overall response rate showed 90% complete response and 10% partial response for the study. Combination therapy was well tolerated and yielded a similar or superior side effect profile to that of individual therapies with excellent cosmesis.

Conclusion: Combination PDT-vismodegib is a potential safe & effective therapy for the treatment of multiple BCCs that may enhance efficacy of individual therapies.

In 2012, the oral targeted therapy vismodegib was FDA-approved for the treatment of metastatic basal cell carcinoma (mBCC) and locally advanced BCC (laBCC). Vismodegib selectively inhibits the hedgehog (HH) signaling pathway, the activation of which provides a common genetic basis for both sporadic & syndrome-associated BCCs [1]. Resistance to vismodegib can occur and is primarily due to mutations in SMO or hyper-activation of components distal to SMO in the HH signaling pathway [2,3]. Long-term follow-up data have confirmed the ability of vismodegib to generate a durable & efficacious clinical response in treatment of advanced BCCs. Reported objective response rates (ORR) after 39 months of therapy include 48.5% in mBCC and 60.3% in the laBCC with median duration of responses of 14.8 months and 26.2 months, respectively [4]. Similarly, a recent systematic review and pooled analysis of interventional studies demonstrated an ORR of 33.6% in mBCC and 64.7% in laBCC [5].

Vismodegib is approved for daily dosing with 150 mg until disease progression or unacceptable toxicity. The most common adverse events (AEs) associated with vismodegib use are muscle spasms, alopecia, dysgeusia, weight loss, fatigue, and nausea [4]. Post-treatment reversibility of AEs has been demonstrated [6]. Despite a tolerable safety profile, however, occurrence of treatment-related AEs is relatively common with reported incidences ranging from 30 to 70% [4,5]. Given this high incidence, chronic low-grade toxic effects often make long-term treatment with vismodegib intolerable for many patients [7]. Moreover, incidence of AEs has been shown to increase with duration of therapy [4].
Recently, several groups have investigated extended applications of vismodegib in the treatment of operable BCCs, given that many clinical trials exist wherein non-surgical approaches may be favored due to lower morbidity and improved cosmesis. Sofen et al. performed an open-label cohort study whereby patients with new, operable, nodular BCC (nBCC) received vismodegib (150 mg/day) followed by excision and Mohs surgery to evaluate histological clearance [6]. Interventions were divided into 3 distinct treatment cohorts including: vismodegib for 12 weeks (wks) followed by excision (cohort 1), vismodegib for 12 wks, then 24 wks of observation before excision (cohort 2), and vismodegib for 8 wks on/4 wks off/8 wks on followed by excision (cohort 3). Complete histologic clearance was achieved in 42%, 16%, and 44% of patients in cohorts 1, 2, and 3, respectively [6]. Interestingly, both safety & efficacy of vismodegib were comparable when dosed continuously versus intermittently (cohorts 1 vs 3). Dreno et al. treated patients with multiple operable BCCs, including those with basal-cell nevus syndrome (BCNS), with one of two regimens: group A (150 mg oral vismodegib per day for 12 wks, then three rounds of 8 wks of placebo daily followed by 12 wks of 150 mg vismodegib daily) or treatment group B (150 mg oral vismodegib per day for 24 wks, then 3 rounds of 8 wks of placebo daily followed by 8 wks of 150 mg vismodegib daily) [7]. Overall, both intermittent dosing regimens demonstrated similar efficacy with no significant difference in reduction from baseline in the number of clinically evident BCCs after 73 wks (62.7% vs 54% for group A vs B). The safety profiles of the both intermittently dosed regimens were also similar and the range of adverse events remained consistent with previous clinical experience [7].

Similar to interventions by both Sofen & Dreno et al., application of intermittent dosing regimes for vismodegib is increasingly used in clinical practice as a strategy to manage adverse events and improve patient’s ability to endure long-term treatment [8]. An exploratory analysis of STEVIE study data explored the effects of intermittent vismodegib dosing on safety and activity in patients with laBCC and nBCC found that the median duration of vismodegib treatment was lengthened by increasing numbers of treatment breaks, without any compromise in drug activity [9]. In this study, the average length of treatment breaks was 22 days. Overall, results from this analysis and others suggest that intermittent vismodegib dosing schedules, or drug holidays, may help strike a balance between drug activity and risk of toxic effects to allow for successful long-term treatment.

Photodynamic therapy (PDT) is a safe and effective treatment for low-risk BCCs [10,11]. Currently in the US, FDA approval for PDT is limited to treatment of actinic keratoses, whereas in the European Union and elsewhere worldwide, approval extends to the treatment of BCC and squamous cell carcinoma in situ [10,12]. Efficacy of PDT in BCC is supported by substantial research and clinical trials. A recent meta-analysis by Wang et al., reviewed data from 8 randomized controlled trials comparing PDT to non-PDT treatments in 1583 patients with nBCC or superficial BCC (sBCC) [13]. Overall, this analysis found PDT to be less effective than surgical excision (SE) in terms of complete clearance and recurrence rates, but with no significant difference in efficacy when compared to other non-invasive therapies (e.g. cryotherapy, topical imiquimod, 5-fluourouracil). Cosmetic outcomes were much better with PDT than surgery [13]. A similar meta-analysis by Zou et al. compared treatment outcomes between PDT and SE for 596 histologically confirmed nBCCs from 5 studies [14]. This analysis observed no significant differences between PDT and SE in terms of complete response rate after 5 years, however, there was an increased cumulative probability of recurrence for PDT compared to SE noted.

In trials of PDT versus surgery for nBCC, recurrence rates are less than 5% for SE versus 14% to 30% for PDT with Ala. In the largest single institution experience with 1440 nBCCs & sBCCs, PDT using systemically administered porphyrin sodium showed an initial (6-month) complete response rate of 92%, with a recurrence rate of less than 10% at 4 years [15]. At this same institution, a 92% complete response rate was achieved with PDT with topical ALA in 330 patients with sBCC, but the response rate dropped to 71% in 75 patients with nBCC [16].

Several clinical studies have reported an increase in the initial response rate with a lower recurrence rate after repeated PDT sessions. Cycles of MAL PDT repeated after 3 months for persistent BCC has been shown to offer high and durable response rates [13]. Both efficacy and safety have also been demonstrated using repeated sessions with red or blue light at follow up times of 3, 6 and 12 months. At Roswell Park Cancer Institute, Oseroff and colleagues safely used repeated sessions of ALA PDT in children with BCNS (multiple BCC), and Gilchrist et al also reported the benefits of ALA PDT with blue light at 2–4 month interval treatments [17,18].

Despite reduced efficacy in comparison to surgical excision, PDT offers several distinct advantages owing to its non-invasive approach including superior cosmesis, shorter recovery times, & improved patient tolerance [11,13,19]. Additionally, PDT has the potential to be combined with other treatments, repeated as often as necessary, and can be performed over large areas with multiple BCCs [20,21]. Together, these unique advantages make PDT a useful approach for patients who have contraindications for surgery, widespread areas of involvement, or larger inoperable lesions [22].

Despite overlapping utility in widespread BCCs or other poor surgical candidates, the combination of PDT with vismodegib therapy remains largely unexplored. Epstein and colleagues completed a trial comparing the effects of intermittent vismodegib versus blue light PDT in patients with multiple BCCs. This was a phase two 28 month study where patients received 7 months of continuous therapy with vismodegib followed by randomization to receive intermittent vismodegib, 150 mg/day, during months 10–13, 16–19, and 22–25 or to receive treatment with PDT at month 10 and at three month intervals thereafter [23]. Preliminary results suggest that PDT-induced maintenance was similar to that of intermittent vismodegib on outcomes [24]. Beyond this unpublished report, however, no study has either directly compared PDT to vismodegib, or explored the utility of combination PDT-vismodegib therapy as a primary treatment modality.

Importantly, the distinct mechanism of action for both vismodegib & PDT has the potential to offer a synergistic anti-tumor response. There have been reports of improved cosmesis in PDT-resistant tumors [21]. Moreover, in an unpublished study, vismodegib effects on intracellular retention of photosensitizer were studied by measuring fluorescence in murine and human cells. In our personal experience, vismodegib has been found to increase the accumulation of PpIX, suggesting that clinical efficacy of PDT could be enhanced by increasing photosensitizer levels within tumor cells (unpublished data).

Given the potential for enhanced clinical efficacy offered by combination modalities of PDT-vismodegib, we conducted an open label to study evaluate this therapy for patients with multiple BCCs. The primary objective of this study was to determine the safety of combination therapy. Secondary objectives included evaluation of the overall response rate (ORR), assessment of treatment-related pain, and cosmesis. To our knowledge, this is the first report on the safety & efficacy of combination red light PDT-vismodegib in the treatment of multiple nodular BCCs.

1. Methods

1.1. Subjects

Men and women of non-childbearing potential and age ≥ 18 years were recruited from January 2016 to August 2016 for this open-label, single center study. All subjects carried a diagnosis of BCC with at least 4 nodular lesions measuring 0.5–5 cm in diameter, located on the head, neck, trunk or extremities. BCC diagnosis was confirmed histologically at baseline with partial shave or punch biopsy of 1–2 lesions no sooner than 2 weeks prior to treatment.

Patients with aggressive BCC subtype, previously treated with a
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