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Patients more Likely to Prefer Surgery to Novel Photodynamic Therapy

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Abstract

Objective: To compare preferences with patients who have undergone both facial skin cancer surgery and photodynamic therapy (PDT).

Design: A survey of patients who had undergone both PDT and surgery to their face.

Setting: Referral skin cancer centre in Australia

Protocol: 34 patients had undergone both PDT and surgery to their face. They were asked which they would choose next time if given both options and why.

Main outcome measure(s): Patient preference of the two treatments

Results: Of the 34 PDT patients, 17 preferred surgery if future treatment was needed, whilst 6 preferred PDT, ($p<0.01$). Prolonged post procedural pain was the most frequent explanation provided for preferring surgery.

Discussion and conclusions: Clinicians should not assume that surgery is less favoured by patients over alternate interventions. Prolonged pain following PDT was a frequent reason not to prefer future PDT treatments.

Keywords: BCC; SCC; Actinic keratoses; Mohs; Reconstruction; Pain; Photodynamic; Analgesia; Prospective; Melanoma

Background

Photodynamic therapy (PDT) has become an established option in the management of skin Cancers [1-3] and precancerous skin lesions [4-7]. It has emerged as an option that can be offered as an alternative or adjunct to surgical excision [2,8]. PDT active ingredients are applied to the affected skin and a light source is then applied to the skin for an illumination following an incubation period. The active ingredient is absorbed and intracellularly converted to protoporphyrin IX, a light-reactive intermediary protein.

Activation of protoporphyrin IX by the PDT light source creates free radicals which are essential to the mechanism of action.

Patients commonly perceive surgery, including skin surgery, as a painful experience [9-11]. PDT has also been reported to frequently cause pain [12-15]. When patients have two treatments of PDT pain is frequently severe with the second treatment [15]. Pain can be more severe when a larger field is treated with PDT [12]. Kasche [16] demonstrated that pain during activation can be such that patients request discontinuation of treatment before reaching the required light dose has been reached. This was more likely if the patient was being treated with aminolevulonic acid (ALA) than if treated with methyl aminolevulinate (MAL). There is a report that pain experienced with PDT in Australia may be greater than elsewhere [17]. Patient pain perceptions may lead them to seek a topical alternative to an invasive approach in the hope that their procedure and post-procedure pain experience and other side effects will be reduced [18].

We have completed and published a prospective randomized controlled trial involving photodynamic therapy that failed to identify a cancer prevention role for this therapy [19].

The intervention patients in this trial had all previously undergone skin cancer surgery to the face. Indeed this was a prerequisite of the protocol. We sought feedback from these trial patients regarding their preferences of the two treatments they have experienced.

The novel ALA product used to treat the patients described herein was marketed and sold by Allmedic Pty Ltd® as a simple, premixed preparation and was promoted as having a prolonged shelf life and requiring a low intensity of activating light.

Aim of study

To enquire of patients who have undergone both photodynamic therapy and skin cancer surgery to their face which they would prefer should they be offered a future choice of both, and why.

Methods

The PDT protocol was approved by Bond University Human Research Ethics Committee. The primary PDT trial sponsor was Allmedic Pty Ltd. (Taren Point, NSW, Australia). All patients were managed in a single skin cancer referral centre in southern Australia. Patients treated with novel ALA for actinic damage had previously experienced one or more histologically proven and surgically cleared facial skin cancers. The protocol involved two PDT treatments 14 days apart. The patient was provided with a 10% alpha hydroxy acid solution to reduce thickened hyperkeratosis to be used twice daily for two weeks prior to PDT. Following a test dose, novel ALA (20% 5-aminolevulinate solution) was applied to the whole face [except for eyelids and near mucosal surfaces] followed by a five hour incubation period during which exposure of light face to the face light was avoided. The border of the face was defined as the hairline superiorly, anterior to the tragus laterally and the lower margin of the mandible inferiorly.

A 30 minute illumination was then undertaken with the PDT light source provided by the sponsor (465 nm blue LED light at 48 J/cm^2 for 20 minutes and then 625 nm red LED light at 64 J/cm^2 for 10 minutes). The sponsor advised that efficacy and safety of their trial ALA had been optimized with this light source. They advised that a combination of blue and red lights was designed to allow for two levels of penetration within the skin. Incubation involved the liquid being massaged into each side of face to provide a thin and uniform cover. Prior to illumination, the face was washed with warm water and dried. During illumination, the eyes and eyelids of the patient were shielded from the light source. Each patient had an attendant(s) present at all times during illumination. A fan to reduce burning sensations was provided as required. The treatment was paused if requested by the patient and discontinued if unable to be tolerated.

Following treatment, the patient was given extensive advice regarding minimizing sun exposure, analgesia etc. They were encouraged to remain indoors in a darkened room for at least 48 hours and were provided with a sunscreen to apply when outside both before and after treatment.

In the course of follow up during December 2012 patients who had undergone PDT were asked whether they would prefer PDT or surgery if their face required future treatment. All PDT patients had previously undergone skin cancer face surgery. Their responses and reasons were noted.

Statistical analysis

Key outcome incidences were analyzed using the chi square test and PDT intervention was compared with skin cancer surgery using 2 x 2.

Results

34 patients underwent PDT at this Geelong trial centre between January and March 2009. All patients had previously suffered one or more skin cancers to the face treated by surgical clearance and closure. The levels of pain experienced by many were severe and for this and other reasons pertaining to trial governance no further patients were treated with this novel PDT. Further recruitment of PDT trial patients was suspended. 19 of the 34 patients were unable to tolerate the complete PDT illumination protocol. The novel PDT used in this study has resulted in over 20% of patients managed with the product reporting pain either uncontrolled with oral analgesics or pain the worst they have yet experienced.

Subsequent to trial suspension the investigators were aware of the obligations of clinicians and investigators to follow up on adverse events whether or not they are specified in the clinical trial protocol until they are resolved with no time limits. This is a requirement of the National Statement of Ethical conduct in human Research and the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. As of April 2016 some trial patients continue to be dealing with adverse events from PDT in 2009 and as such the investigators continue to monitor these patients. Indeed two patients continue to deal with uncontrolled BCC disease effecting their face including deeper structures.

The 34 patients who had undergone PDT were surveyed regarding their preference of PDT versus surgery should their face require further face treatment. 17 patients (50%) indicated a preference for surgery. 6 patients (18%) indicated a preference for PDT ($p<0.01$). 5 patients had no preference and 5 were not contactable. One patient declined to answer. Of the 17 patients who preferred surgery, 9 included severe pain as part or all of the reason for their choice. 4 patients also mentioned other adverse events. 6 patients commented that they considered PDT did not make any difference to their skin. 8 patients indicated that under no circumstances would they have PDT again.

Of the 6 patients who preferred PDT, 4 commented that they considered their skin had improved. One patient highlighted the non-invasive nature of PDT. 4 of these 6 patients commented that the PDT was painful.

Limitations

PDT patients were having their whole face treated rather than a large part of the face. The larger area of treatment may account for part of the explanation for treatment preference.

Discussion

Patients can at times assume that a less interventional or topical therapy will necessarily be easier to endure that surgery. Patients often consider surgery is likely to be painful following the procedure and can seek alternative treatments that may result in less pain11. Patients might associate topical treatments with discomfort rather than pain. However topical treatments used in the management of premalignant skin lesions have been demonstrated to produce pain at the site treated [20-22], including persistent pain [23].

The severe and prolonged pain adverse events noted in this study have been reported to the Therapeutic Goods Administration (TGA) in Australia. The prolonged and severe pain of PDT reported in this study may be due to a preparation variation between this novel agent and existing ALA products.

Conclusion

More patients in this data set indicated a preference for surgery rather than PDT in the future should both interventions be offered as

alternatives. The likelihood of severe post procedural pain is the most likely stated reason to prefer surgery over PDT.

Counselling of likely outcomes associated with treatment should include advice to the patients of high pain expectations following PDT. Clinicians should consider explaining the relative likelihood of pain whenever surgery versus PDT is considered. The pain experienced with this PDT product may not reflect the pain experienced with other PDT products. Occupational therapists should consider that a patient's ability to return to normal activities may be delayed when patients have undertaken PDT treatment.

Disclosure

Family interests of author AD have shares in the sponsoring company. This holding has and is being managed independently with all profits directed to cancer and epilepsy medical research.

References

1. Christensen E, Mork C, Skogvoll E (2012) High and sustained efficacy after two sessions of topical 5- aminolaevulinic acid photodynamic therapy for basal cell carcinoma: a prospective, clinical and histological 10-year follow-up study. Br J Dermatol 166:1342- 1348.
2. Rhodes LE, de Rie M, Enstrom Y, Groves R, Morken T, Goulden V, et al. (2004) Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. Arch Dermatol 140: 17-23.
3. Mosterd K, Thissen MR, Nelemans P, Kelleners-Smeets NW, Janssen RL, et al. (2008) Fractionated 5-aminolaevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial. Br J Dermatol 159: 864-870.
4. Lehmann P (2007) Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. Br J Dermatol 156: 793-801.
5. Wiegell SR, Fabricius S, Gniadecka M, Stender IM, Berne B, et al. (2012) Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp: a randomized multicentre study. Br J Dermatol 166:1327-1332.
6. Sotiriou E, Apalla Z, Chovarda E, Goussi C, Trigoni A, et al. (2012) Single vs. fractionated photodynamic therapy for face and scalp actinic keratoses: a randomized, intraindividual comparison trial with 12-month follow up. J Eur Acad Dermatol Venereol 26: 36-40.
7. Kaufmann R, Spelman L, Weightman W, Reifenberger J, Szeimies RM, et al. (2008) Multicentre intraindividual randomized trial of topical methyl aminolaevulinate-photodynamic therapy vs. cryotherapy for multiple actinic keratoses on the extremities. Br J Dermatol 158: 994-999.
8. Kuijpers DI, Smeets NW, Krekels GA, Thissen MR (2004) Photodynamic therapy as adjuvant treatment of extensive basal cell carcinoma treated with Mohs micrographic surgery. Dermatol Surg 30: 794-798.
9. Hoimyr H, von Sperling ML, Rokkones KA, Stubhaug A, Finnerup K, et al. (2012) Persistent pain after surgery for cutaneous melanoma. Clin J Pain 28: 149-156.
10. Sniezek PJ, Brodland DG, Zitelli JA (2011) A randomized controlled trial comparing acetaminophen, acetaminophen and ibuprofen, and acetaminophen and codeine for postoperative pain relief after Mohs surgery and cutaneous reconstruction. Dermatol Surg 37: 1007-1013.
11. Kuhn S, Cooke K, Collins M, Jones JM, Mucklow JC (1990) Perceptions of pain relief after surgery. BMJ 300:1687-1690.
12. Sandberg C, Stenquist B, Rosdahl I, Ros AM, Synnerstad I, et al. (2006) Important factors for pain during photodynamic therapy for actinic keratosis. Acta Derm Venereol 86: 404-408.
13. Skiveren J, Haedersdal M, Philipsen PA, Wiegell SR, Wulf HC (2006) Morphine gel 0.3% does not relieve pain during topical photodynamic therapy: a randomized, double-blind, placebo controlled study. Acta Derm Venereol 86: 409-411.
14. Babilas P, Knobler R, Hummel S, Gottschaller C, Maisch T, et al. (2007) Variable pulsed light is less painful than light-emitting diodes for topical photodynamic therapy of actinic keratosis: a prospective randomized controlled trial. Br J Dermatol 157: 111-117.
15. Lindeburg KE, Brogaard HM, Jemec GB (2007) Pain and photodynamic therapy. Dermatology 215: 206-208.
16. Kasche A, Luderschmidt S, Ring J, Hein R (2006) Photodynamic therapy induces less pain in patients treated with methyl aminolevulinate compared to aminolevulinic acid. J Drugs Dermatol 5: 353-356.
17. Tran DT, Salmon R (2011) Field treatment of facial and scalp actinic keratoses with photodynamic therapy: survey of patient perceptions of treatment satisfaction and outcomes. Australas J Dermatol 52: 195-201.
18. Katz J, Feldman MA, Bass EB, Lubomski LH, Tielsch JM, et al. (2000) Injectable versus topical anesthesia for cataract surgery: patient perceptions of pain and side effects. The Study of Medical Testing for Cataract Surgery study team. Ophthalmology
19. 107: 2054-2060.
20. Dixon AJ, Anderson SJ, Mazzurco JD, Steinman HK (2014) Novel photodynamic therapy does not prevent new skin cancers--randomized controlled trial. Dermatol Surg 40: 412-419.
21. Cantisani C, Lazic T, Richetta AG, Clerico R, Mattozzi C, et al. (2012) Imiquimod 5% cream use in dermatology, side effects and recent patents. Recent Pat Inflamm Allergy Drug Discov 6: 65-69.
22. Marks R, Owens M, Walters SA (2004) Efficacy and safety of 5% imiquimod cream in treating patients with multiple superficial basal cell carcinomas. Arch Dermatol 140: 1284-1285.
23. Schmid-Wendtner MH, Wendtner CM () Intensified inflammatory reaction of actinic keratosis after single application of topical 5-fluorouracil in a patient treated with nilotinib for chronic myeloid leukemia. Dermatology 219: 341-343.
24. Yi BA, Nirenberg MJ, Goldstein SM, Berger TG (2005) Chronic neuropathic pain associated with imiquimod: report of 2 cases. Journal of the American Academy of Dermatology 52: 57-58.
25. Holmes MV, Dawe RS, Ferguson J, Ibbotson SH (2004) A randomized, double-blind, placebocontrolled study of the efficacy of tetracaine gel (Ametop) for pain relief during topical photodynamic therapy. Br J Dermatol 150: 337-340.
26. Ericson MB, Sandberg C, Stenquist B, Gudmundson F, Karlsson M, et al. (2004) Photodynamic therapy of actinic keratosis at varying fluence rates: assessment of photobleaching, pain and primary clinical outcome. Br J Dermatol 151: 1204-1212.