SHORT COMMUNICATION

Photodynamic Therapy: Influence of Clinical and Procedure Variables on Treatment Response in Basal Cell Carcinoma and Bowen Disease

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Photodynamic therapy (PDT) is one of the most commonly used non-invasive treatments in non-melanoma skin cancer (NMSC). High rates of complete remission can be obtained using PDT with methyl-aminolevulinate (MAL); for basal cell carcinoma (BCC) the response rate is 91% at 3 months and 76% at 5 years, with 5-year recurrence rates of 22% in superficial BCC (sBCC) and 14% in nodular BCC (nBCC) (1, 2), and for Bowen disease (BD) the rate ranges from 88% to 100% at 3 months with 68% to 89% of treated lesions remaining clear for 17 to 50 months, besides PDT provides excellent cosmetic results and a high patient satisfaction rate (1–3).

The primary limiting factors for MAL-PDT are pain during irradiation, tumoural thickness, tumour location (reduced sustained clearance rates for H-zone lesions), and certain histological features of BCCs such as pigmentary, morphoeaform, and infiltrative variants are considered contra-indications to treatment (3). Although the PDT procedure has changed little since its introduction, we conducted a retrospective analysis to evaluate how individual procedural variables relating to PDT influence the clinical response of BCC and BD.

MATERIALS AND METHODS

This retrospective observational study analysed clinical and procedural variables for all cases of BD, nBCC and sBCC treated with MAL-PDT at San Jorge Hospital (Huesca, Spain) between January 2006 and December 2015.

Patients were treated with MAL-PDT (Metvix®, Galderma, La Defense Cedex, France) following the standard procedure (3). Patients with nBCC first underwent curettage debulking of the lesions. After applying haemostatic pressure, MAL was applied to the lesion and a surrounding area of 1 cm in diameter, and was incubated for 3 h under occlusion. The treated area was illuminated with a coherent monochromatic diode light source (630 nm, 37 J/cm^2, Aktilite®, PhotoCure ASA, Norway).

The clinical records of all patients were reviewed and data gathered for the following variables: age at onset, sex, phototype (Fitzpatrick scale I–IV), predisposing factors, location, size and type of tumour. The following procedural variables were considered: number of PDT sessions; fluorescence emitted by the lesion in response to a Wood's lamp; interruption of illumination due to pain; analgesia prior to irradiation and pain score as evaluated using a visual analogue scale (0–10). Clinical response was evaluated at the end of patient follow-up.

Statistical analyses were performed using the statistical package SPSS, version 19.0 (IBM, Armonk, NY, USA). Associations between qualitative variables were assessed using the Pearson chi-squared test or Fisher exact test. The normal distribution of quantitative variables was evaluated using the Kolmogorov-Smirnov test. Depending on the data distribution, associations between binary and quantitative variables were evaluated using either the Student's *t*-test or Mann-Whitney *U*-test. In cases of variables with more than two categories, the ANOVA or the Kruskal-Wallis tests were used. Analyses of the odds ratio (OR) of a good response to PDT were performed using logistic regression. p-values <0.05 were considered statistically significant.

The study protocol was approved by the Ethical Committee for Clinical Research of Aragon, Spain (CP-CI PI12/0096).

RESULTS

The study population consisted of 472 tumours in 249 patients, with a mean ± standard deviation (SD) age of 71.7 ± 13.78 years. Of these, 59% were men and 41% women. The majority (92.6%) had no relevant medical history, only 6.6% had received prior radiotherapy, and the remainder had received transplants. The mean ± SD age of treatment responders (69.98 ± 14.27 years) was lower than that of non-responders (74.45 ± 11.1 years) ($p<0.01$).

The majority of the lesions analysed were nBCCs (60.4%), followed by sBCCs (25.2%), and BD lesions (14.4%). The back was the most common tumour location (19.3%) followed by the forehead (16.1%), it was associated with treatment response, with a poorer response observed for lesions located on the face. Of non-responding patients, 70% had lesions located on the face ($p<0.01$). In the statistical analysis when we divided the lesions according to the facial anatomical area affected, we verified that of the total of 71 lesions that were located in the nose, only 63.4%, demonstrating that the nasal localization was an independent predictor of poor response ($p=0.01$).

A complete clinical response was observed for 81.1% of patients, the mean ± SD follow-up time was 35.96 ± 23.46 months. The number of PDT sessions administered was as follows: 1 session, 11.7% of tumours; 2 sessions, 85.6% of tumours; 3 sessions, 2.6% of tumours.

Bivariate analysis revealed a statistically significant association between clinical response and the following variables: age (69.98 ± 4.27 years in responders vs 74.46 ± 11.07 years in non-responders; $p=0.01$); location, with best response rate (92%) observed for lesions located on the trunk, and the worst response rate (75.62%) observed for those located on the head and

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neck ($p<0.001$); and lesion type, with response rates of 76.8% for nBCC, 93.3% for sBCC, and 77.9% for BD ($p=0.02$). Phototype data were only available for 20% of patients, the most common phototype was type 3 (63.35%) higher cure rates were associated with lighter versus darker phototypes (85.7% vs 57.9%; $p=0.031$).

The mean pain score was 2.44 ± 2.03, and was lower in responders (2.2 ± 1.85) than in non-responders (3.02 ± 2.43) ($p=0.01$). The majority of patients received preventive oral analgesia 30 min before illumination (acetaminophen or metamizole). In the responder group 76% of patients received oral analgesia, 9.5% received local anaesthesia, and the remainder (14.5%) required no analgesia. In the non-responder group, 74.7% received oral analgesia and 17.6% received local anaesthesia. Application of local anaesthesia was significantly associated with a poorer response ($p=0.03$). Table SI[1] shows the bivariate analysis of all the study parameters.

All variables for which the bivariate analysis revealed a significant association with treatment response were included in the multivariate analysis, except for phototype, for which data was missing for a significant number of patients. The highest OR (95% confidence interval (CI)) for complete clinical response was observed for sBCC; 2.8 (1.29–6.21). A poorer response was significantly associated with the following variables: a pain score higher than the median (2) (OR, 0.545; 95% CI, 0.332–0.895); local anaesthesia (OR, 0.479; 95% CI, 0.244–0.943); and lesion location on the nose (OR, 0.411; 95% CI, 0.230–0.734) (Nagelkerke R2 0.117).

DISCUSSION

Our findings indicate a greater probability of complete response to PDT for sBCC than for nBCC or BD. The presence of significant pain during irradiation and the use of local anaesthesia appear to decrease the likelihood of complete response. Furthermore, our results indicate that PDT should not be used in tumours located on the nose, and treatment efficacy may be diminished in patients with a dark phototype.

The effectiveness of PDT may be limited by other clinical and epidemiologic factors, including age. We found that the mean age of treatment responders was significantly lower than that of non-responders. Supporting this observation, Nissen and coworkers found that PDT was more effective in younger patients, and described an age-associated decrease in the formation of PpIX (4). Other authors have found no evidence of such an association (5, 6).

We found that the location of the NMSC was a key determinant of treatment effectiveness. Supporting these findings, Fantini et al. (7) reported better response rates for trunk lesions versus those on the head/neck or limbs. Similarly, Vinciullo et al. (8) found significantly lower CR rates for lesions located on the face/scalp compared with those located on the trunk/neck. Nonetheless, other studies have found that lesion location was not a determinant of the response to MAL-PDT (8–10).

Regarding tumour type, our results are in agreement with the fact that sBCC responded better to PDT compared to nBCC, these differential response rates were due to differences in the tumour thickness, which is a significant limiting factor in PDT (7, 11).

Spraying cold water is our preferred method to relieve pain during irradiation. It has been recently reported that warming the skin may increase the effectiveness of ALA-PDT (12). It remains to be determined whether the use of cold to alleviate pain during irradiation impairs the effectiveness of PDT. Oral analgesia or local anaesthesia are frequently used to improve tolerance and adherence to PDT (13) but is permitted only in the absence of vasoconstrictors in order to preserve an adequate flow of oxygen to the lesion during treatment. However, we report here for the first time that local, but not troncular, anaesthesia may diminish the PDT response. The explanation for this effect may be that all local anaesthetics have pH values >7.4, and ALA and its precursor MAL are unstable in neutral or basic pH media or an inadequate light penetration of the tissue is another mechanism that may account for the reduced effectiveness of PDT.

The main limitation of our study is its retrospective design, which implies variable durations of follow-up.

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The authors have no conflict of interest to declare.

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