The sap from *Euphorbia peplus* is effective against human nonmelanoma skin cancers


Mater Radiation Oncology Centre, Brisbane, Qld, Australia

*Queensland Institute of Medical Research, Post Office Royal Brisbane Hospital, Brisbane, Qld 4029, Australia
†Griffith Medical Research College, Griffith University, Brisbane, Qld, Australia
‡Peplin Biotech Ltd, Brisbane, Qld, Australia

Summary

Background The sap from *Euphorbia peplus*, commonly known as petty spurge in the U.K. or radium weed in Australia, has been used as a traditional treatment for a number of cancers.

Objective To determine the effectiveness of *E. peplus* sap in a phase I/II clinical study for the topical treatment of basal cell carcinomas (BCC), squamous cell carcinomas (SCC) and intraepidermal carcinomas (IEC).

Methods Thirty-six patients, who had refused, failed or were unsuitable for conventional treatment, were enrolled in a phase I/II clinical study. A total of 48 skin cancer lesions were treated topically with 100–300 μL of *E. peplus* sap once daily for 3 days.

Results The complete clinical response rates at 1 month were 82% (*n* = 28) for BCC, 94% (*n* = 16) for IEC and 75% (*n* = 4) for SCC. After a mean follow-up of 15 months these rates were 57%, 75% and 50%, respectively. For superficial lesions < 16 mm, the response rates after follow-up were 100% for IEC (*n* = 10) and 78% for BCC (*n* = 9).

Conclusions The clinical responses for these relatively unfavourable lesions (43% had failed previous treatments, 35% were situated in the head and neck region and 30% were > 2 cm in diameter), are comparable with existing nonsurgical treatments. An active ingredient of *E. peplus* sap has been identified as ingenol mebutate (PEP005). This clinical study affirms community experience with *E. peplus* sap, and supports further clinical development of PEP005 for the treatment of BCC, SCC and IEC.

The spurge family (*Euphorbiaceae*) contains around 7500 plant species, with several traditionally used for medicinal purposes. *Euphorbia peplus*, commonly known as petty spurge in the U.K. or radium weed in Australia, has a long history of use for a variety of conditions. The sap from this plant has been used as a purgative and as a treatment for warts, corns, waxy growths, asthma, catarrh, skin cancers, and cancers of the stomach, liver and uterus. A single case of the home treatment of basal cell carcinoma (BCC) has been reported, and in a survey of home remedies for skin cancer and solar keratoses, topical treatment with the sap was unanimously considered to be effective by the users. The long history of community use with the absence of documented side-effects, except in cases of accidental ocular exposure, permitted the initiation of a phase I/II trial of topical *E. peplus* sap for non-melanoma skin cancer.

Materials and methods

Patients

Consenting patients were recruited from individuals attending the Radiation Oncology Mater Centre outpatients department during 2000–2. Ethical approval was obtained from the Mater Adults Hospital Ethics committee; Peplin Biotech Pty Ltd sponsored the trial. Patients entering the study had one or more histologically confirmed BCC, intraepidermal carcinomas (IEC) or squamous cell carcinomas (SCC). The study was restricted to patients who had failed previous treatments (surgery, radiotherapy, fluorouracil 5% cream and/or liquid nitrogen) and refused surgical treatment (43%), and patients who were deemed unsuitable for surgical treatments (due to multiple nature and site of the lesions, age, anticoagulant use and other
Euphorbia peplus sap is effective against skin cancers, J.R. Ramsay et al.

comorbidities; 57%). Other inclusion criteria for the study were age > 18 years, having measurable disease and giving informed consent. Exclusion criteria were pregnancy, having a serious nonmalignant systemic disease, uncontrolled infection and lesions close to the eye.

Lesions were treated topically once daily for three consecutive days by the oncologist using a cotton bud to apply sufficient sap to cover the surface of each lesion (100–300 μl depending on size). Care was taken to prevent the liquid dispersing to the adjacent skin. A transparent waterproof dressing (OpSite Flexigrid or Post-Op; Smith & Nephew, London, U.K.) was used to cover the skin lesion between applications. At 1, 6 and 12 months post-treatment, the lesions and patients were examined by the treating oncologist for treatment responses and skin and systemic toxicity, respectively. Patients showing complete clinical response (CCR) were asked to undergo a biopsy of the treated area using a 2–4-mm punch biopsy. Histological sections were examined at the Mater Hospital pathology department. Patients having a partial response to the first treatment were offered a second course.

Role of the funding source

Peplin Biotech acted as monitor and sponsor and was responsible for the supply of E. peplus. Peplin Biotech did not participate in the detailed design of the studies, or the data collection, analysis and interpretation, or the writing of the manuscript.

Results

Clinical responses

Thirty-six patients with BCC, SCC or IEC were enrolled. Forty-eight lesions were treated: 28 patients had one lesion, 5 patients had two lesions, 2 patients three lesions and 1 patient four lesions. The average age of the cohort was 69 years (range 44–93). The mean diameter of the treated lesions was 16 mm (range 5–30). Lesions were located on the head and neck (17, 43%), arms (7, 15%), trunk (10, 21%) and legs (14, 29%).

Lesions were assessed by the oncologist at 1 month after treatment; CCR was defined as the absence of tumour after clinical examination (Table 1; Fig. 1). Patient consent was obtained for biopsy of 30 lesions that had shown a CCR (Table 1). Ten lesions showing a partial response at 1 month received a second course 1–3 months later; three showed a complete response at the last follow-up (nine were biopsied). Lesions showing a CCR were followed up for 2–31 months (mean 15 months). Two patients with single lesions were lost to follow-up at 2 and 5 months.

The outcome of treatment of individual lesions at last follow-up was a 57% complete response for BCC, 75% for IEC and 50% for SCC (Table 1). For superficial lesions < 16 mm, the response rates at last follow-up were 100% for IEC (n = 10) and 78% for BCC (n = 9).

Table 1 Number of lesions showing complete clinical response (CCR), partial clinical response (PCR) and stable disease (SD) at 1 month, and complete response at last follow-up. None of the lesions showed progressive disease

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Number of lesions</th>
<th>Clinical response at 1 month*</th>
<th>Biopsy histology (no. negative/no. tested)</th>
<th>Complete response at last follow-upb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CCR</td>
<td>PCR</td>
<td>SD</td>
</tr>
<tr>
<td>BCC</td>
<td>28</td>
<td>23  (82)</td>
<td>5  (18)</td>
<td>0</td>
</tr>
<tr>
<td>IEC</td>
<td>16</td>
<td>15  (94)</td>
<td>0</td>
<td>1  (6)</td>
</tr>
<tr>
<td>SCC</td>
<td>4</td>
<td>3  (75)</td>
<td>0</td>
<td>1  (25)</td>
</tr>
</tbody>
</table>

The percentage figures represent the percentage of lesions within each of these response categories for each tumour type. BCC, basal cell carcinoma; IEC, intraepidermal carcinoma; SCC, squamous cell carcinoma. aAfter one or two treatment courses. bComplete response at last follow-up refers to the number and percentage of treatment sites showing an absence of tumour on clinical examination and/or histology at 2–31 months (mean 15) post-treatment. Six were nodular and 22 superficial.

Treatment site reactions

The post-treatment local acute skin toxicity was zero in 6%, erythema in 6%, dry skin desquamation in 51%, patchy moist desquamation in 28% and necrosis in 9%. Skin reactions returned to normal within 1 month for 62% of the lesions and thereafter only mild erythema persisted for an average of 4 months for 38% of the lesions. No pain was reported by 43% of patients, 37% reported mild pain, 14% reported moderate pain and severe pain (requiring analgesics) was reported by one patient (6%) who was treated for a 10 × 4-cm area of SCC and IEC of the scalp. When encountered, pain was always localized to the site and lasted from 2 h to 2 days.

In all cases of successful treatment, a favourable cosmesis was observed (data not shown and Fig. 1).

Discussion

The cohort enrolled for this study comprised a group of patients with relatively unfavourable lesions. Forty-three per cent of lesions had failed previous treatments, 35% were situated in the head and neck region, and 30% were > 2 cm in diameter. Each of these characteristics has been associated with an approximate twofold increase in recurrence rates.6 Treatment with E. peplus sap in this difficult to treat cohort resulted in a complete response of 50–75% at the last follow-up (Table 1). For superficial lesions < 16 mm, the response rates...
after follow-up were 100% for IEC (n = 10) and 78% for BCC (n = 9). The results are thus comparable with existing non-surgical modalities, with treatment also associated with low toxicity and favourable cosmesis. However, surgical removal of the treated site to demonstrate cure was not undertaken as this cohort had refused or were unsuitable for surgery.

Ingenol mebutate (PEP005) has been identified as an active compound in the sap of \textit{E. peplus}. Sap contains \approx 200 μg mL\textsuperscript{-1} (data not shown). Purified PEP005 at 500 μg mL\textsuperscript{-1} in a gel formulation was effective in phase II clinical studies as a topical agent for the treatment of actinic keratoses\textsuperscript{11,12} and superficial BCC.\textsuperscript{13} PEP005 treatment induces inflammation, primary necrosis of tumour cells and recruits neutrophils, which appear to reduce relapse by destroying residual malignant cells.\textsuperscript{10,14,15}

This clinical study affirms community experience with \textit{E. peplus} sap,\textsuperscript{3,4} and supports further clinical development of PEP005 for the treatment of BCC, SCC and IEC.

\textbf{What's already known about this topic?}

- Anecdotal reports of community use of \textit{Euphorbia peplus} sap for skin malignancies suggest it may be effective as a topical treatment for nonmelanoma skin cancers.
- Ingenol mebutate (PEP005) has been identified as an active ingredient of \textit{E. peplus} sap.

\textbf{What does this study add?}

- This clinical study affirms the community experience with \textit{Euphorbia peplus} sap, and supports further clinical development of PEP005 for the treatment of basal cell carcinomas, squamous cell carcinomas and intraepidermal carcinomas.
Acknowledgment

We thank Jenny Johns for sap analysis.

References

11. Anderson L, Schmieder GJ, Werschler WP et al. Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. J Am Acad Dermatol 2009; 60:934–43.
14. Li L, Shukla S, Lee A et al. The skin cancer chemotherapeutic agent ingenol-3-angelate (PEP005) is a substrate for the epidermal multidrug transporter (ABCB1) and targets tumor vasculature. Cancer Res 2010; 70:4509–19.

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