Title of study: A trial comparing Metvix photodynamic therapy (PDT) followed by Mohs micrographic surgery with Mohs micrographic surgery alone for the treatment of basal cell carcinoma (BCC)

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Study and R&D number: RJ1 06/0017

Date of favourable ethical opinion: 05/12/2005

Commencement date of the trial: 08/05/2005

Study protocol:

The main objective of the study was to assess whether the combination of PDT followed by Mohs micrographic surgery (MMS) is superior to MMS alone in treating BCC in terms of reducing the post Mohs defect and the mean number of stages required to achieve clearance. This was a single-centre, open, randomised, controlled pilot study. The main inclusion criteria were male or female subjects older than 18 years of age with the diagnosis of BCC and requiring treatment with MMS.

Investigational product:

Topical Methyl aminolevulinate (Metvix®) is a cream that acts as a photosensitizer which when followed by light in a specific wavelength causes a phototoxic reaction that can lead to the destruction of tumour cells. Metvix was applied topically (1 mm thick layer) on BCC under occlusion. Two treatments seven days apart are required. In the arm of PDT followed by MMS, this treatment was applied anytime between two to 10 weeks prior to MMS. The other arm of the study involved MMS alone and this procedure may require several stages until tumour clearance has been achieved.

Treatment schedule and follow-up:

All patients who entered the trial had an initial screening visit. Once informed consent for participation in the study was obtained, patients were randomised to either arm. In the arm of

MMS, the procedure was performed within 3 months of the baseline screening visit. Subsequently, all patients were followed up a week afterwards as part of the wound care with regular follow-ups in 3, 6, and 12 months following treatment.

In the arm of PDT followed by MMS two sessions of PDT treatment were applied one week apart within two months of the initial baseline screening visit with MMS being performed within two to ten weeks following PDT treatment. The follow-up schedule was similar to the MMS arm with visits after 3, 6, and 12 months. The trial was subsequently adjusted so that the final follow-up took place at six months following treatment.

Background and rationale for the study:

BCC is a common malignant tumour affecting predominantly the head and neck regions in white skin types. Although it has a very low mortality rate, it can cause significant morbidity by local tissue destruction and invasion which can lead to disfigurement. Several clinical and histological subtypes exist; including superficial, nodular, infiltrative, and morphoeic. MMS was originally described in 1940 as a way of excising difficult tumours. The technique initially involves removing or debulking the visible tumour by excision or curettage and the remaining wound surface is then excised as a saucer shaped piece of skin, one to two millimetres thick. The specimen is subsequently cut into smaller pieces called sections, allowing for histological examination using horizontal sections enabling the examiner to examine the entire excision margin. This is often done on frozen sections, although paraffin-embedded sections are also used in certain occasions where frozen sections may limit the accurate interpretation of the slides. Following initial histological assessment, in case of residual tumour being identified, the involved margin is re-excised and the process repeated until no further tumour is evident. The advantages of MMS include both accurate removal of the tumour and maximal tissue preservation. The overall 5-year cure rate is around 99% for primary BCC and around 95% for recurrent BCCs and therefore MMS is considered the treatment of choice for high risk BCCs including certain sites such as the ears, lips, nose and eyes, aggressive histological subtypes such as morphoeic, micronodular and infiltrative, size greater than 2 cm, recurrent BCCs, and BCCs with perineural invasion.

Other treatment modalities include; predetermined margins surgical excision, curettage and cautery, cryotherapy, radiotherapy, and PDT. Topical PDT is a pharmacological treatment modality for certain types of BCCs. Following absorption of the applied topical photosensitizer, destruction of targeted cells and apoptosis occurs once activated by a specific light source that works through the formation of endogenous photoactive porphyrins. It is an established treatment for actinic keratoses and superficial BCCs and its main advantages are the excellent cosmesis with little or no scarring.

Topical PDT as an adjunct to MMS has been used in a series of four cases published by Kuijpers *et al.* In their cases, PDT was used after MMS in the event of residual superficial BCC on the section rather than performing a further stage of MMS. This allowed for smaller wound defects and therefore better cosmesis. Follow-up for a period of up to 27 months showed no

recurrences. Another study showed Metvix® PDT to be an effective therapeutic modality in BCCs difficult to treat by conventional means. This included large lesions (greater or equal to 15mm on the face or extremities and greater or equal to 20mm on the trunk), ones in the H-zone of the face, on the ear or in any patient with a high risk of surgical complications due to bleeding abnormalities. Overall, there was a complete lesion response rate of 90% at three months, 84% at 12 months, and 78% at 24 months with 84% of patients considering the cosmetic outcome as good or excellent at 24 months. In one patient, PDT was used as an adjunct to MMS for a lesion measuring more than 30mm on the temple. Following PDT, the lesion reduced in size substantially allowing for MMS to be much more limited in extent.

Our pilot study aims to build on this concept and assesses whether there is an advantage to using PDT prior to MMS for the treatment of BCCs, in terms of reducing the post-operative wound defect as well as the number of stages required.

Results:

A total of 19 patients were recruited into the study (95% recruitment target). There were 9 men and 10 women. The age range was 41 to 89 (mean age of 62). Table 1 summarizes all the findings of the trial. The majority of the subtypes was nodular (n=15, 79%). A total of nine patients were randomised to the PDT followed by MMS arm, of whom two withdrew from the study; giving rise to a total of seven patients who completed treatment in the PDT arm. The remaining 10 patients were randomised to the MMS arm, all of whom completed the treatment. This makes a total of 17 patients who completed the treatment (89%), 13 of whom completed the required follow-up period of six months (68%). In the PDT arm, four out of the seven treated patients (57%) had their initial tumour size decreased following PDT treatment prior to MMS. This was similarly the case with surface area size of the tumour. The average number of stages in the PDT arm was 1.85, compared to 2.5 in the MMS arm. The average number of sections in the PDT arm was 4.2, in comparison to 5.2 in the MMS arm.

A total of two patients withdrew from the study (11%), one due to unexpected adverse reaction to the topical Metvix® cream in the PDT arm. All patients were satisfied with the resultant scar from the procedure, with no differences between the two arms. As mentioned earlier, 13 patients (68%) completed the required follow-up at six months. None of the 19 patients had any clinical recurrence(s) observed.

Conclusion:

Our study was a pilot trial involving a relatively small number of patients. Despite this, our findings show that treatment with PDT did decrease the size of the tumour prior to MMS and that on average the PDT-treated patients had fewer stages and sections of MMS in comparison to patients who received MMS alone.

Our target recruitment of 20 patients was not met owing to difficulties in recruitment into the study. This may reflect the difficulties faced in recruiting patients when a single centre is involved. The dropout rate during the trial was relatively low (10%), though only one patient (5%) discontinued due to adverse events. More than two-thirds of the initially recruited patients completed the study with the designated periods of scheduled follow-ups (68%). Though not expected due to the overall high cure rates with MMS, no recurrences of clinically evident tumours were observed in any of the patients in both arms.

In conclusion, our pilot study confirms the previously published observations of a favourable role for PDT as an adjunct in MMS in the treatment of BCCs. Larger trials, preferably multi-centred are desired to examine the role of PDT prior to MMS.

Table 1: summary of results of the trial

Patient	**Age**	**Sex**	**Subtype**	**Baseline size(mm)/ Area(**mm^2**)**	**PDT**	**Post PDT size(mm)/Area (**mm^2**)**	**Stages**	**Sections**	**Post MMS size(mm)/Area(**mm^2**)**
1	84	F	nodular	12 x 16 (180)	yes	12 x 11 (170)	1	2	14 x 19 (300)
2	57	F	nodular	12 x 10 (170)	no	n/a	5	10	20 x 25 (400)
3	52	F	infiltrative	14 x 19 (150)	yes	xx	xx	xx	xx
4	60	M	infiltrative	11 x 16 (160)	no	n/a	2	5	15 x 27 (400)
5	89	M	nodular	11 x 13 (130)	no	n/a	2	4	17 x 25 (400)
6	47	M	nodular	10 x 22 (220)	no	n/a	1	4	28 x 8 (**)
7	72	F	nodular	13 x 8 (115)	yes	12 x 9 (100)	2	6	19 x 48 (**)
8	44	F	nodular	12 x 10 (115)	yes	12 x 10 (115)	2	4	17 x 17 (190)
9	46	F	adenoid	10 x 10 (80)	yes	xx	xx	xx	xx

10	74	F	nodular	11 x 15 (150)	no	n/a	2	3	17 x 23 (325)
11	81	F	nodular	13 x 16 (125)	no	n/a	3	4	20 x 32 (525)
12	61	F	nodular	12 x 20 (240)	yes	11 x 18 (160)	2	4	18 x 33 (380)
13	64	M	nodular	17 x 27 (263)	yes	17 x 22 (237)	2	7	39 x 40 (1000)
14	54	F	micro-nodular	11 x 22 (240)	no	n/a	2	3	25 x 35 (510)
15	51	M	nodular	10 x 11 (110)	yes	10 x 11 (110)	2	4	12 x 15 (180)
16	41	M	nodular	12 x 14 (110)	no	n/a	2	3	14 x 18 (240)
17	79	M	nodular	11 x 19 (225)	yes	11 x 9 (100)	2	4	16 x 19 (200)
18	51	M	nodular	12 x 13 (150)	no	n/a	4	11	36 x 46 (625)
19	73	M	nodular	17 x 24 (325)	no	n/a	2	5	22 x 34 (760)

xx patient withdrew from study

** not measured