Surgery Versus 5% Imiquimod for Nodular and Superficial Basal Cell Carcinoma: 5-Year Results of the SINS Randomized Controlled Trial

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We previously reported modest clinical 3-year benefit for topical imiquimod compared with surgery for superficial or nodular basal cell carcinoma at low-risk sites in our noninferiority randomized controlled SINS trial. Here we report 5-year data. Participants were randomized to imiquimod 5% cream once daily (superficial basal cell carcinoma, 6 weeks; nodular basal cell carcinoma, 12 weeks) or excisional surgery (4-mm margin). The primary outcome was clinical absence of initial failure or signs of recurrence at the 3-year dermatology review. Five-year success was defined as 3-year success plus absence of recurrences identified through hospital, histopathology, and general practitioner records. Of 501 participants randomized, 401 contributed to the modified intention-to-treat analyses at year 3 (primary outcome), 383 (96%) of whom had data at year 5. Five-year success rates for imiquimod were 82.5% (170/206) compared with 97.7% (173/177) for surgery (relative risk of imiquimod success = 0.84, 95% confidence interval = 0.77−0.91, $P < 0.001$). These were comparable to year 3 success rates of 83.6% (178/213) and 98.4% (185/188) for imiquimod and surgery, respectively. Most imiquimod treatment failures occurred in year 1. Although surgery is clearly superior to imiquimod, this study shows sustained benefit for lesions that respond early to topical imiquimod.

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INTRODUCTION

Basal cell carcinomas (BCCs) are the most common form of human cancer, with an estimated 1 million cases diagnosed each year in the United States (Prieto-Granada and Rodriguez-Waitkus, 2015). The incidence of BCC is rising by around 10% each year (Karagas and Greenberg, 1995) in white populations, such as those living in Australia (Perera et al., 2015), yet poor registration of BCC makes it difficult to compare estimates across the world (Hay et al., 2014). A range of genetic factors have been associated with BCC and recurrent BCC (Madan et al., 2010), but unlike cutaneous squamous cell carcinoma, the relationship between sun exposure patterns and different types of BCC is still unclear. Although deaths from BCC are rare (Boyers et al., 2014), considerable morbidity may result because of the local aggressive nature of BCC and BCC recurrences (Hollestein et al., 2014). Trends toward aging populations mean that the supply of appropriate treatment such as excisional surgery may be stretched in state-run health care systems such as the UK National Health Service, and it has been estimated that the number of patients presenting to dermatologists will increase by 50% by 2030 (Madan et al., 2010). Such a trend has resulted in guidance for more family practitioners to provide treatment for low-risk lesions in the community (Fremlin et al., 2016). Although excisional surgery remains the criterion standard for most common types of BCC, a range of nonsurgical approaches is available, including photodynamic therapy (Wang et al., 2015), topical imiquimod cream, topical 5-fluorouracil, and topical ingenol (Clark et al., 2014). We previously published the 3-year results of an independent comparison of topical imiquimod versus excisional surgery for the treatment of low-risk superficial and nodular BCC in the SINS trial (Bath-Hextall et al., 2014). Although the topical imiquimod response rate of 84%, compared with 98% for surgery, failed to meet our predefined noninferiority margin of a relative risk of 0.87, it nevertheless offered a potentially useful treatment option that may be suitable for first treatment of low-risk BCC in the community, with recurrences being dealt with by specialists through more sophisticated treatments such as excisional surgery or Mohs micrographic surgery. One major concern with nonsurgical topical treatments is that the visible superficial portions of a

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Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; PDT, photodynamic therapy; RCT, randomized controlled trial

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BCC may appear to clear on early clinical inspection, only for invasive BCC to emerge some years after treatment. We previously called this phenomenon "submarine lesions" (Williams, 2014). There are additional concerns that some forms of topical chemotherapy, such as 5-fluorouracil, may alter the biological behavior of BCC from a simple to a more difficult to treat lesion such as a morphoeic BCC (Xiong et al., 2014). For these reasons, it is important to follow up BCC trial participants for at least 5 years. Here, we report the 5-year follow-up results of the SINS study participants using histopathology and health care records.

RESULTS

Participants were recruited between June 19, 2003, and February 22, 2007, with 3-year follow-up at the clinic from June 26, 2006, to May 26, 2010, and 5-year follow-up of hospital, general practitioner, and histopathology records completed in 2012. Participant characteristics have been published in the previous 3-year data reports (Bath-Hextall et al., 2014). Participant flow from randomization to 5 years is shown in the Figure 1. A total of 18 patients did not have usable data at year 5. In the imiquimod group, three had died, and we could not determine if recurrence had occurred in four (three not sure from records and one visit not done). In the surgery group, six had died, and we could not determine if recurrence had occurred in five (three not sure, one visit done too early, and one not done).

Recurrences recorded at 5 years compared with 3 years are shown in Table 1, broken down into early treatment failures and later recurrences as recommended in previous correspondence to our article (Bassukas and Gaitanis, 2014). Additional recurrences between 3 and 5 years were small, with one additional recurrence for a superficial BCC treated with imiquimod and one for surgery. Histological subtype was unknown for the one recurrence on topical imiquimod (patient was treated with cryotherapy) and was recorded as superficial BCC for the one recurrence on surgery.

DISCUSSION

The 5-year follow-up data from the SINS study do not suggest a progressive rise in BCC recurrences between years 3 and 5, nor do they suggest that recurrences in the imiquimod group were difficult to spot or that they had transformed from superficial to morphoeic forms, as is the concern with some other topical treatments such as photodynamic therapy (PDT) (Bernabo et al., 2016; Xiong et al., 2014). Most treatment failures with topical imiquimod occurred in the first year of treatment, a finding that throws light on the possible mechanisms of topical immunotherapy for skin cancer, suggesting that once an immunological response has occurred, such a response is sustained. The new data presented in this report do not lend any support to concerns of "submarine" lesions emerging on the skin surface years after early apparent clinical benefit of topical treatment. The absolute response rate for topical imiquimod of 83% at 5 years, although clearly inferior to the 98% for excisional surgery for low-risk BCC, might still represent a clinically useful treatment modality, because a cream treatment can be carried out in a primary care setting, and some patients may also prefer the option of a cream rather than surgery.

Clark et al. (2014) summarized 29 randomized controlled trials (RCTs) and seven systematic reviews of the comparative effectiveness of treatments for BCC published through August 2013 from four databases and cite PDT, topical imiquimod, cryotherapy, and topical 5-fluorouracil as suitable treatment options for primary low-risk lesions. They found insufficient evidence to make recommendations on the use of topical ingenol mebutate, solasodine glycoalkaloids, IFN-α, or intralesional 5-fluorouracil, and no RCT evidence on electrodesiccation and curettage, which is a commonly used procedure for low-risk BCC. Wang et al. (2015), in their systematic review of RCTs of PDT for BCC published through October 2013, found eight studies, two of which included a comparison with surgical excision with 5-year follow-up data. The first of these was an RCT by Rhodes et al. (2007) that compared topical methyl aminolevulinate photodynamic therapy versus simple excision surgery for primary nodular BCC in 97 patients. They estimated a sustained lesion complete response rate of 76% (95% confidence interval [CI] = 59−87%) and 96% (95% CI = 84−99%) for PDT and surgery, respectively, at 5 years. Inspection of the time to event analysis in that study showed a steady increase in recurrences throughout the 5-year follow-up, rather than a pattern of early treatment failures and low recurrences thereafter, as seen for topical imiquimod in this SINS study. The other RCT, which evaluated fractionated 20% 5-aminolevulinic acid−PDT with prior partial debulking versus surgical excision in nodular BCC in 151 patients with nodular BCC (Roozeboom et al., 2013), showed a cumulative probability of recurrence of 30.7% (95% CI = 21.5−42.6%) for 5-aminolevulinic acid−PDT and 2.3% (95% CI = 0.6−8.8%) for surgical excision, but much lower rates of recurrence for tumors at or less than 0.7 mm thick. Their Kaplan-Meir plot suggested a steeper slope for recurrences over years 1−3. Another systematic review of interventions for superficial BCC in 2012 found pooled estimates from 23 randomized and nonrandomized studies of 87.3% for imiquimod (95% CI = 84−91%) and 84.0% for PDT (95% CI = 78−90%) (Roozeboom et al., 2012). A subsequently published noninferiority RCT performed a head-to-head comparison between topical 5-fluorouracil, topical 5% imiquimod, and methyl aminolevulinate-photodynamic therapy in 601 patients with superficial BCC, followed up for 1 and 3 years (Arits et al., 2013; Roozeboom et al., 2016). They found that tumor-free survival at 3 years post-treatment was 58.0% for methyl aminolevulinate-PDT (95% CI = 47.8−66.9), 68.2% for topical fluorouracil (95% CI = 58.1−76.3), and 79.7% for imiquimod (95% CI = 71.6−85.7), with clear evidence that topical imiquimod was superior to methyl aminolevulinate-PDT (treatment failure hazard ratio for imiquimod compared with methyl aminolevulinate-PDT was 0.50, 95% CI = 0.33−0.76, P = 0.001). Tumor thickness does not seem to predict treatment failure for topical imiquimod, PDT, or topical 5-fluorouracil (Roozeboom et al., 2015). We have been unable to identify any further trials comparing topical imiquimod versus other active therapies for the treatment of low-risk nodular or

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