Discuss the impact of targeted molecular skin cancer therapies on dermatological surgery

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"There is no remedy for the black cancer, the only chance for benefit depends on the early removal of disease by operation."

Samuel Cooper, 1840

Introduction

Samuel Cooper, a general surgeon for University College London Hospitals, described the poor prognosis and limited treatment options for advanced melanoma skin cancer in the 19th century[1]. His words remained true for advanced skin cancer in the majority of the intervening years, despite great leaps of progress in science and medicine. Chemotherapy and immunotherapy have been used with varying degrees of success, however, more recently, targeted molecular therapies are proving to be a revolutionary addition to the armamentarium of treatments. As in Samuel Cooper's time, early diagnosis and prompt surgical removal is still the mainstay of treatment for the vast majority of skin cancer in the 21st century, so how far will targeted molecular skin cancer therapies disprove Samuel Cooper's observations? How will they impact dermatological surgery?

What are targeted molecular skin cancer therapies?

Targeted molecular skin cancer therapies are molecules designed to interact with specific proteins that play a key role in cancer development and growth, derived from molecular cancer research. For example, vismodegib is a targeted molecular therapy developed from the study of the genetic basis of nevoid basal cell carcinoma syndrome, a condition where numerous basal cell carcinomas (BCCs) develop[2]. BCCs are a type of

nonmelanoma skin cancer (NMSC) (see Table 1). In almost all cases of BCC the activation of the Hedgehog pathway (Hh) (see Figure 1 for detail) leads to tumorigenesis[3,4]. Therapies such as vemurafenib are being used in the treatment of cutaneous malignant melanoma (MM), a highly aggressive cancer (see Table 1) that often arises from the V600E mutation that activates an oncogene called BRAF[1].

Table 1. Overview of basal cell carcinoma and melanoma

	Basal Cell Carcinoma	**Melanoma**
Epidemiology	• Most common type of cancer in Caucasians • Accounts for 75% of all skin cancers[5] • Incidence increases with age	• Third most common type of skin cancer • 84% are localised melanoma at presentation[6] • One third of cases of malignant melanoma occur in people aged under 55[7]
Presentation	• Commonly on sun exposed sites- head and neck • Slow growing • Often metachronous	• A new or changing mole • Commonly occurs on the legs, trunk and back
Treatment	• Numerous treatment options, of which surgical resection and radiotherapy appear to be most effective[8] • A surgical challenge as may be close to sites such as eye, nose, and ears • Resection of large BCC may be cosmetically disfiguring and cause significant morbidity	• Surgical excision unless too advanced • Consider chemotherapy, immunotherapy, or targeted molecular therapy for advanced disease
Prognosis	• 5% recurrence rate • Metastasis is extremely rare, the literature reports it to be between 0.0028 and 0.55%[9,10]	• 5 year survival for localised melanoma is 98%[6] • 5 year survival of disseminated metastatic melanoma is poor at <5%[11]

Indications, efficacy and safety of targeted molecular skin cancer therapies

Targeted molecular therapies are used in advanced or metastatic cases of skin cancer, where surgical resection is inappropriate. Currently, focus is on their use in advanced or metastatic MM and BCC (see Table 2 for examples of targeted molecular therapies for different types of skin cancer).

Table 2. Examples of targeted molecular therapies for different skin cancer types

Skin cancer type	Target molecule	Targeted therapy
Melanoma	BRAF ^{V600E}	Vemurafenib
	MEK	Trametinib
	C-Kit	Sorafenib
Basal cell carcinoma	Smoothened (SMO)	Vismodegib
		Sonidegib
	EGFR	Cetuximab
Squamous cell carcinoma	EGFR	Cetuximab
Dermatofibrosarcoma protuberans	PDGFR	Imatinib
Kaposi's sarcoma	mTOR	Sirolimus

One third of patients with locally advanced BCC (for whom surgery or radiotherapy is inappropriate) demonstrate a complete response to vismodegib. Metastatic BCC is extremely rare but highly aggressive disease, yet vismodegib was found to result in a complete response in 2 of 29 patients[12]. We do not yet have data for the long term follow up of these patients, however, resistance is beginning to be described, as treatment times are long. The median length of response to vismodegib was 7.6 months in a study with both advanced and metastatic BCC[13]. Sonidegib, and cetuximab have been tried as alternative targeted therapies for BCC with less success[14,15].

Despite initial, almost miraculous responses to BRAF inhibitors for MM, resistance quickly develops because of the multiple survival mechanisms evading BRAF inhibition. In patients that initially respond to the drug, survival is somewhat extended, for example, by 5.3 months in one phase three trial with vemurafenib[16]. Combinatorial approaches are

now being used to overcome resistance and achieve greater success. For example a MEK inhibitor used in addition to a BRAF inhibitor in one trial extended progression-free survival by three months more than a BRAF inhibitor alone[17]. The use of combinations of targeted therapy may have implications on safety profile, tolerability, and cost. However, MM tends to affect people who are relatively young and healthy, and thus the cost and side effects of the drugs must be weighed up against the potential benefit. The molecular heterogeneity of melanoma makes it likely that many more molecular target therapies will emerge as research continues.

Whilst targeted molecular therapies should target cancerous cells specifically, in contrast to the cytotoxic brushstroke of chemotherapy, their considerable side effect profile still limits use. The STEVIE trial investigating vismodegib for advanced BCC (where surgery was contraindicated or inoperable) found that 98% of patients experienced at least one adverse event (AE) from the drug, such as muscle spasms, alopecia, dysguesia and weight loss[12]. Less than half of the patients who stopped taking vismodegib due to AEs had demonstrated complete response to the drug[12]. It is interesting to note that there is some subjectivity in the assessment of patients who are inappropriate for surgery or radiotherapy with locally advanced BCC. Dermatological surgeons may find that marketing from 'big pharma' influence their treatment decisions, however, joint patient and doctor decisions should incorporate a critically appraised evidence base. Long term follow up data is not yet available for vemurafenib for unresectable or metastatic MM with the V600E mutation, however, known side effects perversely include the development of squamous cell carcinoma (SCC)[18], as well as arthralgia, rash, and alopecia.

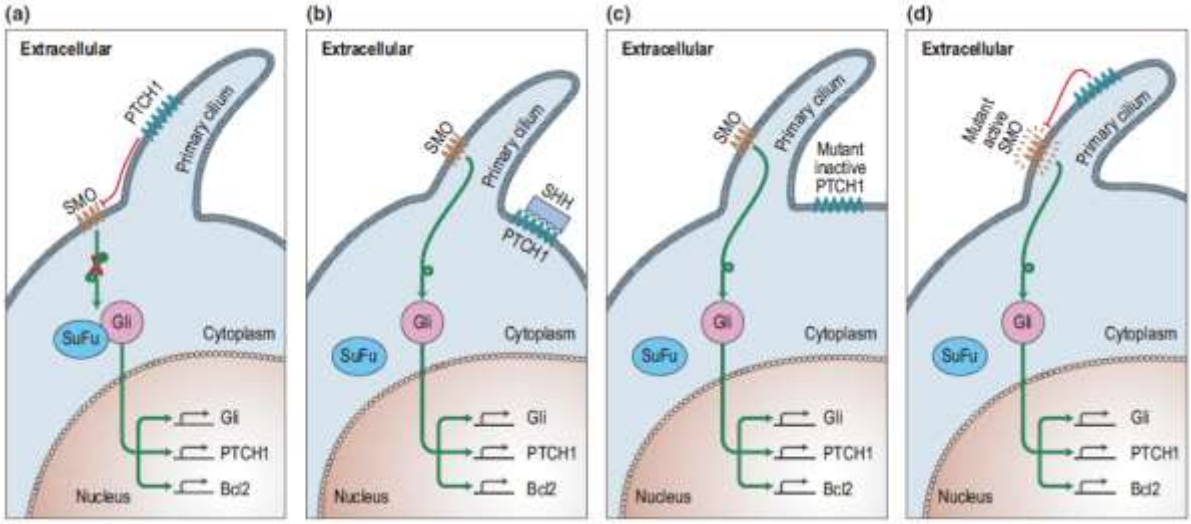

Figure 1. The Hedgehog (Hh) signaling pathway. a) Without Hh, PATCHED1 (PTCH1) inhibits the activity of Smoothened (SMO). b) If PTCH1 binds to soluble protein Hh (SHH), PTCH1 cannot suppress SMO, and SMO activates the Hh signaling cascade. c) The majority of BCCs have PTCH1-inactivating mutations d) and a minority have SMO-activating mutations.[19]

How will targeted molecular skin cancer therapies impact upon dermatological surgery?

Currently, the patients that are eligible for molecular target therapies are not candidates for skin surgery, little affecting the caseload or techniques of dermatological surgery. However, molecular target therapies as adjuvant treatments in order to shrink cancers to a resectable size are beginning to be explored. The use of vismodegib and BRAF-inhibitors as an adjuvant to surgical treatment of locally advanced BCC and MM is being investigated in clinical trials. Recurrence is a concern, as cells that have metastasised early may avoid the targeted therapy[20], or the therapy may leave islands of cancerous cells distant from the surgical site[19]. In both situations, cancerous cells elude surgical resection. A single-arm trial investigating the use of neoadjuvant vismodegib for locally advanced BCC reported one patient out of eleven having recurrence at 17 months after Mohs micrographic surgery (MMS)[21]. This outcome may have been predicted by short treatment times and recurrent (rather than primary) BCCs. Should adjuvant use of

molecular therapies prove successful, a greater proportion of skin cancers will be eligible for surgery, and greater multidisciplinary collaboration between dermato-oncology and dermatological surgery will be needed in order to make increasingly complex clinical decisions. In addition, MMS is likely to be the preferred surgical technique, to which dermatological surgeons will need to adapt.

Targeted molecular therapies are the cornerstone of precision medicine, and dermatological surgery may further need to learn new techniques and methods in order to keep up with advancing science. Non-invasive imaging techniques such as fluorescence confocal microscopy can rapidly and sensitively evaluate BCC tumour histology and margins[22], and definitely treat at presentation without biopsy. In future, similar imaging techniques may be used in advanced cases, and in other types of skin cancer. Whole-exome sequencing of melanoma has now been carried out[23], and with this new information, our understanding of the genetic basis of melanoma has increased. As the costs of genomic analysis fall further, genomic, exome, RNA, or epigenetic sequencing of skin cancers may soon be carried out on every patient, aiding skin cancer specialists in diagnosis and treatment. In the future, precise risk stratifications of skin cancers could allow a treatment plan to be made that encompasses the treatments from dermato-oncologists and dermatological surgeons together, in a multi-disciplinary model.

Despite our advancing understanding in etiology of skin cancer, the incidence of skin cancer continues to rise, and the capacity of dermatological surgery will have to increase. Melanoma incidence rates in the US doubled from 1982 to 2011, and are set to rise further to an estimated 112,300 new cases in 2030[24]. NMSC (including BCC and SCC) account for 90% of all skin cancers and registered incidence has risen by 30% in the past decade[25]. Despite rising incidence, mortality rates are predicted to remain steady until

2030[24]. This suggests that the proportion of patients who have the capacity to benefit from targeted molecular therapies will not change. However, the absolute numbers of patients requiring any treatment modality will rise, representing an enormous burden on health services. This presents a serious challenge as the ratio of consultant dermatologists to the UK general population is much lower than in the rest of Europe with 1 consultant per 130,000 [26], and dermatology training is unlikely to be increased[27]. Unless health services plan to increase the dermatologist workforce, patient access to screening and treatment may decrease. Surgeons from other specialties, who may not be appropriately trained, could increasingly perform dermatological surgery. Without early and definitive treatment from appropriately experienced surgeons, patients may unnecessarily find themselves in need of targeted molecular therapies.

Conclusion

Despite the great promise that targeted molecular therapies hold, every effort should still be made to ensure prevention and early presentation of skin cancers. Educating the public how to identify melanoma has been successful, yet further education is needed to ensure that melanoma is not the only type of skin cancer in the public's consciousness. Whilst targeted molecular therapies are prolonging survival in some patients with advanced disease, the risk of resistance and recurrence suggest that Samuel Cooper's words are not yet ready to be forgotten. Prognosis for advanced cases of skin disease remains poor. The *best* chance for benefit *still* depends on the early removal of disease by operation, and dermatological surgery remains of paramount importance.

Word count: 1500 (excluding references)

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