Local Treatment Options for BCC

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Cutaneous basal cell carcinoma (BCC) is the most common human tumour and its incidence is rising worldide. Until a few years ago, the therapeutic options were limited fo patients with advanced BCC including both metastatic and locally-advanced BCC. Over the last years, promising systemic therapies have been investigated for the treatments of advanced BCC. In particular, the Hedgehog signaling inhibition have shown remarkable results for this population. Currently, the Hedgehog inhibitors representing by vismodegib and sonidegib are approved be the Food and Drug Administration and European Medicines Agency for the treatment of both locally advanced and metastatic BCC with generally a well safety profile.

Keywords: non-melanoma skin cancers ; basal cell carcinoma ; locally-advanced BCC

1. Introduction

Non-melanoma skin cancers (NMSCs) include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), representing the most common cancers in the Caucasian population [1].

BCC, first described in 1827 [2], is the most commonly diagnosed skin cancer worldwide [3]; thus, comprising approximately 80% of NMSCs. The incidence of BCC is increasing worldwide, by approximately 1% annually [4]. The increase in incidence of BCC could be due to changes in the environment or lifestyle risk factors. The most well-known risk factor is represented by solar ultraviolet (UV) exposure, especially early in life, or as a result of intermittent exposure.

For most BCCs, including small, well-defined tumors or intermediate-sized, low-risk tumors in low-risk areas, primary treatment options usually include surgical excision, Mohs micrographic surgery, cryotherapy, and radiation therapy. Thus, the multidisciplinary approach is critical in the management of patients suffering from BCC.

Although BCC could be effectively counteracted by radical surgical excision, sometimes it can acquire aggressive hallmarks, as well as recurrence, local tissue destruction, and (infrequently) distance dissemination. In a subset of cases, BCC can become excessively invasive or destructive; these are known as advanced BCC, and are defined as BCC in which current treatment modalities are contraindicated. Patients affected by advanced BCC, including locally-advanced BCC (laBCC) or metastatic BCC (mBCC), typically had, up until a few years ago, limited therapeutic options.

In particular, advanced BCC is a common cutaneous malignancy, mostly occurring in elderly populations [5]. To this regard, factors, including social isolation and multiple comorbidities, leave the elderly population at high risk of neglecting potentially malignant skin cancers, causing them to progress to advanced diseases [6]. In this context, several factors should be considered in order to plan BCC treatment, including tumor location, size, and nature of the lesion [7]. Other clinical factors, such as symptoms, age, and performance status of the patient, as well as the cost of therapy, are also critical. Moreover, the treatment should ideally include removal of the whole tumor, with preservation of healthy tissue, function, and cosmetic appearance.

2. Local Treatment Options for BCC

Current BCC clinical practice guidelines focus on the curative intent of removing as much malignancy as possible. Unfortunately, there are no clear recommendations in clinical practices for a tailored approach for elderly patients who have special needs and priorities.

Several treatment options, including surgical excision, electrodessication and curettage, cryosurgery, imiquimod, photodynamic therapy, 5-fluorouracil, radiation therapy, Hh inhibitors, combination therapy, and observation may be considered in the BCC management.

Given the wide range of therapeutic options, the choice of the best treatment should be tailored to meet patient care goals based on their life expectancy.

2.1. Surgical Excision

Surgery with negative margins is the standard treatment for localized BCC. It has been reported that larger surgical margins, as well as the negative margin on histopathological examination, ensure better outcomes [8]. Indeed, a systematic analysis has reported that recurrence rates for 5-, 4-, 3-, and 2-mm surgical margins are 0.39, 1.62, 2.56, and 3.96 percent, respectively [9]. In addition, cumulative recurrence rate for primary BCC after surgical excisions also seems to depend on the anatomic tumor site [10]. Nevertheless, total excision has been reported to have a 5-year cure rate for BCC, as high as 98% [11].

In the surgical management of BCC in elderly populations, several factors should be taken into account. For example, wound healing after surgical procedures in geriatric patients is not as smooth as in the younger population. Indeed, it has been reported that elderly patients (>65 years) show a significant delay in the epithelialization process after a split-thickness wound, leading to increased infection risk [12][13]. Epithelialization in the elderly can be complicated by common multiple comorbidities, such as vascular disease and diabetes mellitus [14]. Furthermore, the evaluation of the elderly patient's compliance is strongly decisive in the choice of the best procedure.

Mohs micrographic surgery (MMS), a complete surgical excision with examination of margins in horizontal sections, is the preferred surgery technique for high risk BCC, because it allows the intraoperative analysis of 100% of surgical margins (differently from standard vertical margins examination). High-risk tumors include BCC on the central aspect of the face, as well as large, recurrent, or aggressive lesions in cosmetically or functionally important areas. The cure rate for MMS is estimated at 99% [11]. MMS is associated with a recurrence rate 1% and 5.6% for primary and recurrent BCC, respectively [15][16]. This recurrence rate is lower than any form of alternative local treatment.

Interestingly, both Mohs and standard surgery are well tolerated in elderly patients [17][18]. Several studies analyzed the surgical outcome of BCC in elderly patients, reporting that the BCC extension (>1 cm^2), the aggressive histology (morpheaform and micronodular), and an age over 80 years are strong predictors for two or more MMS procedures to achieve complete excision [19][20]. However, advanced age would not seem to affect the recurrence rate and the survival rate after surgery [21][22][23].

2.2. Radiation Therapy

Any type of radiation therapy, including superficial, conventional, or brachytherapy is an alternative to surgery for BCC that is not able to be eradicated with surgery, or for elderly patients with severe comorbidities who refuse it. Some studies suggest that radiotherapy has a 5-year cure rate for BCC, of 93% to 96%, which is comparable to the surgical excision in terms of cure rate [11]. However, the efficacy of radiotherapy is lower than surgical approach in terms of local relapse [24]. Adjuvant radiotherapy should be considered after primary resection in case of cartilage invasion or both perineural and bone infiltration.

2.3. Destructive Therapies

Destructive therapies with curettage and electrocautery (electrodessication), cryotherapy, cryosurgery, and laser treatment are therapeutic options for small and low-risk non-facial BCC.

Curettage and electrodesiccation: curettage and electrodesiccation are recommended treatments of choice for low-risk primary BCC. The therapeutic procedure is based on intradermally anesthetized skin, followed by curettage, alternating with apply light electrodesiccation. The procedure is aimed at removing all of the soft and friable tumor material [25]. Although it has been associated with cure rates as high as 97% to 98.8%, the efficacy of curettage and electrodessication is highly operator-dependent [26][27].

Cryotherapy and cryosurgery: cryotherapy is the destruction of tissue by the direct application of a cryogenic agent, such as liquid nitrogen. Therefore, this approach is useful to treat a wide variety of skin conditions, including small, multiple, and low-risk BCC [28][29].

In cryosurgery, tissue destruction is caused by freezing leading to sudden loss of heat and subsequent vascular stasis and cell death, thus, representing an appropriate and easily available therapeutic modality with hardly any contraindications [30]. Cryosurgery is cost-effective, requiring minimal anesthesia. Finally, cryosurgery has cure rates as high as 99% [11].

Laser treatment: several types of laser, using both selective and ablative methods, are utilized in oncology [31]. Carbon dioxide (CO2) and erbium yttrium aluminum garnet (Er: YAG) lasers remove tumors by the vaporization of water element [32]. A pulsed dye laser, on the other, selects tumor vasculature, so it destroys the tumor's blood supply [33]. Laser ablation with CO2 may be able to complete the remission of superficial BCC similarly to what happens for cryotherapy [34]. The response to the treatment, in the absence of a histological examination, evaluated under a confocal microscope, is able to demonstrate the absence of the tumor in the residual tissue [35]. However, studies are still ongoing on the effectiveness of combined laser treatment on BCC.

2.4. Topical and Intralesional Therapies

Imiquimod therapy: imiquimod is an immune response modifier used for the treatment of small BCC (sBCC) [36]. The mechanism of action of the drug is not yet fully elucidated. Imiquimod, acting as an agonist of the toll-like receptor 7 (TLR7), enhances dendritic cell survival and promotes the activation of tumor-specific T-lymphocytes [37]; thus, inducing secretion of several cytokines, such as interferon-α, interleukin-6, and tumor necrosis factor-α. The cream is applied 5 days/week for six weeks. Imiquimod represents a useful treatment for low risk, single or multiple sBCC, with a maximum diameter of 2 cm. It has been reported that imiquimod has a cure rate of 83% [11]. Therefore, imiquimod could represent a valid alternative in the treatment of elderly patients with major comorbidities and poor compliance.

Photodynamic therapy: PDT with 5-aminolevulinic acid (ALA) or its methyl ester (methyl-5-amino-4-oxopentanoate, MAL) can be effective for small and superficial BCC, with a thickness not exceeding 2 mm, if the surgical intervention is not indicated for lack of radicality or for the patient's health conditions (age and comorbidity, drugs) [38]. PDT is a therapy for the non-surgical treatment of actinic keratosis, superficial BCC, and recently, Bowen's disease. The therapeutic rationale exploits a photodynamic reaction on the tumor cells for the interaction of light with a photosensitizing substance, which, when activated, releases species reactive oxygen, capable of destroying the cell in which they formed. In elderly patients or with contraindications to surgery, combined therapies could represent the gold standard for BCC treatment. Nevertheless, studies are contradictory regarding the effective role of PDT in the elderly population. To this regard, it is still debated whether the elderly population respond differently to treatment with PDT. Moreover, acute post-procedure hypertension is reported as a potential side-effect of PDT, most prevalent in elderly populations, especially in patients with hypertension in their medical history.

Finally, 5-Fluorouracil: 5-FU, with a 5% cream formulation is advised in the treatment of superficial BCC with the following dosage schedule: 2 daily applications for 2–4 weeks. High response rates have been reported in the literature, in particular for sBCC. Indeed, it has been reported that 5-FU has a 5-year cure rate of 80% [11]. Regarding the real effectiveness of this topical therapy on sBCC, a direct comparison between 5-FU, imiquimod and MAL-PDT shows that imiquimod has a higher probability of success than 5-FU, except for sBCC on lower extremities in older patients [39]. In addition, the application of 5-FU could be difficult for elderly patients with lesions on hard-to-reach locations.

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