

Rationale for the Use of Neoadjuvant Vismodegib Plus Mohs Surgery in Patients with Locally Advanced Periocular Basal Cell Carcinoma in Real Life

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Abstract

Background: Vismodegib has shown to induce tumor shrinkage in locally advanced periocular basal cell carcinoma (LAP-BCC). The combination of neoadjuvant Vismodegib + Mohs surgery (MMS) in LAP-BCC represents an excellent option.

Methods: We present a 50-year-old man, with a 2.8 cm infiltrative BCC of the left inner canthus.

He received Vismodegib for a total of six months with a 4-month interruption due to cost-related issues.

Results: He presented a complete response (CR). During MMS, frozen sections showed BCC at the area corresponding to the lacrimal sac. We completed the resection of the lacrimal apparatus (bone and soft tissues) under general anesthesia. Final margins were clear. The patient is currently without evidence of disease 10 months after MMS.

Discussion: There is small experience about neoadjuvant Vismodegib + surgery for LAP-BCC. This strategy has several advantages: Treatment time is limited, this by the way is less expensive and decreases side effects. Obviously, compliance is improved.

Vismodegib success is hampered by primary or secondary (acquired) resistance.

Two recent systematic reviews showed that CR after Vismodegib for LA-BCC was 31.1%, and that only 40% of the cases sustained the CR at 36 months after drug discontinuation.

The reported case was considered as CR but we found a small, deep remnant of tumor, impossible to predict by clinical examination or imaging. This highlights the rationale of using MMS to perform a complete resection and to confirm histologically the response to the drug.

We believe Vismodegib should not be restricted only to inoperable patients. Specific indications beyond those already approved need to be further discussed.

Background

Locally advanced periocular basal cell carcinoma (LAP-BCC) is the most frequent cause of orbital exenteration [1].

Surgery with margin control or Mohs micrographic surgery (MMS) are the mainstay of treatment for periocular BCC with cure rates between 95%-99% for primary BCCs [2,3].

Vismodegib is a Hedgehog inhibitor (HHI) that has shown its capacity to reduce tumor size of locally advanced BCC, allowing for a less morbid surgical resection [4-11].

Obviously, the most important goal in LAP-BCC is to avoid exenteration, but preservation of normal tissue is critical to allow easier functional and cosmetic reconstruction of the eyelids.

Therefore, we believe there is a clear role for Vismodegib as neoadjuvant for LAP-BCC, even in operable cases. We present a case that combines the use of HHI + MMS that illustrates the advantages of this therapeutic approach.

We adhere to the ethical principles of the declaration of Helsinki.

The Instituto Oncología Angel H. Roffo Ethics Committee approved this publication under number 725.



Figure 1: Clinical presentation.



Figure 3: First margin layer of Mohs surgery.



Figure 2: CR after HHI treatment.



Figure 4: Defect after Mohs surgery.

The patients in this manuscript have given written informed consent to publication of their case details.

Case Study

We treated a 50-year-old man, Fitzpatrick skin type II, blue eyes and along history as outdoor worker. He presented a two-year history, infiltrative BCC of the left eye. The tumor was 2.8×2 cm and involved completely the inner canthus and partially the superior eyelid. TNM (AJCC 8th edition) was T4b (invasion of lacrimal sac/nasolacrimal duct) (Figure 1).

Before written consent was obtained, he received Vismodegib 150 mg daily during three months. After that time, we observed a major partial response (PR) (over 80%). At that time, drug supply was interrupted because of cost-related difficulties with his health insurance. He re-started treatment 4 months later and completed a new period of 3 months with the HHI. After this period, we only observed scar tissue, with

no sign of the previous tumor. This was considered as a complete response (CR). The adverse effects were: Severe alopecia and mild dysgeusia and muscle cramps type I (Figure 2).

He was then submitted for MMS. The first layer was done with a 0.4 cm lateral margin and included scar tissue and periosteum of the nasal bone. The frozen sections were positive for BCC at the area corresponding to the lacrimal sac (Figure 3, Figure 4 and Figure 5).

The procedure was completed under general anesthesia. This allowed us to perform the resection of the lacrimal apparatus (bone and soft tissues). At this time, histologic margins were negative both in frozen and permanent sections. For reconstruction we combined a glabellar flap, a cheek advancement flap and a Burow's graft. The patient is currently with no evidence of disease (NED) 10 months after MMS (Figure 6, Figure 7, Figure 8 and Figure 9).

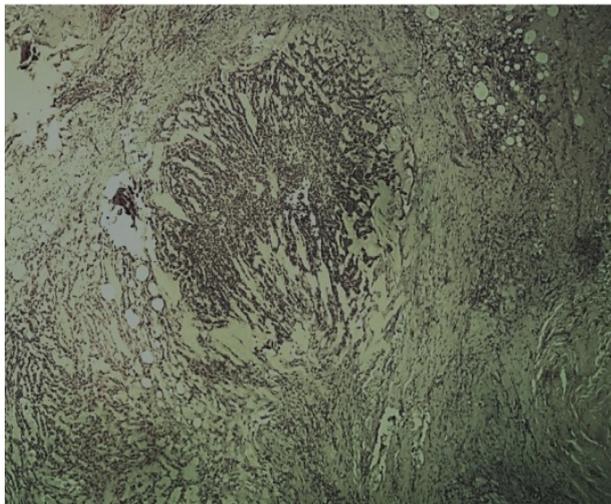


Figure 5: Positive deep margins (lacrimal sac area).



Figure 6: Defect after resection of bone and soft tissues of the area of the lacrimal sac.



Figure 7: Reconstruction with advancement + glabellar flap + skin graft.

Discussion

The key component of the hedgehog signaling pathway is a protein called Smoothed (SMO), which has inherent tendency to send a proliferative signal



Figure 8: Final result.



Figure 9: Final result.

within the cell. The aberrant proliferative signal through SMO in virtually all BCCs creates a uniform point of therapeutic vulnerability. Targeted SMO inhibitors, such as Vismodegib are directed to this point.

There is small experience about the use of neoadjuvant Vismodegib + surgery for LAP-BCC [9-11].

Kahana informed a single case of a patient with a BCC invading the medial orbit. The MRI showed a 2.7 × 1.6 × 1.9 cm mass. To avoid orbital exenteration the patient received oral Vismodegib 150 mg/d. After 4 months the new MRI showed significant reduction of tumor size to 0.7 × 0.7 × 0.5 cm. One month later, due to painful muscle spasms, the patient decided to cease medical treatment. The tumor shrinkage after HHI

permitted a complete excision with clear margins and eye preservation. Interestingly, permanent histology showed dispersed residual tumor cells with squamous differentiation and low proliferative capacity. Reported follow up was only two months.

Sagiv reported 8 cases treated between 2013 and 2017. All patients presented a T4 tumor, and 6 were previously treated. Vismodegib was administered for a median of 14 months (4-36 months). All patients underwent an eye-sparing surgery with clear margins after HHI treatment. Five cases had a CR, that was confirmed histologically. Three patients presented a major PR and showed residual tumor in final pathology. Mean follow-up after surgery was 18 months (6-43) and all patients are alive and NED.

We treated 8 patients between June 2014 and December 2016 with neoadjuvant Vismodegib + MMS [11]. Tumors were staged as T2 (2 cases), T3 (3) and T4 (2) according to the 8th edition of the AJCC. Three cases were previously treated. The indication was to avoid an orbital exenteration in 3 patients and to preserve normal tissue in 4 operable cases. The remaining patient included in our series presented a 1.5 cm lower lid BCC and refused initial surgery. Mean time of neoadjuvant Vismodegib was 6.6 months (range 4-10). One (12.5%) patient progressed and needed an orbital exenteration and 7 (87.5%) showed a CR. Of these 7 patients, 1 refused surgery and is NED after 34 months. We confirmed 5/6 complete histologic responses and found persistent tumor after MMS in 1 patient. With a mean follow up of 34.6 months, one patient recurred at 17 months and was retreated with MMS (currently NED 18 months later). One patient died of unrelated cause (cardiovascular surgery) at 12 months of follow up.

The present case is part of a group of patients treated lately with the same approach, and not included in that publication.

One interesting point is the histologic finding of a small tumor remnant in the deep portion of the resection, although clinical evaluation was CR. The persistent tumor was too small and deep, almost impossible to predict by clinical examination or imaging.

Some authors found that persistence was more frequent in the deep tumor planes. They propose this may be related with suboptimal blood perfusion, and therefore lower Vismodegib tissue levels [6,12].

This highlights the rationale of using MMS to perform a complete resection and to confirm histologically the response to the drug.

The use of Vismodegib as neoadjuvant has several advantages.

The first benefit is that treatment time is limited.

This, by the way is less expensive and decreases side effects. Obviously, compliance is improved.

The cost of Vismodegib is around U\$7500 per month. Even in developed countries this has been a limit. Ozgur reports that 2 out of 12 patients discontinued treatment because of cost-related issues [13].

In real life and outside the developed world, cost is a main concern for physicians. We prescribed Vismodegib to 17 patients with LAP-BCCs and our recommendation clearly enlightened the benefit of using HHI for eye preservation. Nevertheless, 1 patient was denied the medication and in a second patient the administration of the drug was suspended after 2 months because of cost-related issues. As seen previously, our reported case also had delays and interruption during his drug supply.

The mean delay for obtaining the drug for 16 cases was 1.9 months (range 1-8 m). There was a clear difference between patients depending on the type of medical insurance. Ten patients obtained the drug with almost no wait (1-2 months), but in six cases, the mean delay was 6.2 months (4-8).

Considering this real-life scenario, cost is one of the main reasons we decide to use Vismodegib as neoadjuvant. One of the major limitations of Vismodegib is the incidence of treatment related adverse events (AE). The STEVIE Study was a multicentric trial to assess the safety of Vismodegib 150 mg/daily dose in patients with LA-BCC (468) and metastatic BCC (31) [14]. AEs happened in 98% of the patients. Treatment was discontinued in 80% patients; 36% had adverse events, 14% had progressive disease, and 10% requested to stop treatment. In addition, 46 deaths (3.8%) were reported, but only 2 were investigated as drug relate [14].

According to a comprehensive review the majority of AEs are low grade, and muscle spasms (66.4%), alopecia (61.1%) and dysgeusia (57.3%) are the most common [15]. Serious AEs average 21.4% and 28.2% of the patients discontinue HHI because of AEs.

Another argument against extended medical treatment is the risk of secondary or acquired resistance. This event is characterized by regrowth of tumor after initial shrinkage, different from primary resistance, in which the tumor never responds to treatment.

Papastefanou reported a patient with a recurrent LAP-BCC treated with HHI, that achieved an almost CR after 3 months. Nine months later the patient recurred while still on treatment, due to drug resistance and required an orbital exenteration [16].

Chang observed 21% of secondary resistance at a mean time of 13 months in a series of 28 patients treated with HHI [4].

Secondary drug resistance may be connected to acquired mutations in SMO or to cells that have or develop resistance to HHIs [17]. It has been found that BCCs harbor the highest mutational burden of all human cancers [18].

Molecular studies revealed that acquired resistance is mostly due to selection of SMO mutant clones under Vismodegib treatment [19]. Lastly, Pleasance suggests that tumor size may be related with tumor multiclonality [20].

Another issue of growing concern is the event of skip tumor areas, small remnants of tumor cells dispersed between the healthy tissue that replaced the original tumor after HHI treatment [17]. Skip lesions, due to primary or acquired resistance should be considered when deciding surgical treatment. MMS, or comparable techniques of complete circumferential peripheral and deep assessment are available and offer the best option [21].

The rationale for neoadjuvant Vismodegib is supported by the results of two recent studies [15,22].

Jacobsen carried out a systematic review of series published between 2009 and 2015 that included 704 clinically evaluable patients with LA-BCC and mBCC. The CR rate in 597 LA-BCC was 31.1%.

Hermes reported a multicenter study to evaluate the durability of CR after discontinuation of Vismodegib. The research was conducted in nine French onco-dermatology units and included 116 patients with LA-BCC that discontinued treatment after achieving a CR between March 2012 and January 2016. The relapse free survival rate at 36 months was 40.0% for LA-BCC (excluding patients with Gorlin syndrome). Almost half of the patients that relapsed were re-challenged with HHI, but only 37% achieved a CR. This suggests that they might potentially become resistant to Vismodegib.

Both studies are based on large number of patients and reflect consistent results. Therefore, we may expect that around 30% of the patients with LA-BCC will achieve a CR after Vismodegib and three years later we should anticipate that only about 12% (40% of 30%) will still maintain the CR. Even adding the re-challenged patients, we could anticipate a CR rate of around 15% at 4 years after treatment.

Clearly the rate of long-term CR after medical treatment is low. Besides, these numbers reflect the outcomes of clinical studies, not real-life patients, that we know, usually do worse.

In the case of inoperable cases, because of tumor extent or due to medical reasons that preclude surgery, Vismodegib presents a significant improvement. Although less than 20% of patients will be cured, almost

two thirds of the cases benefit from tumor shrinkage and attenuation of symptoms. Besides, considering the age of the patients with LA-BCC, and that 31.7% die of unrelated causes, palliation by Vismodegib is of great value [23].

This does not apply to operable patients. As seen, the numbers support the opinion of several authors that consider the effect of HHI on BCC more suppressive rather than curative [6,8,24]. They propose that Vismodegib should be used in combination with definitive surgical resection.

Ching described the experience in 6 patients with LA-BCC averaged 151.83 cm² in size, with underlying bone invasion in 4 cases who received HHI as initial treatment [6].

Maximal effect of the HHI treatment was reached when tumor regression ceased (3) or the patient could no longer tolerate the side effects of HHI treatment (3). At this time, surgical intervention was reconsidered and found to be acceptable to both, patient, and surgeon.

In each case, a less extensive surgery was performed than estimated before HHI treatment. In 3 cases, significant bone resection was avoided, and four specimens exhibited clear margins. All resected specimens contained BCC, although during HHI treatment and before resection multiple superficial biopsies showed no evidence of BCC (similar to clinical trials) [23]. However, all post-HHI treatment surgically resected specimens exhibited deeper, residual BCC. The authors conclude that although HHI treatments are not always curative for extensive BCC, they can decrease the morbidity of surgical treatment and increase the likelihood of curative resection [6].

The final issue we'd like to discuss is the timing of surgery after neoadjuvant treatment.

Usually in four months the response to Vismodegib is well-defined. Therefore, patients that show an insignificant PR, stable disease or progression should interrupt the medication.

On the other hand, patients with a major PR probably should continue treatment with the intention of obtaining a CR, for how long?

The question is in case of a CR at 4-6 months: Should we operate or continue with neoadjuvant Vismodegib for a limited time (one-two months?) to consolidate the result.

It seems reasonable that more cycles of HHI may increase the probability of eliminating subclinical remnants of tumor. The excellent results by Sagiv in a series of 8 patients with T4 periocular BCCs after a median period of 14 months of HHI treatment seem to confirm this opinion [10].

On the other hand, a longer treatment increases side effects, costs, and the risk of secondary resistance.

There is no evidence-based answer to this question. Currently, if the drug is available, and if side effects are well tolerated, our approach is to continue treatment for one or two months before MMS.

In conclusion, the aid of Vismodegib in LAP-BCCs tumor shrinkage is remarkable and has been proved. We believe HHI should not be restricted only to inoperable patients. Specific indications beyond those already approved need to be further discussed. This should be tested in large, prospective series.

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