ORIGINAL RESEARCH

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Vismodegib for Patients with Advanced Basal Cell Carcinoma: One Center's Experience

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ABSTRACT Objective: Vismodegib is the first-in-class oral small molecule inhibitor in advanced basal cell carcinoma (BCC). We herein report the treatment experience with vismodegib at the oncology department of the Gaziantep university medical faculty. **Material and Methods:** This was a retrospective analyze of consecutive 15 BCC patients with locally advanced and metastatic stage between August 2016 and June 2019. While the primary endpoint was progression free survival, secondary endpoints were efficacy and toxicity. **Results:** The mean duration of treatment was 9.1 months on vismodegib (range, 0.97-28.60 months) with a lengthy median follow-up time of 17.6 months. The overall response rate (ORR) was 73.3%, with 20% (n=3) of patients having complete response, 53.3% (n=8) having partial response and 20% (n=3) exhibiting stable disease. Progression was observed in 6.7% of the patients. Eight patients (%53) discontinued the treatment. The most common reason for discontinuation was drug side-effects (%53). Mainly side-effects (all grades) were fatigue (80%), muscle cramps (60%), loss of appetite (53.3%) and dysgeusia (46.6%). The median PFS was 9.66 months (95% CI; 2.05-17.28). **Conclusion:** Our PFS results seem contradictory to the reports indicating longer PFS with vismodegib, in the lack of difference in response rate. This study also confirmed that vismodegib has notable adverse effects in agreement with previous reports. The most frequently encountered problem was high dropout rates of treatment. It seems essential to manage toxicity and provide coping strategies for adverse effects in daily clinical practice. It was considered higher dropout from treatment may be associated with shortened PFS.

Keywords: Vismodegib; basal cell carcinoma; skin cancer; hedgehog pathway

Basal cell carcinoma (BCC) is caused by keratinocytes located in the basal epidermis, which firstly infiltrate the epidermis and then the dermis. Clinically, it usually occurs on the face and neck.[1,2] BCC has five main clinical variants: nodular-ulcerative, superficial, sclerosing-morphea, pigment-ulcerated and fibroepithelial.[3] The incidence rate of BCCs in the US reportedly spiked by 145% between 2000 and 2010 with the reasons for this significant increase including the aging of the patient population, increased awareness of the overall population, increased number of surgical cases, better record-keeping, and UV radiation.[4]

BCCs are slow-growing cancers with low metastatic potential and can be cured with surgical resection. The underlying treatment principle is the complete removal of the tumor with an ample resection margin. Reconstructive surgery can be performed depending upon the type of tumor and the size of the defect. While healing by primary closure is the appropriate surgical option for small lesions, grafts, and flaps are preferred for larger lesions. Primary radiotherapy can be an important treatment alternative for locally advanced diseases where surgical excision can lead to a severe loss of function or cosmetic problems.

In the case of advanced diseases, surgery and radiation therapy often do not provide a cure. The estimated risk of BCC-related metastasis is under 1%.[5] The prognosis for metastatic BCCs is very poor and the overall survival, once metastasis has occurred, is ten months.[6] The benefit of chemotherapy has been

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shown in metastatic BCC only in small clinical trials and case studies. In most cases, activation of the Hedgehog pathway is an important therapeutic goal.[7] The PTCH1 gene mutations were first observed in Gorlin Syndrome and this mutation is present in more than 90% of the sporadic BCC cases. SMO gene mutations have also been detected in BCC cases.[8,9] Two molecular targeting agents of vismodegib and sonidegib were approved by the FDA, in 2012 and 2015, respectively for the treatment of advanced BCC. Vismodegib is an oral SMO inhibitor, which blocks the activation of the Hedgehog signal pathway.[10]

The ERIVANCE trial was a Phase II, non-randomized, multicenter study, in which 104 advanced BCC patients were administered with vismodegib. In total, the treatment results for 96 patients (63 locally advanced, 33 metastatic) were assessed and analyzed. The treatment response rate was 30% for metastatic BCC and 43% for locally advanced BCC. Following that study, vismodegib was approved by the FDA for locally advanced and metastatic BCC.[10] The STEVIE trial was an open-label population study showing the efficacy of vismodegib. Vismodegib response rates (RR) were 68.5% and 36.9% in metastatic (mBCC) and locally advanced BCC (laBCC), respectively. Complete response (CR) rate was 33.4% in laBCC and 4.8% in mBCC. The median PFS was 23.2 months in laBCC and 13.1 months in mBCC.[10]

MATERIAL AND METHODS

The aim of this study was to retrospectively analyze the clinical-pathological characteristics and prognoses of BCC patients who were locally advanced or metastatic. Between August 2016 and June 2019 consecutive patients aged over 18 years were retrospectively analyzed. Before commencement, approval for the study was obtained from the ethics review board of Gaziantep university. All the patients received a dose of 150 mg/day vismodegib. They continued the treatment until progression or unacceptable toxicity. While the primary endpoint was progression free survival, secondary endpoints were efficacy and toxicity. The median follow-up time was 17.6 months.

Metastatic or locally advanced BCC cancer patients with pathological confirmation were included in the study. Responses to vismodegib were evaluated with two different methods. The first method was radiologic response according to response evaluation criteria for solid tumors (RECIST) v1.0 and the second was the clinical assessment of the primary tumor. A visible measure of the lesion or radiologic dimension of the tumor such as a >30% decrease, was accepted as partial regression, a >20% increase or new lesion was accepted as a progressive disease and complete resolution of the tumor was accepted as the complete response. Tumor responses were assessed every three months. The Kaplan-Meier method was used to calculate the median PFS. All the patients were studied for toxicity analyses. The following parameters were recorded: age, gender, co-morbidities, presence of squamous cell carcinoma, duration of treatment, type of previous treatments (surgery or radiotherapy), primary tumor sites and metastasis, the latest stage of treatment, response rates, vismodegib-related side effects, and reasons for discontinuation of vismodegib therapy. Statistical analyses were performed using the statistical package for social sciences, version 22.0 software (SPSS, Chicago, IL, USA).

RESULTS

An evaluation of a total of 15 patients was made comprising 10 males (66.6%) and 5 females (33.3%) with a median age of 73 years (range, 46-86 years). The baseline demographic and clinical characteristics of all the patients are shown in Table 1. The most common tumor location was the nose (46.6%) and the periorbital area (33.3%). No patient had squamous cell carcinoma, one patient had lung metastasis and the remainders were in locally advanced stages (93%). Primary radiotherapy had been applied to one patient, surgery to three and the remaining eleven patients had not received any treatment for advanced BCC before starting treatment with vismodegib.

Efficacy: When the analysis was completed, seven patients were still undergoing treatment and eight had discontinued treatment due to disease progression or patient non-compliance due to drug toxicity. The mean duration of treatment was 9.1 months

TABLE 1: Demographic and clinical characteristics of patients receiving Vismodegib.

Characteristics	N %
Age	
Median (Range)	73 (46-86)
Gender	
Female	5 (33.3)
Male	10 (66.6)
Comorbidity	
Yes	6 (40)
No	9 (60)
Site of tumor localization	
Nose	7 (46.6)
Periorbital	5 (33.3)
Scalp	2 (13.3)
Cheek	1 (0.6)
Presence of squamous cell carcinoma	
Yes	0
No	15 (100)
Site of metastasis	
Local	14 (93.3)
Local+Systemic (Lung)	1 (0.6)
Type of previous treatments	
Resection	4 (26.6)
Radiotherapy	1 (0.6)
No	10 (66.6)
Latest state of treatment	
Continue	7 (46.6)
Stop	8 (53.3)
Reason for discontinuation of treatment	
Progression	1 (12.5)
Side-effect	4 (50)
Others (patient desire, treatment non-compliance)	3 (37.5)
Final state of the patient	
Exitus	2 (13.3)
Alive	13 (86.6)

(range, 0.97-28.60 months). The overall response rate (ORR) was 73.3%, with 20% (n=3) of patients having complete response, 53.3% (n=8) having partial response and 20% (n=3) exhibiting stable disease. Progression was observed in 6.7% of the patients (Table 2). Vismodegib-related side-effects are shown in Table 3. The most common side-effects (all grades) were fatigue (80%), muscle cramps (60%), loss of appetite (53.3%) and dysgeusia (46.6%). Two patients died from non-cancer related causes. The median PFS was 9.66 months (95% CI; 2.05-17.28) (Figure 1).

Toxicity: Primary analysis of the study showed that vismodegib is tolerable and its safety profile is similar to that reported in previous studies.[11] This study also found that long-term use (longer than 12 months) neither improves nor worsens its side-effects. The toxicity profile in the study was consistent with that reported in the primary analysis.[12] The most common side-effects were fatigue, loss of appetite, muscle cramps and a bad taste in the mouth. It has been reported that fatigue and loss of appetite are associated with long-term use of vismodegib. Of the observed side-effects, grade 3 fatigue was observed in four patients, causing 3 to discontinue treatment. It was also observed that one patient experienced grade

TABLE 2: Response rates observed with vismodegib.

Response	N %
Complete response	3 (20)
Partial response	8 (53.3)
Stable disease	3 (20)
Progression	1 (0.6)

TABLE 3: Vismodegib-related side effects.

	Any Grade (N %)	Grade 1 (N %)	Grade 2 (N %)	Grade 3 (N %)
Fatique	12 (80)		10 (66.6)	4 (26.6)
Loss of appetite	8 (53.3)	3 (20)	4 (26.6)	1 (6.6)
Dysgeusia	7 (46.6)	2 (13.3)	4 (26.6)	1 (6.6)
Nausea	3 (20)	2 (13.3)	1 (6.6)	
Muscle cramp	9 (60)	4 (26.6)	5 (33.3)	
Abdominal pain	2 (13.2)	1 (6.6)	1 (6.6)	
Alopecia	1 (6.6)		1 (6.6)	
Rash	1 (6.6)			1 (6.6)

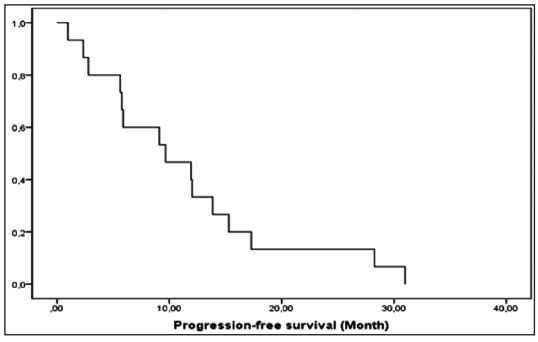

FIGURE 1: The progression-free survival of vismodegib treatment (Median: 9.66 months (%95 CI; 2.05-17.28).

3 anorexia while one patient suffered from grade 3 rashes and these effects resulted in discontinuation of the treatment.

The changes in mouth taste are not related to the cumulative dose of the drug; this is evident from the fact that in one out of the four patients affected, it developed in the first month of the treatment while in another it developed in the third month. Changes of taste in the mouth are a common side-effect of cancer therapies in patients taking vismodegib who usually suffer from a metallic taste in the mouth. It is assumed that such a sensation is related to the reduced secretion of saliva. While this does not normally lead to discontinuation of the treatment, it can lead to patient discomfort. In such patients, pilocarpine and salivary secretion stimulants can be used to increase salivary secretion after addressing oral, periodontal and sinusoidal infections, zinc deficiencies and salivary gland dysfunctions. The symptoms can be managed with throat lozenges, chewing gum and mint. Other measures may include oral zinc tablets, alpha-lipoic acid preparations, dietary changes, and psychological support. Alopecia, the common occurrence of which was reported in the STEVIE population, was observed much less frequently in the current study. This may be due to the fact that this was a retrospective study and the study population did not report alopecia as a side-effect, having accepted it as a natural outcome of cancer treatment and not at the level of total hair loss.

DISCUSSION

BCC is a disease that has become increasingly common in recent years. Although the occurrence of metastasis is relatively rare, a locally advanced form of the disease can lead to loss of organ function. Treatment methods such as surgical intervention or radiation therapy can provide a cure in rare cases or may cause serious morbidity. In this respect, advanced BCCs are a relatively neglected medical problem that has not received the attention it deserves. Vismodegib is an oral inhibitor of the Hedgehog signaling pathway and sonidegib is another agent with a similar active mechanism. In mBCCs, the ORR was 39.7% with vismodegib and 14.7% with sonidegib. The side-effects were similar for both agents.[12] In recent years, itraconazole has also shown benefit in BCC in a phase II trial by acting on SMO, with a 42.1% reduction observed in tumor size in 8 out of 19 cases.[13] Further studies are required to demonstrate its clinical usefulness.

The results published in the present study are in accordance with those reported in previous studies and demonstrate the efficacy of treatment with vismodegib. The average length of treatment with vismodegib is 9.1 months. The mean PFS is 9.6 months and the ORR is 73.3%. Compared to previous cohort studies prior to treatment with vismodegib, the results appear to be superior to the response rates achieved with chemotherapeutic agents, particularly platinum-based ones.[14] The results of this study reflect real-life data in many respects (e.g., age, gender, co-morbidity, tumor site, etc.). The follow-up duration and response rates were similar to those reported by STEVIE but differ in terms of PFS (9.6 months versus 23 months).[11] The lower rate of primary radiotherapy compared to other studies might be due to the high rate of diseases around the eye region.

BCC cases not responding to treatment with vismodegib have also been reported in the literature. A genomic study showed that a protein called GLI1, a component of the Hedgehog signaling pathway, is active in BCC cases with drug resistance and also demonstrated higher concentrations of a protein called MLK1 in the nucleus of cancer-resistant cells. In experiments with mice, it has also been shown as to how the inhibi-

tion of MLK1 inhibits the progression of BCCs.[15] These studies may be helpful in the development of new drugs that are effective in the treatment of BCCs.

CONCLUSION

Vismodegib is still the most effective treatment method for advanced BCCs. This study confirmed that vismodegib has also notable adverse effects in agreement with previous reports. It is important to develop strategies for the management of side-effects to ensure that the patients benefit from treatment as long as possible. Because, the most frequently encountered problem was high dropout rates of treatment in our trial. It was considered higher dropout from treatment may be associated with shortened PFS. Therefore, the best strategy would be to recommend patients to take a short break from treatment and resume it only after the side-effects have been mitigated.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Havva Yeşil Çınkır;* ***Design:*** *Havva Yeşil Çınkır;* ***Control/Supervision:*** *Havva Yeşil Çınkır, Fatih Teker;* ***Data Collection and/or Processing:*** *Havva Yeşil Çınkır;* ***Analysis and/or Interpretation:*** *Fatih Teker;* ***Literature Review:*** *Özlem Nuray Sever;* ***Writing the Article:*** *Havva Yeşil Çınkır, Fatih Teker;* ***Critical Review:*** *Fatih Teker;* ***References and Fundings:*** *Fatih Teker;* ***Materials:*** *Havva Yeşil Çınkır.*

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