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Clinical Characteristics and Treatment Outcomes of Patients with Dermatofibrosarcoma Protuberans Treated with Imatinib at Tikur Anbessa Specialized Hospital

Hospital-based cross-sectional study May-September 2020 G.C.

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A Thesis to be submitted to the Department of Internal Medicine, School of Medicine, College of Health Sciences, Addis Ababa University, in partial fulfillment of the Specialty Certificate in Internal Medicine

December 2020 G.C.

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ACKNOWLEDGEMENT

First, I am grateful to express my gratitude to Dr. Amha Gebremedhin for his invaluable guidance and sharing his constructive comments throughout this research project. I would also like to acknowledge AAU, college of health sciences for supporting this research project financially. I would also like to thank the department of internal medicine for giving me an opportunity to conduct a research for a postgraduate program. Finally, I would like to acknowledge TASH outpatient unit and the nursing staffsin hematology unit who were very cooperative and helpful in providing all the necessary records that enabled me to collect data.

ABSTRACT

Background:DFSP is a rare soft tissue tumor with indolent growth and low probability of distant metastasis. More than 90% of cases are positive for CD34 and are characterized by translocation of chromosome 17 and 22 (t (17; 22)) resulting in the expression of fusion gene-*COL1A1-PDGFRb.* A TKI, imatinib targets this fusion gene and showed efficacy in treating both locally advanced and metastatic DFSP.

Objective: The aim of this study is to describe the clinical characteristics of patients and to evaluate response to imatinib of patients with DFSP treated in Tikur Anbessa Hospital.

Methods: We assessed retrospectively 26 patients with DFSP treated with imatinib from 2004-2020 at hematology unit of Tikur Anbessa Hospital, in Addis Ababa. Clinical data was extracted from medical records and patients and analyzed with SPPS version 26. Response to imatinib was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST).

Results:18 of the patients were males and 8 were females with a median age of 35 years (range: 22-66). Trunk is the commonest location of primary tumor constituting 61.5%, followed by head and neck. Twelve patients have been treated with imatinib for locally recurrent disease, which was difficult to resect surgically, and 6 (50%) showed partial response, 3 (25%) complete response, 1 (8.33%) patient had stable disease and 2 (16.67%) had disease progression. On the other hand, thirteen patients underwent surgery for locally recurrent disease followed by imatinib therapy for residual disease. Six (6) of these patients had complete response, 3 patients had partial response and 4 patients had progressive disease while on imatinib. One patient had recurrent disease with liver metastasis and he underwent surgery for local recurrence and imatinib was given for liver metastasis which disappeared after 3 months. The overall clinical response rate was 73.1%. The major adverse effects of imatinib were: GI upset in 38.5%, skin depigmentation in 34.4%, anemia in 23%, leukopenia in 23% and edema in 19.2%, which were all transient and self-limiting.

Conclusion: DFSP is highly recurrent tumor after surgical resection. We found out that Imatinib is well tolerated and an effective treatment option for locally recurrent and advanced disease that is difficult for complete surgical resection, with over all clinical response of 73.1%.

ACRONYMS AND ABBREVATIONS

AAU: Addis Ababa University

COL1A1: Collagen type I alpha

CR: Complete Response

CTCAE: Common Terminology Criteria for Adverse Events

DFSP: Dermatofibrosarcoma Protuberans

DFSP-FS: Dermatofibrosarcoma Protuberans Fibro-Sarcomatous variant

FDA: Food and Drug Administration

GIPAP: Glivec International Patient Assessment Program

NCCN*:* National Comprehensive Cancer Network

*PDGF*β: platelet-derived growth factor subunit β

PR: Partial Response

RECIST: Response Evaluation Criteria in Solid Tumors

SSA: Sub Saharan Africa

TASH: Tikur Anbessa Specialized Hospital

TKI: Tyrosine Kinase Inhibitor

US: United States

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1. INTRODUCTION

1.1. Background

Dermatofibrosarcoma protuberans (DFSP) is a rare infiltrative soft tissuetumor, with a tendency for local recurrence but little capacity to result in distant metastasis[1].Darier and Ferrand initially characterized it as a keloid-like sarcoma in 1924 and one year later Hoffmann gave it its current name[2][3].

DFSP is a relatively rare disease with limited epidemiological data in most parts of the world[4]. The reported annual incidence is 4.1-4.2 cases per million according to data from two large US registries[5][6]. In sub-Saharan Africa (SSA), it constituted about 3% among pathology reports for 1900 patients with 14 different cutaneous malignancies from Kijabe Hospital in Kenya from 1992 to 2008[7].

The mean age at diagnosis of DFSP was 40.2-41.9 years, although it has been described in all age groups, including a number of congenital cases DFSP. Blacks were about twice more affected than whites did and it showed slight female predominance according to the data from the above two US registries. However, studies in China(74% male), Italy(male: female ratio of 1.5) and India (56% male) showed that the incidence is higher in males[8][9][10].

The data from US registries showed that the trunk is the most common anatomic location of this tumor followed by upper limb, lower limb, head, and genitals (representing 41.7%, 21.2%, 20.8%, 12.9%, 1.0% respectively)[6].

More than 90% of DFSP tumor cells are reactive for CD34 and are genetically characterized by the presence of a translocation involving distinct regions of chromosome 17 and 22[11]. This t(17:22) leads to expression of a COL1A1-PDGFRβ fusion protein, which is a potent mitogen for mesenchymal cells and results in constitutive production of collagen and uncontrolled cell growth[1][12].

DFSP in its classic histologic appearance on hematoxylin and eosin (H&E) staining consists of a proliferation of monotonous dermal spindle cells with little pleomorphism and a low mitotic index, and infiltrate into the subcutaneous fat[13][14][15].

DFSP is locally aggressive but rarely metastasizes, with an estimated rate of metastases between 0.5% and 5%[16]. Complete surgical resection with negative margins is considered the gold standard for treatment of localized primary or recurrent cases of DFSP. Resection may be using either wide local excision or Moh's microscopic surgery, the latter being shown to be associated with better tissue preservation and less complicated wound closures[17][18]. Despite surgery being the cornerstone of treatment, there are cases that are deemed unresectable owing to tumor extension or size, or risk of cosmetic disfigurement or functional impairment[9][19].

Advances in the understanding of the molecular mechanisms of DFSP led to the hypothesis that inhibition of PDGFR with TKIs may have clinical efficacy in the treatment of DFSP. In 2002, the first case report showing the efficacy of a PDGFR inhibitor, imatinib mesylate in a 25-year-old patient with metastatic DFSP of the lower limb was published[20]. Based on this initial efficacy, a number of case series subsequently evaluated the role of imatinib in the treatment of DFSP. The US FDA in 2006 approved Imatinib for DFSP[21][22][23]. After the phase 2 study published in 2010, showing objective response rate approaching 50% in locally advanced or metastatic DFSP, the NCCN also incorporated imatinib into its treatment algorithm and recommends imatinib for metastasis and/or recurrences when disease is unresectable or unacceptable functional or cosmetic outcomes with resection are predicted[24][25].

Imatinib is generally well tolerated but is not without risk. The most common adverse reaction to imatinib is edema, followed bygastrointestinal upset and myalgia. Hematologic adverse events such as leukopenia, neutropenia and thrombocytopenia of variable degree may also occur[21].
In a systematic review of 9 studiesincluding 152 patients, done from 2002-2017 to evaluate the usefulness of imatinib for treating DFSP, the adverse events were present in at least 73.5% of cases (78 of 106); but severe adverse events were present in 15.1% of cases (20 of 132)[19].

In Ethiopia, there are no published studies regarding epidemiology and clinical characteristics of DFSP. Since 2004, the hematology unit of TASH has been following patients with DFSP referred after surgery for possible molecular targeted therapy. Most of these patients have been enrolled into GIPAP and receiving

imatinib mesylate; however, their response to treatment has not been systematically evaluated.

1.2. Statement of the problem

Dermatofibrosarcoma protuberans (DFSP) is a rare infiltrative skin tumor of intermediate malignancy, with a tendency for local recurrence but little capacity to produce distant metastasis. Annual incidence 4.1-4.2 per million according to data from two large US registries[5][6].

Complete surgical resection with negative margins, using either wide local excision or Moh's microscopic surgery, is considered the gold standard for treatment of localized primary or recurrent cases of DFSP. In some cases however, surgical resection is difficult owing to tumor extension or size, or risk of cosmetic disfigurement, functional impairment or medical comorbidities[17][18].

More than 90% of DFSP tumors cells are positive for CD34 and are genetically characterized by the presence of t(17:22) that leads to expression of a COL1A1-PDGFβ fusion protein. Imatinib mesylate, a TKI targeting this fusion gene was assessed for the treatment DFSP and showed efficacy[11].

In Ethiopia, there are no published studies regarding epidemiology and clinical characteristics of DFSP. Since 2004, the hematology unit of TASH has been following patients with DFSP referred after surgery for possible molecular targeted therapy. Most of these patients have been enrolled into GIPAP and receiving imatinib mesylate; however, their response to treatment has not been systematically assessed. Therefore, this study is aimed to evaluate clinical characteristics and treatment response of patients with DFSP treated with imatinib mesylate in hematology unit of TASH.

1.3. Rationale of the study

DFSP is a rare soft tissue tumor with annual incidence 4.1-4.2 per million according to data from two large US registries[5][6]. There have been no published studies describing the clinical characteristics and treatment outcomes of this tumor in Africa including Ethiopia. In TASH there are some patients diagnosed with DFSP, enrolled into GIPAP and taking imatinib mesylate;

however their clinical characteristics and response to this treatment has not been studied so far. Therefore, this study will be the first one in its kind in the country to look in to these above variables and the results will serve as a base line data for further research in this area.

2. LITERATURE REVIEW

2.1 Definition and historical background

Dermatofibrosarcoma protuberans (DFSP) is a rare infiltrative skin tumor of intermediate malignancy, with a tendency for local recurrence but little capacity to produce distant metastasis[1]. Taylor first described it in 1890[2]. Darier and Ferrand were credited with establishing DFSP as a clinicopathologic entity when they described an unusual progressive and recurring tumor of the skin of fibromatous or fibrosarcomatous character as a keloid-like sarcoma in 1924. One year later, Hoffmann reported several similar cases and coined the neologism, "dermatofibrosarcoma protuberans”[3].

2.2 Epidemiology of DFSP

DFSP is a relatively rare cutaneous sarcoma with limited epidemiological data in most parts of the world[4]. In US, data obtained from 1973 to 2002 from 9 population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) program managed by the US National Cancer Institute, reported the incidence of DFSP at 4.2 per million, accounting for approximately 0.1% of all cancers. In this study, the annual incidence among blacks was almost double the incidence among whites (3.9 vs 6.5 per million; P<.005, 95% CI of difference 2.02-3.22). Women had also higher rates of incidence than men did (4.4 vs 4.2 per million per year; P = .052, 95% CI of difference -0.002 to 0.60)[5].

According to data from the 18 registries of the same SEER Program from 2000 to 2010 including 7,000 patients, the overall incidence was almost similar (4.1 per million person-years). Similarly, incidence among women was 1.14 times higher than men (95% CI of rate ratio: 1.07–1.22) and incidence among blacks was almost 2 times the rate among whites (95% CI of rate ratio: 1.8–2.1[6]).

Pertaining to sex distribution of DFSP, there were studies that showed different results from the above two US registries. For instance, one study in Italy to review the treatment outcomes of 136 patients with DFSP treated at a single institution in 20 years (April 1983 and December 2003) showed male to female ratio of 1.5[8]. Data from some Asian studies also showed male predominance. In study that assessed clinical profile and management outcomes of 82 cases of DFSP treated from 1994 to 2016 in a single institution in India, males represented 74%[10]. Another chinse study including 80 patients treated in 10 years period in a single institution also showed male predominance (56 vs 44%)[8].

The mean age at diagnosis of DFSP is 40.2-41.9 years, although it has been described in all age groups, including a number of congenital cases[8][28].

In Africa, there are limited published studies in the epidemiology DFSP. One study with the objective of establishing the demographics of primary cutaneous malignancies in sub-Saharan Africa reviewed database for 1900 specimens of all cases of primary cutaneous malignancies from over 70 rural hospitals in and around Kenya submitted to pathology department of Kijabe Hospital from 1992 to April 2008. According to this review, DFSP accounted about 3% of all 1900 cases of 14 different types of primary cutaneous malignancies in SSA[7].

2.3 Clinical characteristics of DFSP

DFSP is a slow-growing, insidious tumor that may be misdiagnosed clinically, often delaying definitive diagnosis for many years after original presentation. DFSP most commonly presents as an asymptomatic skin-colored plaque that slowly enlarges over months to years, eventually becoming nodular[3][29]. In the case of neglected tumors, initial size at presentation can be large, measuring up to many centimeters. The tumors are usually adherent to the overlying skin, which may develop atrophic changes[8]. DFSP is usually freely mobile over deeper structures, although long-standing tumors may be connected to underlying bone or fascia. The tumors can sometimes ulcerate and may be painful[4].

The data from US registries showed that the trunk is the most common anatomic location of this tumor followed by upper limb, lower limb, head, and genitals(representing 41.7%, 21.2%, 20.8%, 12.9%, 1.0% respectively)[6]. This

was true of both sexes and all age groups except men older than 80 years of age for which the proportion of cases at the head was greatest[6]. The Chinse,Italian and Indian studies also revealed that the trunk is the most common anatomic location of this tumor[8][9][10].

DFSP demonstrates local infiltrative growth but seldom metastasizes distally. In a study of incidence and survival of primary dermatofibrosarcoma protuberans in the US, from 6780 cases, > 90% were localized or regional disease and 9.9% were unstaged but only 0.5% of patients had disease with distant metastasis[6].

2.4Molecular Pathogenesis of DFSP

More than 90% of DFSP tumors cells are reactive for CD34 and are genetically characterized by the presence of a translocation involving distinct regions of chromosome 17 and 22, most commonly as a supernumerary ring chromosome[11]. This t(17:22) leads to a fusion in the *COL1A1* and *PDGF*β genes and results in the expression of a COL1A1-PDGFβ fusion protein. The PDGFβ protein is a potent mitogen for mesenchymal cells with autocrine and paracrine activation of the PDGF receptor (PDFGR) on tumor cells leading to the constitutive production of collagen and uncontrolled cell growth[1][12]. The identification of the aberrant activation of the PDGF pathway led to the hypothesis that inhibition of PDGFR may have clinical efficacy in the treatment of DFSP[33].

2.5 Histopathology of DFSP

DFSP in its classic histologic appearance on hematoxylin and eosin (H&E) staining consists of a proliferation of dermal spindle cells that infiltrate into the subcutaneous fat. These proliferations are made up of monotonous cells with little pleomorphism and a low mitotic index. The spindle cells in the deep dermis are often arranged in a storiform or cartwheel pattern, and the infiltrating portion of the tumor is characterized by tentacle- like projections into the underlying fat, resulting in a honeycomb appearance[13][14][15].

2.6 Treatment Options of DFSP

2.6.1 Surgical Treatment

Complete surgical resection with negative margins is considered the gold standard for treatment of localized primary or recurrent cases of DFSP. Although wide local excision (2- to 3-cm margins) has historically been the treatment of choice for DFSP, Mohs micrographic surgery (MMS) has emerged as an attractive treatment option, with a growing body of literature supporting its use because it may enable some tissue preservation and allow for less-complicated wound closures[17][18].

Despite surgery being the cornerstone of treatment, there are cases that are deemed unresectable owing to tumor extension or size, or risk of cosmetic disfigurement or functional impairment, such as tumors located on the head and neck, genitalia, hands, and feet. Similarly, some cases may be inoperable owing to medical comorbidities. Inadequate initial resection may also result in local recurrence or disease progression[9][19].

2.6.2 Molecular Targeted Treatment

Advances in the understanding of the molecular mechanisms of DFSP and the identification of the aberrant activation of the PDGF pathway led to the hypothesis that inhibition of PDGFR may have clinical efficacy in the treatment of DFSP. These have resulted in the introduction to clinical practice of targeted therapy acting on PDGFR. The first effective systemic therapy in DFSP introduced into clinical practice was imatinib mesylate, which is a tyrosine kinase inhibitor specifically directed at BCR/ABL, KIT, FMS (receptor for colony stimulating factor 1), ARG (ABL-related gene) and PDGFR-α and –ß[30][31][32].

In 2002, the first case report showing the efficacy of a PDGFR inhibitor imatinib mesylate in a 25-year-old patient with metastatic DFSP of the lower limb was published. The patient was severely impaired but able to walk 2 weeks after initiating treatment and surgery was performed 1-month later[20]. Based on this initial efficacy, numerous case series subsequently evaluated the utility of imatinib in the treatment of DFSP[22][23]. The US FDA in 2006 approved Imatinib for DFSP[21]. After the phase 2 study published in 2010, showing objective response rate approaching 50% in locally advanced or metastatic DFSP, the NCCN also incorporated imatinib into its treatment algorithm[24]. The NCCN guidelines recommend imatinib for metastasis and/or recurrences when “disease is

unresectable or unacceptable functional or cosmetic outcomes with resection are predicted[25].

One study in France assessed the role of imatinib as a neoadjuvant treatment in 25 patients from 2004-2006. A clinical response was achieved in nine (36%) patients (95% confidence interval, 18.9-57.5). The median relative tumoral decrease was 20% (range, −12.5 to 100). The results of study supported the use of imatinib in a neoadjuvant setting, if DFSP is non-resectable or when surgery is difficult or mutilating[26].

Long-term results of treatment of advanced dermatofibrosarcoma protuberans (DFSP) with imatinib mesylate in 31 Caucasian patients was assessed in Poland. A 5-year progression-free survival (PFS) rate was 58% (median 6.8 years), 5- year overall survival rate (OS) was 64%. The shorter PFS and OS correlated with FS-DFSP and presence of metastatic disease, 5- year PFS rate was 93% for classic DFSP and 33% for FS-DFSP[27].

In a recently published systematic review of 9 studiesincluding 152 patients, done from 2002-2017 to evaluate the usefulness of imatinib for treating DFSP, complete response was seen in 5.2% of patients (8 of 152), partial response in 55.2% (84 of 152), stable disease in 27.6% (42 of 152), and progression in 9.2% (14 of 152). Some of the studies included in this review used 400 mg daily and others used 800 mg of daily doses imatinib. However, there were no significant differences in response rate using 400-mg or 800-mg daily doses (67.5% or 27 of 40 patients for 400-mg dose vs 67.1% or 49 of 73 patients for 800-mg dose complete or partial response; $P > .99$)[19].

2.7 Adverse effects of imatinib treatment

Imatinib is generally well tolerated but is not without risk. The most common adverse reaction to imatinib is edema, followed bygastrointestinal upset and myalgias. Hematologic adverse events such as leukopenia, neutropenia and thrombocytopenia of variable degree may also occur[21].

In a systematic review of 9 studiesincluding 152 patients, done from 2002-2017 to evaluate the usefulness of imatinib for treating DFSP, the adverse events were present in at least 73.5% of cases (78 of 106); but severe adverse events were present in 15.1% of cases (20 of 132)[19].

3. OBJECTIVES

3.1. General objective

The general objective of this study was to describe the clinical characteristics and evaluate treatment outcomes of patients with dermatofibrosarcoma protuberans (DFSP) treated with imatinib in Tikur Anbessa Specialized Hospital.

3.2. Specific Objective

The specific objectives of this study were:

- To describe the demographic and clinical characteristics of patients with DFSP treated at hematology unit of TASH.
- To evaluate the response of patients with DGSP to imatinib.
- To assess the duration of treatment required to achieve a reasonable response.
- To evaluate the adverse events of imatinib in the treatment of DFSP.

4. METHODS and MATERIALS

4.1. Study setting

The study was conducted at Tikur Anbessa specialized hospital, which is a teaching hospital for Addis Ababa University and one of the largest referral hospitals in Addis Ababa, the capital of Ethiopia. The hospital provides specialized care for both in-patients and outpatient settings in different departments and subspecialties. This study was conducted in the department of internal medicine, hematology unit. The study was conducted from May-September, 2020.

4.2. Study Design

A cross sectional hospital based retrospective study was done to evaluate clinical characteristics and treatment outcomes of patients with DFSP.

4.3. Eligibility of the study participants

4.3.1. Inclusion criteria

All patients with biopsy proven DFSP who were treated and followed at hematology unit from 2004-2020were included.

4.3.2. Exclusion criteria

The following group of patients were excluded from this study.

-Patients who lost to follow up

-Patients whose medical records were incomplete and whose outcome was unknown.

-Patients who took imatinib for less than 3 months

4.4. Data collection and analysis

Forty-two (42) patients enrolled into Glivec International Patient Assessment Program (GIPAP) for DFSP from 2004-2020 at hematology unit in Tikur Anbessa Hospital were identified. Out of these, 16 patients were excluded, because 4 patients died with the cause of death being unknown, 4 patients were lost to follow up and for 8 patients medical chart couldn't be found. We have analyzed retrospectively collected data from the remaining 26 patients. All patients included in the analysis, had histologic diagnosis of DFSP, have been treated with imatinib 400 mg orally twice a day for at least 3 months and had consent form signed stating the date the treatment was started. However, molecular analysis fort(17;22) and COL1A1-PDGFβ fusion protein that is a target for imatinib, was not determined because the test was not available in the country.

We used structured questionnaire to extract clinical data from patients' medical records (charts and electronic medical records) as well as from the patients themselves. Data analysis was done using SPSS version 26. Clinical characteristics of patients have been described and response to imatinib evaluated using Response Evaluation Criteria in Solid Tumors (RECIST). Accordingly, complete response

was considered if the target lesion has disappeared, partial response if the target lesion has decreased by at least 30% from baseline while progressive disease if the target lesion has increased by 20% in size from the baseline or if new lesion has developed. We also evaluated occurrence of adverse drug reactions to imatinib therapy,which was graded based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

4.5. Operational Definition

Imatinib mesylate: a TKI approved for the treatment of CML, GIST and DFSP.

Metastatic disease: disease that spread to organs outside the site of origin

Complete response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Progressive disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study or relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

4.6. Ethical clearance

Approval of ethical clearance was grantedfrom AAU-CHS, department of internal medicine, ethics review committee (IRC).

5. RESULTS

The study participants included 18 males and 8 females with the median age of 35 years (age range: 22-66 years). The location of primary tumor was trunk in 16 (61.5%), head and neck in 5 (19.25%), extremities in 4 (15.4%) and perineum in 1

(3.85%) of the patients. On presentation, 25 (96.15%) of the patients had locally recurrent disease, while1 (3.8%)patient had a recurrent disease with liver metastasis. The mean duration of the illness at the time of this study was 14 (range: 4-40) years.Demographic and clinical characteristics of the patients is depicted in Tables 1 and 2.

Table 1. Demographic characteristics of the patients

Characteristics	**No.(%)**
Sex	
Male	18 (69.2)
Female	8 (30.8)
Age in years	
Median	35
Range	22-66

All of the study participants underwent surgery during their initial presentation, and had at least one local recurrence (the mean number of recurrences: 3.5 and range: 1-10 times); 53.8 % had recurrence 2-4 times and 26.9% had ≥5 times.

Twelve (12) of the patients received imatinib for locally recurrent disease, which was difficult to resect surgically whereas thirteen (13) patients for residual disease following surgical resection of the locally recurrent disease. The remaining one (1) patient had a recurrent disease with a liver metastasis.

Table 2. Clinical characteristics of the tumor

Characteristics	No. (%)
Primary tumor location	
Trunk	16 (61.5)
Head and neck	5 (19.25)
Extremities	4 (15.4)
Perineum	1 (3.85)
Presentation disease	
Locally recurrent	25 (96.15)
Recurrent metastatic	1 (3.85)
Duration of disease in years	
Median	12
Mean	14
Range	4-40
Number of recurrences	
Mean	3.35
Range	1-10
Number of surgeries	
Mean	3.77
Range	1-10

From the twelve (12) patients who received imatinib, for locally recurrent unresectable disease, 6(50%) had partial response, 2(16.67%) had complete

response, 1 (8.33%) patient had stable disease and 3(25%) patients had progressive disease while on imatinib therapy. The average time required to achieve partial response was 3-6months and for the complete response it was about 1 year. Out of the thirteen (13) patients who were treated with imatinib for post-operative residual disease, in 6 (46.15%) patients the residual lesions disappeared and had no recurrence or appearance of new lesion until the time of this study (the mean duration of imatinib: 3.6 years, range: 1-7 years). The other 3 (23.08%) patients achieved partial response and the remaining 4 (30.77%) patients developed progression of the tumor while on imatinib and imatinib has been discontinued.

Table 3. Response to Imatinib Therapy

Patient category	**No.(%)**
Recurrent unresectable disease	12
Partial response	6 (50%)
Complete response	2 (16.67%)
Progressive disease	3 (25%)
Stable disease	1 (8.33%)
Recurrent metastatic disease	1
Partial response	1
Recurrent resected disease	13
Complete response to imatinib	6 (46.15%)
Progression while on imatinib	4 (30.77%)
Partial response to imatinib	3 (23.08%)

A patient with metastatic disease is a 44 years old male with recurrent anterior abdominal wall tumor for which surgical resection was done twice (1 year apart) and had 3rdrecurrence on the same area and secondary lesions in the liver on ultrasonography. At that time, imatinib was given and the liver lesions disappeared on repeated ultrasound after 3 months while the locally recurred tumor

was regressed by >75% in 6-12 months. He is still on imatinib (for 7 years) and has no progression or appearance of new lesion.

The occurrence of any adverse drug reaction to imatinib therapy was present in 75% of the patients. The main adverse drug reactions were gastrointestinal upset (nausea and dyspepsia), skin pigmentation constituting 38.5% and 34.6% respectively. Lower extremity edema was also reported in 19.2% of patients. Hematologic adverse reaction as well occurred in 8 (30.8%) patients, anemia, leucopenia and thrombocytopenia in 6, 6 and 3 patients respectively. In only 2 patients was the leucopenia necessitated in temporary discontinuation of the drug. The rest of all the side effects were mild, transient and self-limited. The observed adverse drug reaction to imatinib are listed in table 4.

Table 4. Adverse Drug Reaction to Imatinib Therapy

Adverse drug reaction	**Frequency**
Hematologic	
Anemia	6 (23%)
Leucopenia	6 (23%)
Thrombocytopenia	3 (11.5%)
Non-hematologic	
GI upset	10 (38.5%)
Cutaneous	9 (34.6%)
Edema	5(19.2%)

6. DISCUSSION

This is a first study in DFSP patients in Ethiopia, describing their clinical characteristics and evaluating their response to imatinib. In this study, males were more affected with male to female ratio of 2.25. This is similar to finding from studies in China, Italy, India and New York hospital in US, that also showed male

predominance[8][9][10][14]. In contrast, the findings from two large US registries showed that DFSP isslight more common in females[5][6].

Trunk was the commonest anatomic location for primary tumor accounting for 61.5% followed by head and neck and extremities. This is similar with the findings from previous studies in US, china and Italy[6][8][9].

DFSP is a highly recurrent tumor following local surgical resection with a mean number of recurrences of 3.35 (range: 1-10) even though distant metastasis is rare presenting only in one patient in this study. The number of local recurrences following surgical resection was relatively higher in our study than reports from previous studies in other parts of the world. This may be related to the extent and type of surgery. The reported rate of recurrence following surgery was 29.8% in DFSP-FS variant and 13.7% in typical DFSP in one systematic review of 24 studies including 1442 patients in US[33].In another report from New York cancer center showed local recurrence rate of 25% over 5 years of follow up and positive microscopic margin and DFSP-FS variant were associated with higher rate of recurrence[14]. There is no clear explanation for higher recurrence rate following surgical resection in our patients (i.e. 100% have at least 1 recurrence), but it may be because of inadequate surgical margin. Some patients might have also DFSP-FS variant that was shown to be associated with high risk of recurrence in other studies, even though there was no specific report of DFSP-FS variant in histologic results of our patients[14][33].Most of patients included in this study underwent surgery for their primary and recurrent tumors in other hospitals and the details of surgical procedures could not be obtained.

Imatinib mesylate is an effective treatment option in locally recurrent DFSP, which is difficult to manage surgically because of cosmetic disfigurement or functional impairment. The overall clinical response rate of imatinib was found to be 73.1% (3.8% SD, 38.46% PR and 30.775% CR rate). These finding is slightly lower than the finding in study done in Poland that evaluated the response to imatinib in 15 patients with locally advanced and metastatic cases of DFSP and showed the best overall response of 80% (67% PR and 13% stable disease)[27]. In a systematic review of9 studies that including 152 patients, the overall response was even higher (88%)[19]. Another small study done in India including 7 patients with inoperable DFSP also showed an overall response rate of 85.7%[34].

The occurrence of any adverse drug reaction to imatinib therapy was present in 75% of the patients in this study. However, major side effect (i.e. grade 3 neutropenia)that necessitated in transient drug discontinuation occurred in onlv two (2) patients. The rest of the side effects were transient anc
systematic review of 9 studiesincluding 152 patients, done from 2002-2017 in US to evaluate the usefulness of imatinib for treating DFSP, the overall occurrence of any adverse events was similar presenting in 73.5%) of cases. However, the rate of severe adverse events was higher compared to our studies presenting in 15.1% of cases[19].

7. LIMITATIONS OF THE STUDY

The limitation of this study is that the molecular analysis to evaluate t(17;22) and COL1A1-PDGFβ fusion protein that serves as a noble target for imatinib therapy in these patients, has not been done because the test is not locally available. This was one of the inclusion criteria in most previous studies. In addition, the surgical procedure notes and perioperative details regarding the extent of local excision and achieving negative tumor margin, that is one of the major determinants of local recurrence, couldn’t be obtained as most of the patients underwent surgery in other hospitals. Other important factors that might affect the response rate such as the presence of fibrosarcomatous changes in histology were not reported in biopsy results.

8. RECOMMENDATION

Based on our findings, we recommend imatinib as an effective treatment option for recurrent DFSP when surgical resection is limited due to functional impairment, cosmetic reasons or advanced disease. We also recommend a further study to evaluate the response to imatinib prospectively and to assess the determinants of treatment response in patients with DFSP.Moreover, we recommend a multidisciplinary treatment approach and follow up for these patients.

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10. ANNEXES

Annex 1. Declaration

I, the undersigned, declare that this postgraduate thesis is my original work, has not been presented for a degree in this or any other university and that all sources of material used for the thesis have been duly acknowledged.

Postgraduate Candidate: Niguse Gebray(MD, Internal Medicine Resident)

Signature: …….

Date of Submission: December 29, 2020

This thesis has been submitted with my approval as advisor.

Advisor: Amha Gebremedhin (MD, Internist, Hematologist)

Signature: …….

Date: …….

Place: Addis Ababa, Ethiopia

Annex 2. Questionnaire for Ethiopian patients with Dermatofibrosarcoma protuberans

Code_____ MRN/I-Care_____

Part I: Clinical characteristics of patients with DFSP in HRC, TASH

1. Demographic Data

   Name _____ Age _____ Sex _____

   Address _____ Occupation _____

2. Time of initial diagnosis _____
3. Duration of symptoms at the time of initial diagnosis in months _____
4. Location of the tumor
   a) Trunk ☐
   b) Extremities ☐
   c) Head and neck ☐
   d) Genitalia ☐
5. Approximated tumor size in centimeters at initial diagnosis _____
6. Stage of the disease at initial diagnosis
   a. Localized ☐
   b. Locally advanced ☐
   c. Metastatic ☐
7. Diagnostic work up
8. Biopsy: a. Yes ☐ b. No ☐

If yes, what was the finding? a. typical DFSP ☐ b. DGSP-SF ☐

c. others ☐ specify _____

9. Radiologic studies:
   a. X-ray
   b. Ultrasound
   c. CT scan
   d. MRI
   e. None
10. Treatment offered during initial diagnosis
   a. Surgical resection alone ☐
   b. Surgical resection with radiotherapy ☐
   c. Surgical resection with neoadjuvant or adjuvant systemic chemotherapy ☐
   d. Surgical resection with neoadjuvant or adjuvant molecular targeted treatment ☐
   e. Radiotherapy alone ☐
   f. Systemic chemotherapy alone ☐
   g. Molecular targeted treatment alone ☐
   h. None ☐
11. History of recurrence after initial surgery: Yes ☐ No ☐
12. If yes to question 8, how many timies? _____
13. If yes to question 8, what is the time gap in months between initial surgery and recurrences? _____
14. Treatment of recurrent disease
   a. Surgical resection alone ☐
   b. Surgical resection with radiotherapy ☐
   c. Surgical resection with neoadjuvant or adjuvant systemic chemotherapy ☐

d. Surgical resection with neoadjuvant or adjuvant molecular targeted treatment ☐
e. Radiotherapy alone ☐
f. Systemic chemotherapy alone ☐
g. Molecular targeted treatment alone ☐
h. None ☐

15. History of herbal medicine: Yes ☐ No ☐

Part II: Glivec International Patient Program Assessment (GIPAP) for DFSP

1. Date of histologic diagnosis _____
2. Molecular study done? Yes ☐ No ☐
3. Date patient enrolled in GIPAP: _____
4. Indication for molecular targeted treatment (imatinib):
    a. Locally advanced disease which was difficult to resect ☐
    b. Metastatic disease ☐
    c. Recurrent and difficult to resect disease ☐
    d. Neoadjuvant for surgical treatment ☐
    e. Adjuvant to surgical treatment ☐
5. Dose of imatinib used: _____
6. Response of disease to imatinib
    i. At 3 months
        a. Complete response ☐
        b. Partial response ☐
        c. Stable disease ☐
        d. Progression while on treatment (no response) ☐
    ii. At 6 months
        a. Complete response ☐
        b. Partial response ☐
        c. Stable disease ☐
        d. Progression while on treatment (no response) ☐
    iii. At 12 months
        a. Complete response ☐
        b. Partial response ☐

c. Stable disease ☐
d. Progression while on treatment (no response) ☐

iv. Beyond 12 months
a. Complete response ☐
b. Partial response ☐
c. Stable disease ☐
d. Progression while on treatment (no response) ☐

7. Adverse events during treatment
a. Hematologic ☐
a. Anemia ☐
b. Thrombocytopenia ☐
c. Leucopenia/neutropenia ☐
d. Febrile neutropenia ☐
b. Non-hematologic
a. Mucocutaneous ☐
b. Gastrointestinal ☐
c. Metabolic ☐
d. Musculoskeletal ☐
e. Others, specify_____

Table 5. Revised RECIST guideline (version 1.1)Evaluation of target lesions

Response	***Required criteria***
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Table 6. CTCAE version 4.0 Hematologic Toxicity

Blood element	Grade 1	Grade 2	Grade 3		5
Neutrophils	<LLN to 1500/microL	1000 to 1500/microL	500 to 1000/microL	<500/microL	
Platelets	<LLN to 75,000/microL	50,000 to 75,000/microL	25,000 to 50,000/microL	<25,000/microL	
Hemoglobin	<LLN to 10 g/dL	8.0 to 10.0 g/dL	<8.0 g/dL	Life-threatening consequences; urgent intervention indicated	Death
Lymphocytes (total)	<LLN to 800/microL	500 to 800/microL	200 to 500/microL	<200/microL	
CD4 count	<LLN to 500/microL	200 to 300/microL	50 to 200/microL	<50/microL	
Febrile neutropenia			ANC <1000/microL with a single temperature >38.3°C (100.4°F) or a sustained temperature ≥38°C (100°F) for more than one hour	Life-threatening consequences; urgent intervention indicated	Death