Published in final edited form as:

Clin Adv Periodontics. 2017 August ; 7(3): 115–120. doi:10.1902/cap.2016.160050.

Oral Effects and Early Implant Survival Results After Imatinib Discontinuation Therapy for Chronic Myelogenous Leukemia: A Case Report

Douglas R. Dixon* and Alaa Yassin*

*Department of Periodontics, University of Washington, Seattle, WA

Abstract

Introduction—Little is known regarding the success, failure, or complication rates of advanced implant procedures in patients after discontinuation therapy of long-term medications for the treatment of chronic myelogenous leukemia (CML). This case report presents initial results of a case involving implant placement in the mandible and maxilla as well as reduction of palatal oral pigmentation in a patient discontinuing long-term tyrosine kinase inhibitor (TKI) therapy for CML.

Case Presentation—A 57-year-old male was referred to the Department of Periodontics, University of Washington, Seattle, Washington, for an assessment of edentulous areas (tooth sites #3 and #14) and failing tooth #19. Previous medical treatment included oral administration (>10 years) of TKI for the treatment of CML. Systemic complications arising from long-term TKI therapy were treated with discontinuation of this medication. Concurrently, after multispecialty dental and medical consultation, extraction of tooth #19 with immediate implant placement and bilateral sinus augmentation with simultaneous implant placement were successfully performed during three separate surgical appointments. Additionally, marked reduction of oral palatal pigmentation was observed during the surgical and restorative phases after TKI discontinuation.

Conclusions—Patients with a history of long-term TKIs for CML are at risk for developing complications that result in discontinuation of therapy. Long-term benefits of therapy may allow these patients to enjoy remission with an extended and improved quality of life. Patients undergoing discontinuation therapy may seek dental care. Therefore, dental providers need to understand these systemic interactions and, with multispecialty consultation, may help effectively treat these individuals.

Graphical abstract

CORRESPONDENCE: Dr. Douglas R. Dixon, Department of Periodontics, School of Dentistry, University of Washington, 1959 NE Pacific St., Box 357444, Seattle, WA 98195-7444. ddixon@uw.edu.

The authors report no conflicts of interest related to this case report.

Keywords

Dental implants; palate; periodontium; pharmacology

Background

Chronic myelogenous leukemia (CML) is a hematologic disorder characterized by unregulated proliferation of myeloid cells within the bone marrow resulting in accumulation of these cells within the blood, with 8,000 new reported cases annually.^{1–3} Genetically, CML has been linked to a chromosomal translocation abnormality involving chromosomes 9 and 22 (coined the Philadelphia chromosome).^{4,5} In 2001, targeted therapies like Bcr-Abl tyrosine kinase inhibitors (TKIs) were introduced to inhibit the myelo-proliferation responsible for CML.^{6,7} This therapy was found to allow for regrowth of normal bone marrow stem cells, stabilizing mature white blood cell (WBC) populations, and effectively inhibiting the progression of CML in adults.^{6–8} With TKI medications and associated targeted therapies, patients with CML now enjoy an improved quality of life and longevity similar to that of the general population.⁹

Over time, problems associated with long-term therapy with TKIs have arisen owing to either high financial costs or reported complications such as chronic diarrhea, cardiotoxicities, oral pigmentation, skin hypopigmentation, or additional patient concerns related to impaired fertility and/or teratogenesis potentials.^{10–12} These concerns have prompted TKI discontinuation therapy trials with complete remission of CML reported in certain patients. However, little is known regarding early dental implant survival or related surgical complications in patients undergoing discontinuation therapy after long-term treatment for CML. Therefore, this report describes the early healing results of implant-related therapy in the mandible and maxilla, as well as changes in palatal pigmentation, in a patient who discontinued TKI treatment for CML after 15 years of therapy.

Clinical Presentation

A 57-year-old male was seen in 2014 within the Graduate Department of Periodontics, University of Washington, Seattle, Washington, for his hygiene reevaluation appointment. The patient's current chief concern was related to the existing edentulous areas (tooth sites #3 and #14) and failing tooth #19. The patient's medical history was significant for a previous diagnosis of CML and subsequent treatment with a first-generation TKI (400 mg imatinib,[†] daily) starting in 2002. Past dental history was sporadic but included routine restorative care and previous osseous surgery for probing depth (PD) reduction. Non-compliance with previous space-maintaining devices resulted in mesial tipping of tooth #15

and inadequate restorative space. Periodontal examination of the oral cavity revealed generalized mild-to-moderate gingivitis superimposed on a reduced periodontium, with maxillary and mandibular PDs ranging from 2 to 4 mm and partial edentulism. Deeper PDs, Class III furcation, and Class II mobility were associated with vital tooth #19. Also observed was a non-symptomatic oral hyper-pigmentation of the palatal mucosa (Fig. 1) that was not previously recorded.

Consultation with the patient's primary care physician revealed that although TKI treatment (>10 years) resulted in complete remission of CML (Bcr-Abl) markers, symptoms of renal and intestinal toxicity were becoming apparent, and discontinuation therapy was suggested and ultimately accepted by the patient. Any recurrence of CML symptoms would be managed with reintroduction of the same TKI or second-generation TKIs or alternative targeted therapies. Owing to absence of symptoms and stabilization of the patient's condition, including normal blood and laboratory values, no contraindications to dental or implant therapy or healing was suspected. After medical consultation and treatment planning discussions, the patient provided oral and written consent for treatment.

Case Management

In preparation for the proposed implant therapy to replace the lost maxillary and mandibular teeth, the patient's primary care physician suggested 2 g prophylactic amoxicillin (AMOX) 60 minutes before surgical therapy. Presurgical blood analysis showed normal components (Table 1) with slightly elevated creatinine and urea nitrogen values (supplemental chemistry panel not shown). In two separate appointments, both the maxillary sites (tooth sites #3 and #14) underwent simultaneous sinus augmentation and implant placement via a lateral wall approach, with 5 × 10-mm-diameter internal connection implants placed (≈ 35 Ncm final torque) and submerged after primary closure was achieved. A representative example of the surgical procedure is shown in Figures 2a through 2e. Additionally, in a third appointment, the mandibular left first molar was extracted, an immediate implant (5 × 10-mm-diameter internal connection implant) was placed with 30 Ncm initial stability, and the residual site defect was grafted[†] and covered with an inner collagen membrane[§] and outer nonresorbable membrane.^{||} After each surgical appointment, a 7- to 10-day continuation dose of AMOX (500 mg, three times daily), acetaminophen (as needed), reduced dosages of narcotic analgesics (as needed), and chlorhexidine oral rinses were prescribed. Discontinuation of TKI treatment occurred during the healing phase of the final implant placement.

Clinical Outcomes

Figures 2f through 2j show the representative early healing results post-surgically characteristic for this patient. At ≈ 12 months after implant placement, triplicated resonance frequency analysis was performed,[¶] and implant stability quotient values averaged 72 to 75

[†] Gleevec/Glivec (imatinib mesylate), Novartis, Basel, Switzerland.

[‡] Alloplast, LifeNet Health, Virginia Beach, VA.

[§] OsseoGuard, Zimmer Biomet, Palm Beach Gardens, FL.

^{||} Cytoplast barrier membrane, Osteogenics Biomedical, Lubbock, TX.

[¶] Ostell, Columbia, MD.

and 83 for the maxillary and mandibular implants, respectively. Implant #14 was used as orthodontic anchorage to distalize tooth #15. Figure 3 shows the sequential radiographic healing results spanning 6 (Fig. 3b) and 12 (Fig. 3c) months after implant placement. Figure 1 shows the reduction of oral pigmentation, which appeared to normalize around 9 months. The multispecialty team, including the patient's primary care physician and oncologist, recommended continued oral care follow-up during the healing phase, and the patient's complete blood count and associated laboratory values remained stable throughout all treatment phases. The patient was placed on a strict 4- to 6-week recall program with periodontal, dental, and oral mucosal reevaluations.

Discussion

Long-term side effects of TKIs have been associated with mild-to-moderate adverse outcomes or events, including peripheral edema, muscle cramping, musculoskeletal pain, diarrhea, and nausea, as well as rash or associated skin issues potentially impairing or significantly impacting quality of life.^{10,13} More severe adverse events have also been reported to include neutropenia, anemia, liver enzyme elevation, and serious birth defects.¹⁰ These events have prompted development of second-generation TKIs and alternative therapies.

Although early therapeutic approaches using TKIs for patients with CML suggested that therapy be continued indefinitely,¹³ the prevalence of long-term-adverse events and new research may be challenging this initial approach. Discontinuation trials have reported substantial and continued reduction in CML markers after discontinuation and minimal residual disease, with event-free survival reported in almost 90% of patients after 60 months.^{10,13,14}

Although these initial results are extremely promising, little is known regarding the effects that changes in CML therapy will have on dental surgical healing and implant survival. In this particular case, all periodontal and implant-related surgical procedures were successful without any significant complications observed. Palatal discoloration associated with long-term TKI therapy was significantly improved (Figs. 1a through 1c and 4a), and all implants placed were restored and fully functional (Figs. 3c and 4).

To the authors' knowledge, this is the first report of evaluation of early healing of advanced implant procedures in a patient undergoing TKI discontinuation therapy. Additionally, the apparent improvement of a long-standing, oral pigmented lesion observed on the palate is clinically characterized. These results suggest that successful implant therapy and improved oral conditions may be expected in patients undergoing a change or discontinuation of therapy for long-standing diseases like CML.

References

* indicates key references.

1. Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: Biology and therapy. *Ann Intern Med.* 1999; 131:207–219. [PubMed: 10428738]

- 2*. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med*. 1999; 340:1330–1340. [PubMed: 10219069]
3. American Cancer Society. *Cancer Facts & Figures*. New York: American Cancer Society; 2016. p. 1-72.
4. Nowell PC. Discovery of the Philadelphia chromosome: A personal perspective. *J Clin Invest*. 2007; 117:2033–2035. [PubMed: 17671636]
5. Rowley JD. Genetics. A story of swapped ends. *Science*. 2013; 340:1412–1413. [PubMed: 23788787]
- 6*. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med*. 2001; 344:1038–1042. [PubMed: 11287973]
- 7*. Kantarjian H, Sawyers C, Hochhaus A, et al. International STI571 CML Study Group. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med*. 2002; 346:645–652. [PubMed: 11870241]
- 8*. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: Results of a phase 2 study. *Blood*. 2002; 99:1928–1937. [PubMed: 11877262]
9. Gambacorti-Passerini C, Antolini L, Mahon FX, et al. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. *J Natl Cancer Inst*. 2011; 103:553–561. [PubMed: 21422402]
- 10*. Melo JV, Ross DM. Minimal residual disease and discontinuation of therapy in chronic myeloid leukemia: Can we aim at a cure? *Hematology Am Soc Hematol Educ Program*. 2011; 2011:136–142. [PubMed: 22160025]
- 11*. Romeo U, Palaia G, Fantozzi PJ, Tenore G, Bosco D. A rare case of melanosis of the hard palate mucosa in a patient with chronic myeloid leukemia. *Case Rep Dent*. 2015; 2015:817094. [PubMed: 26451262]
12. Wang Y, Zhao Y, Liu L, et al. Inhibitory effects of imatinib mesylate on human epidermal melanocytes. *Clin Exp Dermatol*. 2014; 39:202–208. [PubMed: 24479586]
13. Druker BJ, Guilhot F, O'Brien SG, et al. IRIS Investigators. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med*. 2006; 355:2408–2417. [PubMed: 17151364]
14. Ross DM, Branford S, Seymour JF, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: Results from the TWISTER study. *Blood*. 2013; 122:515–522. [PubMed: 23704092]

Summary

Why is this case new information?

- Little to no information related to early healing and implant success rates of patients initially treated with a TKI (imatinib) and subsequent discontinuation
- During the observation period, reduction and continued improvement over time of significant oral pigmentation on the palate, a suspected result of long-term therapy with imatinib, after discontinuation of the drug

What are the keys to successful management of this case?

- Understanding the potential complications as well as successful outcomes associated with leukemia and its treatments
- Proper coordination of dental professionals with multidisciplinary medical teams
- Careful monitoring of patient medical conditions with appropriate dental therapy to improve quality of life

What are the primary limitations to success in this case?

- Disrupted or lack of coordination between medical and dental professionals
- Access to care or lack of patient compliance

FIGURE 1.

Initial palatal pigmentation versus 6- and 9-month results after imatinib discontinuation.

Arrows depict representative pigmented areas at the time. **1a** Palatal view during initial examination revealed a non-symptomatic, bilateral, diffuse, blue to bluish-gray pigmentation centered on the hard palate (with a slight soft palate extension) that did not blanch on palpation or pressure application. **1b** Palatal view 6 months after discontinuation therapy revealed overall hard and soft tissue pigmentation reduction. **1c** Palatal view 9 months after discontinuation therapy revealed continued pigmentation reduction. Arrows removed for easier comparison.

FIGURE 2.

Representative implant surgical procedure (tooth #3 sinus augmentation with simultaneous implant placement and early healing). **2a** Measurement and outline of lateral window approach to the maxillary right sinus after full-thickness flap elevation. **2b** Elevation and preservation of outer osseous wall (window) and initial sinus membrane elevation without perforation. **2c** Autogenous bone collected and mixed with xenograft material (in a 50:50 ratio) under sterile conditions. **2d** Two-thirds sinus fill after medial, anterior, and lateral elevation of membrane in the projected implant site. **2e** Simultaneous implant placement was performed with initial implant stability obtained in residual basal bone beneath the sinus floor. Remaining autograft–xenograft mixture (50:50 ratio) was placed over implant; a bioabsorbable membrane was placed over the grafted bone, and complete closure was obtained. **2f through 2j** Typical early healing response of patient over the initial healing period: 1 week (2f); 2 weeks (2g); 4 weeks (2h); 8 weeks (2i); and 18 weeks, 2 weeks after second-stage uncovering (2j). Between the second and fourth week postoperative appointments (2g and 2h), imatinib therapy was discontinued.

FIGURE 3.

Preoperative and postoperative radiographic assessments. **3a** Preoperative panoramic radiograph shows pre-initial examination results before initiation of care and imatinib discontinuation therapy. **3b** Six-month postoperative panoramic radiograph shows the sinus and implant healing response in the maxilla and mandible. Discontinuation of imatinib therapy occurred at 6 months. **3c** Postoperative (12 months after implant placement/imatinib discontinuation) panoramic radiograph shows results after sinus and implant healing in the maxilla and mandible.

FIGURE 4. Thirteen-month clinical assessment after implant placement and imatinib discontinuation. Maxillary (**4a**) and mandibular (**4b**) occlusal photographs reveal stabilized reduction of palatal pigmentation and successful functional loading of implants without apparent complication.

TABLE 1**Presurgical Hospital Blood Laboratory Results**

Blood Test	Result	Hospital Laboratory Reference Range
WBCs (th/mm ³)	5.6	3.4 to 10.8
Neutrophils (ANC th/mm ³)	3.28	1.4 to 7.0
Lymphocytes (AB th/mm ³)	1.68	0.7 to 3.1
Monocytes (AB th/mm ³)	0.45	0.1 to 0.9
Eosinophils (AB th/mm ³)	0.17	0.0 to 0.4
Basophils (AB th/mm ³)	0.0	0.0 to 0.2
Red blood cells (mil/mil ³)	4.79	4.14 to 5.80
Hemoglobin (g/dL)	11.7	12.6 to 17.7
Hematocrit (%)	43	37.5 to 51
Platelets ($\times 10^3/\mu\text{L}$)	182	150 to 379

ANC = absolute neutrophil count; th = thousands; AB = absolute; mil = millions.