

## **Prospective study establishing a management plan for impacted third molar in patients undergoing hematopoietic stem cell transplantation**

Kenji Yamagata, DDS, PhD,<sup>a</sup> Kojiro Onizawa, DDS, PhD,<sup>b</sup> Toru Yanagawa, MD, DDS, PhD,<sup>b</sup>  
Yasutoshi Takeuchi, DDS,<sup>c</sup> Yuichi Hasegawa, MD, PhD,<sup>d</sup> Shigeru Chiba, MD, PhD,<sup>e</sup> Hiroki Bukawa,  
MD, DDS, PhD,<sup>f</sup>

<sup>a</sup> Assistant Professor, Department of Oral and Maxillofacial Surgery, Institute of Clinical Medicine,  
University of Tsukuba, Tsukuba, Japan

<sup>b</sup> Associate Professor, Department of Oral and Maxillofacial Surgery, Institute of Clinical Medicine,  
University of Tsukuba, Tsukuba, Japan

<sup>c</sup> Chief, Division of Dentistry and Oral and maxillofacial Surgery, Mito Saiseikai General Hospital,  
Mito, Japan

<sup>d</sup> Associate Professor, Division of Hematology, Institute of Clinical Medicine, University of Tsukuba,  
Tsukuba, Japan

<sup>e</sup> Professor, Division of Hematology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba,  
Japan

<sup>f</sup> Professor, Department of Oral and Maxillofacial Surgery, Institute of Clinical Medicine, University  
of Tsukuba, Tsukuba, Japan

*Reprint requests:* Dr. Kenji Yamagata

Department of Oral and Maxillofacial Surgery, Institute of Clinical Medicine, University of Tsukuba,  
1-1-1 Tennodai, Tsukuba, Ibaraki, 305-8575, Japan

Tel: +81-29-853-3052, Fax: +81-29-853-3052

E-mail: [y-kenji@md.tsukuba.ac.jp](mailto:y-kenji@md.tsukuba.ac.jp)

**Objective.** Although dental treatment before hematopoietic stem cell transplantation (pre-HSCT) is essential to prevent serious infections from oral sources, the best management plan for impacted third molar (ITM) is unclear.

**Study design.** This study was planned to establish a management plan for ITM. Eighty-four candidates for HSCT therapy were consecutively enrolled in the prospective trial. The management plan, which was evidence-based and prospectively decided, was to extract the symptomatic ITMs and to leave the asymptomatic ones untreated, regardless of their impacted position.

**Results.** Eighty-seven ITMs were observed in 35 patients. The ITMs were in the maxilla of 25 patients and the mandible of 28 patients. Dental extraction of 7 teeth was performed in 6 patients without complications. All the patients received the scheduled HSCT therapy and none experienced odontogenic infection while myelosuppressed.

**Conclusions.** This management plan for ITM appears to be appropriate for pre-HSCT patients. Moreover, the experienced dental provider is suggested being needed and valuable for as a part of the HSCT team.

Hematopoietic stem cell transplantation (HSCT) has become one of the most essential treatments for myelosuppressed patients with malignant and non-malignant hematological diseases, including acute and chronic leukemias, aplastic anemia, myelodysplastic syndromes, and lymphomas.<sup>1,2</sup> Although HSCT is an effective treatment modality for these patients, successful engraftment after HSCT often requires severe myelosuppression, which is accomplished by total body irradiation (TBI), chemotherapy (CTX), or a combination of the two. The patients' myelosuppressed status predisposes them to infection, resulting in an increased incidence of infectious complications that may be life-threatening.<sup>2,3</sup>

The oral cavity is a potential site of origin for infectious complications in patients receiving HSCT therapy, because it is an important source of bacteremia for agents that can cause systemic infections.<sup>4-7</sup> To prevent these odontogenic complications, comprehensive pre-transplant dental management has been incorporated into the preparatory steps for patients scheduled to receive HSCT therapy. This approach is supported by the National Institutes of Health consensus statement on oral complications of cancer therapy (1989), which states, "All cancer patients should have an oral examination before initiation of cancer therapy, and the treatment of preexisting or concomitant oral disease is essential in minimizing oral complications in all cancer patients. Dental foci are potential sources of systemic infections that need to be eliminated or ameliorated before commencement of anticancer therapy."<sup>8</sup> Therefore, to prevent significant morbidity, it is very important that patients scheduled to receive HSCT therapy have a pre-transplant dental evaluation to identify and treat potential sources of infection.<sup>2,9-13</sup> Recently, the oral health care providers are needed to an integrated oncology team.

Although management protocols defining the appropriate treatment modality for dental caries, apical periodontitis, and marginal periodontitis,<sup>12,13</sup> have been established, the management plan for impacted third molar (ITM) has been unclear. There are two basic treatment options for managing an

asymptomatic ITM. Some clinicians advocate prophylactic extraction as soon as possible,<sup>14, 15</sup> whereas others prefer a more conservative approach,<sup>16, 17</sup> because the risk of developing diseases associated with the third molar can be reduced by good oral hygiene. A previous study showed that 40% of patients who underwent the prophylactic removal of ITMs, whether symptomatic or asymptomatic, experienced postoperative complications, such as bleeding, alveolitis, trismus, or infection, in the course of intensive cancer therapy, including HSCT.<sup>16</sup>

This prospective study was carried out to establish a management plan for ITM in patients scheduled to receive HSCT therapy for hematological malignancies.

### **Patients and Methods**

Between 2000 and 2008, 84 candidates for HSCT therapy were referred from the Division of Hematology to the Department of Oral and Maxillofacial Surgery, Tsukuba University Hospital, to be screened for dental pathologies. All 84 patients had hematological malignancies and underwent HSCT therapy after the dental assessment. Thirty-five of the 84 patients (41.7%) had one or more ITMs, and were consecutively enrolled into the prospective trial. The 35 patients in the ITM group included 18 males and 17 females, ranging in age from 16 to 64 years with a mean of 32.1 years. The patients in the non-ITM group at the time of HSCT included one of the ITM patients whose symptomatic third molar had been removed, and therefore was made up of 50 patients. All participants gave informed consent prior to proceeding with treatment.

The dental status of all the patients was evaluated at the initial visit, before HSCT, by two experienced dentists. The oral evaluation consisted of a clinical examination of the hard and soft oral tissues and a radiographic survey, including a panoramic x-ray. All dental diseases encountered, including apical and marginal periodontitis and impacted third molar, were recorded for each patient. Usually, infusion of hematopoietic stem cell is performed day 0 and conditioning regimen start day

-7. Dental treatment must be completed at least 21 days before infusion of hematopoietic stem cell, to give the patient time to undergo the conditioning regimen for HSCT. In this study, symptoms associated with ITM and the position of the ITM on the panoramic radiograph were recorded. The relative depth of the third molar was scored according to the classification of Archer.<sup>18</sup> Using the panoramic radiographic survey to evaluate the horizontal position of each ITM, we classified them relative to the second molar. At position A, the highest point of the third molar is on the same level or below the occlusal plane of the adjacent second molar. At position B, it is below the occlusal plane but above the cervical line of the second molar. At position C, it is below the cervical line of the second molar (Fig. 1).

The management plan for ITM was decided according the results of our previous study.<sup>12</sup> Symptomatic teeth with gingival swelling, pain, and/or purulent drainage were extracted, and asymptomatic third molars were not treated, regardless of their impacted position. Other caries, and apical and marginal periodontitis were managed according to our previous reports,<sup>12, 13</sup> and all dental management was finished before HSCT. We describe the details of the treatment:

Teeth with dental caries are restored in patients with sufficient time for dental treatment, but observed in those without enough time. Teeth with recently symptomatic apical periodontitis or asymptomatic apical periodontitis and periapical radiolucency of the maximal diameter greater than 5 mm are treated with root canal treatment or dental extraction. Marginal periodontitis, teeth with gingival swelling, pain and purulent discharge, a probing depth greater than 8 mm, or severe mobility are removed, whereas teeth with marginal periodontitis but without these signs and symptoms are observed and tooth brushing instruction and/or scaling is provided.

For the HSCT procedure, all patients were admitted to a disinfected room. During the conditioning period, each patient experienced at least one episode of fever higher than 38 °C and an absolute white blood cell count (WBC) of less than 1,000/ $\mu$ l lasting more than several days, as

manifestations of their myelosuppressed status. The dental follow-up was conducted during HSCT hospitalization for approximately two weeks. Any patient with local signs and symptoms consistent with odontogenic infections, such as swelling, pain, redness, and sensitivity of the gingiva surrounding the teeth had a dental consultation and was given treatment as necessary. The frequency and occurrence of oral complaints and complications were recorded on the patients' medical charts and investigated throughout the course of HSCT therapy, and the effectiveness of the management plan for ITM was assessed by the attending dentists and hematologists.

## **Results**

The hematologic diagnoses were shown in Table I. Hematopoietic stem cells were collected from the bone marrow of 51 patients, the peripheral blood of 30, and the umbilical cord blood of 3. Conditioning regimen was CTX and TBI for 40 patients and only CTX for 40 patients (Table I).

The dental status of all the patients was evaluated between 3 and 492 days before the commencement of HSCT therapy, with a median of 60.5 days. The time available for dental treatment was less than 1 month for 23 patients, from 1 to 2 months for 19, from 2 to 3 months for 17, and more than 3 months for 25. Patients whose dental examination was carried out more than 2 months pre-HSCT were re-examined within one month of HSCT to check for new dental disease. Dental caries were observed in 50 patients (192 teeth), marginal periodontitis in 45 patients (250 teeth), and apical periodontitis in 29 patients (64 teeth). Eighty-seven ITMs were observed in 35 patients, located in the maxilla of 25 patients (40 teeth) and the mandible of 28 patients (47 teeth).

Of the 40 maxillary third molars, 18 were in position B and 22 were in position C. Of the 47 mandibular ones, 7 teeth were in position A, 35 in position B, and 5 in position C. Symptomatic teeth were observed in 7 mandibular ITMs (14.9%), 3 of which were in position A, 3 in position B, and 1 in position C (Table II). The pericoronitis of position C was associated with apical lesion of

second molar. There was no significant correlation between the position and the incidence of ITM symptoms. The distribution of ITMs according to patient age was 33 teeth in patients younger than 20, 28 in patients aged 21 to 30, 6 in patients aged 31 to 40, 17 in patients aged 41 to 50, and 3 in patients 51 and older.

The 7 symptomatic teeth of 6 patients were extracted, and the other 80 teeth of 29 patients were not treated. One of the patients whose symptomatic ITMs were extracted had no asymptomatic ITMs, so this patient was included with the none-ITM group for the rest of the study. As described above, all of the extracted (i.e. symptomatic) teeth were mandibular. The dental extractions were performed successfully under oral administration of amoxicillin (AMPC), and no postoperative complications occurred. The planned management of the third molar was completed for all patients before the initiation of the conditioning regimen. None of the 84 patients, including the 34 that had asymptomatic ITMs, who all underwent HSCT therapy, showed signs or symptoms of odontogenic infection caused by the third molar. In a 25-year-old female patient with acute myeloid leukemia, pericoronitis of the asymptomatic left mandibular ITM was seen 3 months after HSCT. This odontogenic infection was mild and resolved by treatment with an antibiotic drug (Fig. 2).

There were no significant differences in the gender, age, origin of hematopoietic stem cells (i.e., from bone marrow or other tissue), or in the period from the first pre-HSCT dental visit to HSCT between the patient groups with or without ITM. The median number of days in which patients' temperature was higher than 38 °C was 5, ranging from 1 to 23 days for patients with asymptomatic ITMs, and 0 to 60 days for 3 patients without ITMs. This difference in fever duration was not significantly different for patients with or without ITMs. There was also no significant difference between the patient groups in the median number of days on which the patient's WBC was less than 1,000/ $\mu$ l or in the minimum WBC. In no case was there odontogenic infection associated with the third molar. Sepsis did occur from oral mucositis in 2 patients in the ITM group

and 4 in the non-ITM group, and this difference was not statistically significant. The sepsis associated with oral mucositis was diagnosis with severe symptom and blood bacterial examination.

The post-HSCT long-term survival was 13 of 34 patients in the ITM and 35 of 50 patients in the non-ITM group, and this difference was significant (Table III). The median survival period for patients with or without ITM undergoing HSCT was 15.5 and 33.9 months, respectively, which was not significantly different. The median number of days on which the patient's WBC was less than 1,000/ $\mu$ l was 17 days, with a range of 6 to 75 days for patients who died, and 13 days, with a range of 0 to 36 days for patients who survived. This difference was significant ( $p < 0.05$ ).

## **Discussion**

Dental extraction guidelines for patients scheduled to receive HSCT therapy have been published. Extractions should avoid trauma as much as possible, should include alveolectomies as necessary, primary closure should be with multiple interrupted sutures. When possible, the extraction should be performed during remission and 10 to 14 days before the start of conditioning. If the platelet count was  $< 40,000/\mu$ l, platelets should be transfused before surgery. If the absolute granulocyte count was  $< 2,000/\mu$ l on the day of extraction, a prophylactic antibiotic should be used.<sup>6,</sup>

<sup>19</sup> Because there is a higher risk of postoperative complication for ITM, especially for HSCT patients,<sup>16, 17, 20</sup> dental extraction of ITMs should be more aggressive than for other teeth and be performed 14 to 21 days before the start of conditioning. If a postoperative complication occurs, conditioning must be delayed. Therefore, the extraction of ITMs should be minimal as long as the risk of odontogenic infection during HSCT is not elevated. In our study, only symptomatic teeth (i.e., gingival swelling, pain, and/or purulent drainage) were extracted, and asymptomatic ITMs were not treated, as indicated by our previous reports,<sup>12, 13</sup> and none of the patients who underwent HSCT therapy showed signs or symptoms of odontogenic infection caused by ITMs. This outcome indicates that

dental extraction for symptomatic ITMs and non-surgical intervention for asymptomatic ones is safe. Advances in HSCT, such as the use of stem cells isolated from the peripheral blood instead of bone marrow, have resulted in more rapid engraftment and thus a shorter duration of pancytopenia.<sup>21</sup> Our dental management plan for ITM was supported by shorter duration of pancytopenia during HSCT.

Fernandes *et al.*<sup>22</sup> reported the incidence of symptoms arising in previously asymptomatic ITMs in otherwise healthy subjects: 23.1% of partially erupted teeth and 10.5% of unerupted teeth became symptomatic during the one-year study period. The authors also found that the risk of developing symptoms was significantly higher for ITMs in the mandible than in the maxilla, and gave the incidence for developing symptomatic mandibular ITMs at the various vertical positions as 30.6% at A, 33.8% at B, and 17.9% at C. Nonetheless, the authors concluded that the status of the third molar was not related to the subsequent development of symptoms if good oral hygiene was maintained.<sup>23</sup> In agreement, all of the ITMs of the maxilla were asymptomatic in our patient group, and we did not find any significant differences between ITM position and symptoms in the mandible. Because of the successful outcomes in our previous reports,<sup>12, 13</sup> we extracted only symptomatic teeth before HSCT and educated the patients on eliminating dental plaque, which produces pericoronitis.

Although there was a statistical difference in the long-term survival between patients with and without ITM, no significant difference was found in the survival period after HSCT. The median survival period in the ITM group was 15.5 months after HSCT. Moreover, odontogenic infections caused by ITM did not occur during myelosuppression in any patient. The median number of days of WBC less than 1,000/ $\mu$ l was significantly longer in patients who died than in surviving ones. Therefore, although the cause of the statistical difference in long-term survival was unclear, we believe that the myelosuppressed condition of the ITM group was severe, and the poor outcome reflected the severe myelosuppression and not the ITM.

One patient experienced pericoronitis 3 months after HSCT. The principal aim of the previous dental evaluation was to reduce morbidity and mortality that could arise from odontogenic infection associated with HSCT therapy during the myelosuppressed state. All potential sources of oral infection should be eliminated by dental treatment before the initiation of the conditioning regimen, but time limitations and the severity of a patient's disease status frequently interfere with complete treatment.<sup>6, 7, 24</sup> The available median time for treatment was reported to be between 15 and 47 days.<sup>24, 25</sup> In the present study, the median time available for dental treatment was 60.5 days, which was sufficient to treat dental pathologies. Pre-HSCT oral examinations are performed routinely in our hospital, and patients who are candidates for HSCT are screened for dental pathologies. The extraction after radiotherapy of head and neck cancer patients who have received high-dose radiotherapy to the jaw had the risk of osteoradionecrosis<sup>26</sup>. Although TBI is sometimes utilized as part of conditioning about 8 - 12 Gy, the TBI does not represent a risk factor for osteoradionecrosis for ITM extraction after radiotherapy. There was no previous report of osteoradionecrosis for jaw after TBI. Post-HSCT, immunosuppressants and corticosteroids may be given to the non-autologous transplant patient to prevent chronic graft versus host disease. Therefore, ITM extraction carries a risk of infection and delayed wound healing for these patients, to prevent post-HSCT odontogenic infections continual oral care would be needed.

Some studies report that systematic oral assessment, regular encouragement of patient self-care, and consistent oral care may be the most important factors related to the prevention or amelioration of oral infection during HSCT therapy.<sup>7, 19, 27</sup> In addition to the management of ITM, patient caregivers should provide careful instructions in advance about oral care during myelosuppression. Before dental treatment, all the patients in the present study were educated to eliminating dental plaque, which produces dental caries, marginal periodontitis, and pericoronitis. The extent to which the instruction influenced the absence of pericoronitis in the present study is

unknown, but we believe the instruction was beneficial. Although, odontogenic infections caused by ITM did not occur during myelosuppression in any patient, study limitation was that patients had marginal periodontitis and apical periodontitis with ITM simultaneously. Further studies with a larger sample size are required to confirm the appropriateness of the management plan proposed here for ITM.

In conclusion, our new management plan for pre-HSCT ITMs, which is to extract symptomatic teeth with gingival swelling, pain, and/or purulent drainage, and to leave asymptomatic ITMs untreated, regardless of their impacted position, appears effective to avoid odontogenic infection HSCT, at least in this small patient sample. Moreover, the experienced dental provider is suggested being needed and valuable for as a part of the HSCT team.

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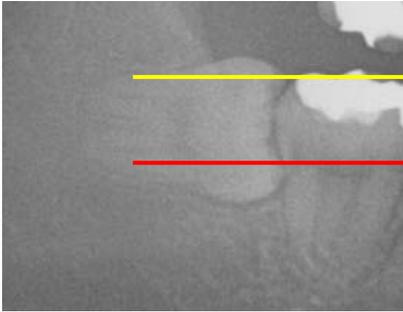
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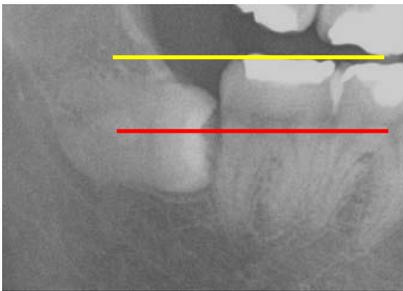
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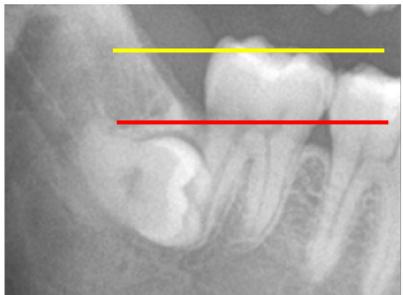
**Fig.1. Classification of third molar position**



**Position A**



**Position B**



**Position C**

Position A: The highest point of the third molar is on the same level, or below the occlusal plane of the adjacent second molar.

Position B: The highest point of the third molar is below the occlusal plane but above the cervical line of the second molar.

Position C: The highest point of the third molar is below the cervical line of the second molar.

**Fig. 2. Panoramic x-ray of the patient with post-HSCT pericoronitis**



Pericoronitis occurred at the asymptomatic left mandibular partially erupted third molar, 3 months after HSCT, in a 25 year-old female with AML. Arrow shows third molar that caused the pericoronitis.

**Table I. Oncologic diagnoses**

Disease	No. of patients
ML	24
CML	18
AML	15
ALL	12
MM	5
MDS	5
Others	5

Medical treatment	No. of patients
BMT	51
PBSCT	30
UCBT	3

Conditioning regimen	No. of patients
CTX+TBI	40
CTX	40
Unknown	4

ML, malignant lymphoma; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; MM, multiple myeloma; MDS, myelodysplastic syndrome; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; UCBT, umbilical cord blood transplantation

CTX, chemotherapy; TBI, total body irradiation

**Table II. Radiographic survey of ITM positions and symptom incidence**

Position*	Symptomatic teeth/No. of teeth (%)	
	Maxilla (n=25)	Mandible (n=28)
A	0/0 (0)	3/ 7 (42.9)
B	0/18 (0)	3/35 ( 86)
C	0/22 (0)	1/ 5 (20.0)
Total	0/40 (0)	7/ 47 (14.9)

\*Each position was determined as shown in Fig.1.

**Table III. Association between ITMs at HSCT and patient or HSCT factors**

	ITMs at HSCT		P
	Present (n=34)	Absent (n=50)	
Gender (M/F)	16/18	28/22	n.s.
Age* (years)	29 (16-64)	47.5 (22-66)	n.s.
BMT	23	28	n.s.
Period from first visit to HSCT* (months)	2.1 (0.1-16.4)	1.8 (0.2-8.1)	n.s.
Febrile days during HSCT* (more than 38 °C)	5 (1-23)	3 (0-60)	n.s.
Compromised days* (WBCs<1,000/ $\mu$ l)	16 (3-36)	12 (0-75)	n.s.
Minimum WBC* (/ $\mu$ l)	0 (0-200)	0 (0-400)	n.s.
Infection associated with third molar	0	0	n.s.
Sepsis associated with oral mucositis	2	4	n.s.
Long-term survival (death/survival)	21/13	15/35	<0.01
Survival period from HSCT (months)*	15.5 (0.5-103.7)	33.9 (0.67-133.1)	n.s.

\*Median (range)

BMT, bone marrow transplantation; HSCT, hematopoietic stem cell transplantation;

WBC, White blood cell