Dental abnormalities of a long-term survivor of a childhood hematological malignancy: literature review and report of a case

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The treatment of haematological malignancy is multimodal and involves chemotherapy, radiotherapy and/or bone marrow transplants. With the advancement in cancer therapy, there is an increase in the survival of many children with childhood haematological malignancy. In addition, the late effect of the oncology treatment to the orofacial and dental development becomes significant in terms of the potential clinical impact that may affect the quality of life of the survivor. The severity of the long-term effects is dependent on the age of the child at initiation of treatment and whether chemotherapy is combined with radiation or not. The dental treatment may become more complex if the patient requires advanced restorative dental care and the roots malformation may complicate orthodontic treatment. Therefore these patients may require a scheduled careful preventive programme, long-term follow up, with prophylactic treatment and intervention at appropriate time to minimize the consequences of the disease and the given therapy.

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INTRODUCTION

The First Report of the National Cancer Registry Cancer Incidence in Malaysia 2002[1] reported that the chances for a Malaysian to acquire cancer in his lifetime is in the ratio of 1:4. In addition, for the youngest age group reported (below 14 years old) leukaemia comprised nearly half of all cases in both sexes followed by tumour of the brain and eye. Currently, there is no reported data on paediatric cancer survival in Malaysia. However, Wallace *et al*.[2] reported that in the United Kingdom, the overall survival five years after diagnosis is 70% for all paediatric malignancies. Thus, there is a growing survivor population of long-term childhood cancer.

Leukaemia is a malignant neoplasm of hematopoietic stem cells characterized by diffuse replacement of bone marrow by neoplastic cells. The immune response is depressed because the function of neoplastic cells is reduced or because the number of normal white cells is lowered. The disease can be acute or chronic.[3] Acute leukaemia affects immature or blast cell lines and if untreated results in rapid clinical deterioration.

In children, 80% of acute leukaemias are acute lymphoblastic leukaemia (ALL) acute myeloid leukaemia (AML) accounts for approximately 15 to 20%. Unlike the increasing incidence of AML that occurs in adults with aging, the incidence of AML in children is relatively constant throughout childhood, with the exception of a peak during neonatal period and a slight increase during adolescence.[4] Chronic leukemias affect more differentiated, mature cell lines and are associated with a longer clinical course.[5]

Childhood cancer may be treated with surgery, chemotherapy, radiotherapy and/or bone marrow transplantation (BMT).[2] Treatment for haematological malignancy consisted of a period of chemotherapy, radiotherapy prior to BMT.[6] Current treatment regimes divide therapy into induction, consolidation and central nervous system (CNS) prophylaxis, and maintenance treatment. Induction chemotherapy (aimed at an initial induction in blast cell percentage in the bone marrow to 5% or lower) consists of treatments with various chemotherapeutic agents depending on the type of leukaemia. Following induction, a consolidation phase is done, which consists of an intensified period of treatment combines the use of antimetabolites and other agents with intrathecal (IT) chemotherapy or cranial

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irradiation for CNS prophylaxis; to kill malignant white blood cells in the brain and spinal cord, which are hidden from cytotoxic effects of systemic chemotherapeutic agents by the blood-brain barrier. Maintenance therapy continues for a period of 1-1/2 to 2 years with various chemotherapeutic agents.[6]

The basic principles of use of radiation and chemotherapy for management of paediatric oncology patients are summarized by Goho.[7] Essentially, radiation therapy attempts to destroy tumour cells that are reproducing at a higher rate with minimal damage to normal tissue. Hence only cells in the path of an external radiation beam or near implanted radioisotopes may be affected. Cell sensitivity to radiation depends upon the location in the cell cycle during irradiation. Cells are most susceptible to damage during increased mitotic activity. However, very high dose radiation affects even non-proliferating cells in phase. The effects of radiation are cumulative and dependent on per dose. If the radiation dose exceeds a certain level, cells are not able to repair the damage and the cell dies. Cells that are farther from the radiation target or protected by shielding receive less radiation and show limited damage.[8] Sufficiently high radiation doses cause ameloblasts and odontoblasts to die, regardless of position in the cell cycle. Even non-proliferating odontogenic precursor cells are destroyed, resulting in complete tooth agenesis. Partially formed teeth have remaining development halted, resulting in tooth and root agenesis.[9,10]

Chemotherapy also attempts to destroy tumour cells with minimal toxicity to normal cells.[9] Chemotherapy is selectively toxic to actively proliferating cells by interfering with DNA synthesis and replication, RNA transcription and cytoplasmic transport mechanisms. Since tumours consists primarily of rapidly proliferating cells, they are most susceptible to chemotherapy.[7]

Chemotherapeutic agents are either cell cycle phase specific or cell cycle phase non-specific.[7] Phase specific agents interfere with DNA synthesis or cell division. Phase non-specific drugs are toxic to cells in all phases of the active cell cycle. The only cells not affected are non-proliferating cells. These agents interfere with DNA replication by cross-linking DNA bases. Since tumour cells replicate asynchronously, they are not in susceptible phases during the initial chemotherapy exposure. Chemotherapeutic agents are eliminated rapidly and a single dose does not affect tumour cells entering a susceptible phase at a later time. Furthermore, chemotherapy works on first order kinetics, in which only a percentage of cells are killed with each dose, leaving some undamaged cells. Chemotherapy agents are therefore administered in multiple (fractionated) doses, so that tumour cells unaffected by the first dose are destroyed by following doses.[7]

Chemotherapy damage is related directly to the doses and repetition of the various agents.[7] Odontoblasts and ameloblast in susceptible phases in the cell cycle are damaged easily. Cells in non-proliferative germinal stages at the time of chemotherapy were reported to be unaffected and should develop normally. This differs from high dose radiation therapy, in which even non-proliferating dental cells may be destroyed. Furthermore, although radiation only affects cells in its path, chemotherapy is systemic in effect. Thus developing odontogenic cells far from a tumour are susceptible to chemotherapy damage that include arrested root development, inhibition of dentin formation and enamel defects.[11,12] Therefore tumour cells not destroyed by one mode of therapy may be destroyed by another. Multiple agents make it difficult to attribute defects specifically in odontogenesis to any single agent or therapy.[13]

Various studies had been conducted to determine the effects of the various modalities of oncological treatment to the craniofacial and dental development.[11-18] However, it was noted that the effects of radiation to the dentofacial region were associated with the age of patient at initiation of treatment and the use of cranial radiation.[19] The abnormalities were more severe in patients, who received radiation at an earlier age and at a higher dosage.[14] Chemotherapy may also have significant effects on growth.[20] The particular risks of growth impairment for any individual survivor depend upon the cancer type, the type of treatment given and the age at presentation.[21] Effects to dentofacial region due to chemotherapy are difficult to determine because of the variety of chemotherapeutic agents administered.[22]

Jaffe *et al.*[13] reported the occurrences of dental and maxillofacial abnormalities that were detected in long-term survivors of childhood cancer. The authors evaluated 68 long-term survivors of childhood cancer that comprised of 45 patients treated with maxillofacial radiation and 23 patients with chemotherapy. They noted that dental and maxillofacial abnormalities were detected in 82% of irradiated patients. Dental abnormalities observed were foreshortening and blunting of roots, incomplete calcification, premature closure of apices, delayed or arrested tooth development and caries and maxillofacial noted were trismus, abnormal occlusal relationship and facial deformities.

In the group of patients, who had chemotherapy, the authors observed possible chemotherapeutic effects in only five of 23 patients, who received treatment for tumours located outside the head and neck region. The abnormalities reported were amelogenesis imperfecta, microdontia of bicuspid teeth and a tendency toward thinning of roots with an enlarged pulp chamber.

Welbury *et al.*[23] examined 64 children, who were in remission from malignant disease reported that there was increased incidence of hypodontia (19%) and hypoplasia (36%) and the authors felt that that in some cases could be due to the original disease or treatment. Similarly, Maguire *et al.*[14] in a radiological examination

of 85 patients aged 3 to 22 years, who were in long-term effect remission from malignant disease found that 70% of the sample showed abnormalities that could be related with the time of treatment. The abnormalities found included hypodontia, microdontia, enamel hypoplasia and abnormal root development. Rosenberg *et al.*[11] also found altered root development of the premolar teeth in 17 patients treated for acute lymphoblastic leukaemia by combination chemotherapy before reaching 10 years.

Sonis *et al.*[19] evaluated the effect of therapy on dentofacial development in 97 children, who were diagnosed with acute lymphoblastic leukaemia before 10 years of age and treated with chemotherapy alone, chemotherapy plus 18 Gy cranial irradiation or chemotherapy plus 24 Gy. They reported that all patients younger than 5 years of age at diagnosis and 94% of all patients had abnormal dental development. The severity of these abnormalities was greater in children, who received treatment before 5 years of age and in those who received radiotherapy. Observed dental abnormalities included tooth agenesis, arrested root development, microdontia and enamel dysplasias. Craniofacial abnormalities occurred in 18 of 20 (90%) of patients, who received chemotherapy plus 24Gy of radiotherapy before 5 years of age.

The immediate effects of chemotherapy and irradiation on soft tissues are well documented.[7] With improving survival rate in childhood malignancies, there is an increasing interest in the long-term survivors of childhood cancer and the quality of life as long-term survivor of childhood cancer may later suffer from problems related to growth, which include obesity, puberty and reproduction, cardiac, thyroid dysfunction and cognitive and psychosocial outcomes.[21] However, the late effects to the childhood cancer survivor are the potential clinical impact on orofacial and dental development, which may affect function and aesthetics. In dentistry, this may imply an increase in the complexity of treatment that involves a scheduled long-term follow up, with prophylactic treatment and intervention at appropriate time to reduce the consequences of the disease and the therapy given. Oeffinger *et al.*[6] defined late effect as any chronic or late occurring physical or psychosocial outcome persisting or developing more than 5 years after the diagnosis of cancer.

The following is a case report of a long-term survivor of childhood haematological malignancy, who presented with multiple developmental anomalies.

CASE REPORT

A 10-year-old girl came to a local hospital complaining of overlapping lower front teeth.

Medical history revealed that patient was a survivor of haematological malignancy. Patient was diagnosed with AML at age one year in 1994. She was subsequently treated at the Prince of Wales Children's Hospital in Australia for autologous BMT in June 1995. Her treatment regime consisted of induction with chemotherapy using Berlin-Frankfurt-Muenster 87 (BFM 87) protocol followed by consolidation and maintenance phase. The chemotherapeutic agents used consisted of Ara-C, Daunorubicin, Etoposide, Thioguinine, Vincristine, Cyclophosphomide, Busulfan and VP16. She was tested positive for cytomegalovirus (CMV) and treated with Ganciclovir. Subsequently she developed low-grade fever and was put on multiple antibiotics (Flucloxacillin, Imipenen and Vancomycin).

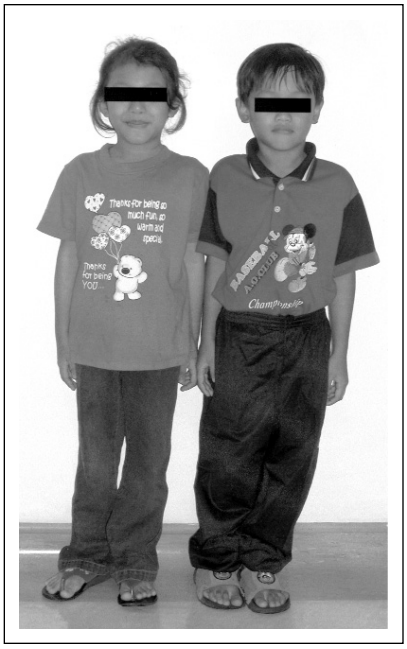


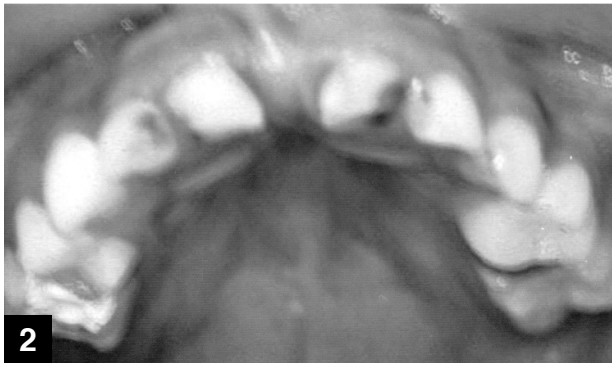
Figure 1. Patient (left) aged 10 as compared to her 6-year-old brother.

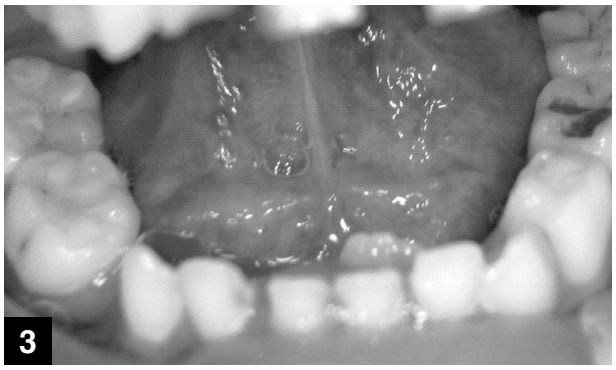
At the time of the visit, the patient was 9 years post BMT and she was healthy and currently on annual follow-up at Paediatric Institute, Kuala Lumpur.

Dental history indicated that the patient was an irregular attender and only visited the dentist when she had dental problems. She has had simple restorations and extraction done previously.

Patient is the eldest child of three children in the family. Both her younger brother, who is 6 years old and a 2-year-old sister, are healthy.

Extra-oral examination showed that the patient was small for her chronological age. She was 111cm tall and weighed 20kg and physically, she was about the same height and size as her 6-year-old younger brother (Figure 1). Subsequent checks of the medical records showed the height and weight that were taken on two previous occasions were below the 5th percentile (Figure 2). The patient had been referred to National University Hospital Malaysia for management of her short stature and is currently under the care of a paediatric endocrinologist.





Figures 2 and 3. Intra-oral views showing caries and enamel defects of 46.

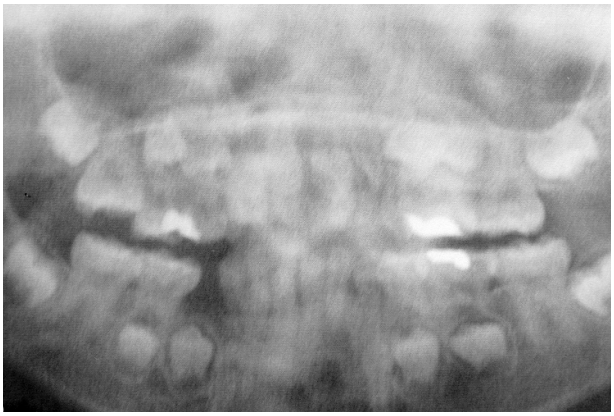


Figure 4. Panoramic radiograph showing generalized delayed dental development and malformation of roots of 16, 26 and 46.

Universal precautions for cross infection were practiced, whenever the patient was seen or treated and intra-oral examination showed that the patient is in mixed dentition stage and oral hygiene was fair and gingivae was healthy. The following teeth were present:

16 55 54 53 52 51 61 62 63 54 65 26

46 85 83 82 81 31 32 73 74 75 36

Caries were present on anterior as well as posterior teeth (Figures 3 and 4). Except for 46, which showed some whitish enamel opacity (Figure 3) the morphology and structure of all the erupted teeth appeared relatively normal.

Panoramic radiograph (Figure 4) showed the presence of all permanent tooth germs at varying stages of development. There was taurodontism of 26 and 16 and shortening of roots of 16 and 46. The crowns of the premolars and the second permanent molars appeared to be fully formed, however there was no evidence of root formation. Periapical radiograph (Figure 5) showed that the apices of 31 and 41 were almost fully formed, while only 2/3 of root formations were noted for 32 and 42. Also, these teeth have very slender and thin roots.

Management of the patient included intensive preventive measures: professional and home preventive treatment. Following satisfactory results of haematological assessment, extraction of 71 was undertaken under local anaesthesia. The patient is currently monitored for dental and facial growth development and she has been placed on a regular 6 months recall to coincide with her medical follow-up.

DISCUSSION

Children treated with radiation and chemotherapy exhibit acute complications in the oral cavity and long term complications in the dental and craniofacial development. Unlike the immediate effects of chemotherapy and irradiation on soft tissues, which are well documented,[22] most clinicians are not fully appreciative of the potential clinical impact on orofacial and dental development that may affect function and aesthetics. In dentistry, this may imply an increase in the complexity of treatment that involves a scheduled long-term follow up, with prophylactic treatment and intervention at appropriate time to reduce the consequences of the disease and the therapy given.

Without a doubt, children, who had cellular changes during the growth and development period, are more likely to suffer dental damage in the dentofacial area than adults, especially in the structural formation such as teeth and bones.

With increasing survival rate of children after treatment of childhood malignancy, the potential clinical impact on orofacial and dental development is considerable. Numerous factors have been suggested as affecting the growth and development of children under treatment for haematological malignancies. These factors include the chronic disease itself, the treatment modalities employed and the age of the individual at the time of illness and treatment given.[13]

Physically, the stature and weight of the patient was almost the similar to her brother, who was four years younger. Her stature and weight at 5-, 8- and 10 years old were below the fifth percentile and it also appeared that

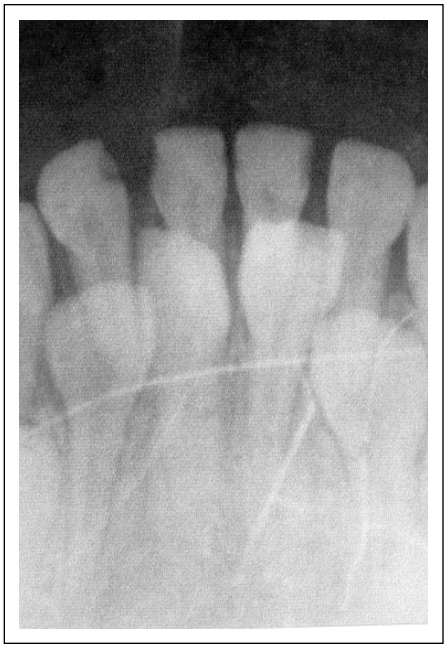


Figure 5. Periapical radiograph showing mandibular incisors with slender and thin roots.

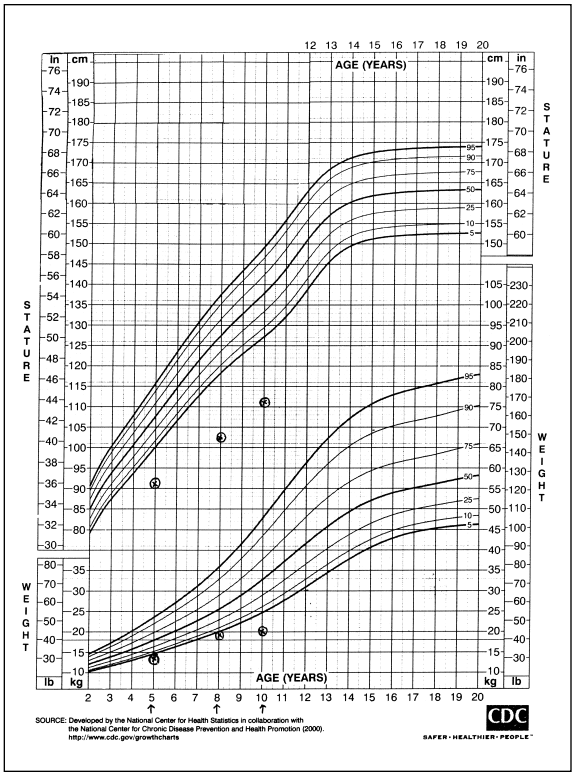


Figure 6. Patient's Stature and weight at aged 5, 8 and 10 years old. 2 to 20 years: Girls stature-for-age and weight-for age percentiles.

her growth chart is "dipping downward" rather than following the growth chart (Figure 2). Impaired growth before, during or after successful treatment of the cancer is a recognized entity among long-term survivors of childhood malignancies. It is thought that it could be due to the disease process itself, complications of treatment (infection), direct effects during treatment (anorexia, vomiting) and direct and indirect late effect due to therapy.

This patient had chemotherapy and BMT at age 1-1-1/2 years-old. At that age, the crowns of all the permanent teeth are in varying stages of tooth formation/calcification. Initiation of odontogenesis of permanent teeth is a prolonged process that begins that *in-utero* and is completed once the roots of the third permanent molar have developed in early adulthood.[24] This process is very delicate and is subjected to many external and internal influences that may affect the resultant dentoalveolar complex during its formation. The degree of risk of damage to developing teeth and bone depends on the timing, duration and severity of extrinsic or intrinsic insults. External influences upon dental development are irradiation and trauma. Internal influences upon dental development are antineoplastic chemotherapy, antibiotic therapy, fevers and metabolic disturbances resulting from nutritional imbalance or genetic disorders.[22]

The enamel organ can be disrupted so that the tooth fails to develop and the crown can be affected, resulting in microdontia or hypoplasia. If a group of ameloblasts is disturbed during development then the resultant enamel may be defective or hypoplastic. If the disturbance is severe enough then the whole tooth may fail to form.[9] Therefore, the defects in the dental tissues that were observed in long term survivors of cancer, either from disturbances caused by the disease it self, or from the treatment with chemotherapy or irradiation. Thus, it is quite surprising that clinically, except for enamel opacities on 46, the morphology and tooth structure of all erupted teeth appeared relatively normal. However, there was delayed dental development of the teeth (crowns and roots) as well as generalized delayed eruption of the permanent teeth. Based on clinical and radiographic finding, this patient would appear to be about 6 to 7 years old as compared to the patient chronological age of 10-years-old (Table 1). Thus, it would appear that the chemotherapy that was given during early childhood is exerting a chronic long-term effect on this patient.

Other than delayed development of teeth, defect of dental enamel was also seen in this patient. Purdell-Lewis *et al.*[12] reported that 80% of children, who had malignancies during childhood had exhibited some type of opacities and 90% had displeasing grooves and pits. In the control children, they reported these defects were almost always white, while in 45% of the study children they range in colour from yellow to dark brown.

Table 1. Dental growth and development of the patient

Teeth	Crown Formation	Root formation	Eruption	
			Maxilla	Mandible
Central incisors	Fully formed	5/6 formed	Unerupted	Erupted
Lateral incisors	Fully formed	5/6 formed	Unerupted	Unerupted
Canines	Fully formed	3/4 formed	Unerupted	Unerupted
First premolars	3/4 formed	Nil	Unerupted	Unerupted
Second premolars	3/4 formed	Nil	Unerupted	Unerupted
First molars	Fully formed	Fully formed	Erupted	Erupted
Second molars	3/4 formed	Nil	Unerupted	Unerupted
Third molars	Nil	Nil	Unerupted	Unerupted

Other interesting features observed were the abnormal morphology of the roots of the teeth. At this stage, only the FPM and mandibular incisors have erupted and enamel defects was only observed on 46. The roots of mandibular incisors appeared rather slender and thin and there was marked shortening and tapered roots of 16 as well as taurodontism of 26. While most studies[11-13,18,23,25] have also reported that the root development of permanent teeth was affected following chemotherapy, Dahllöf *et al.*[15] found there was no significant difference between the chronological and dental age of 44 patients with haematological malignancy, who were treated with chemotherapy as compared to the healthy controls and the authors concluded that chemotherapy given to children with haematological malignancies did not interfere with dental maturity or eruption of permanent teeth.

Abnormalities to the teeth occur as a result of the disturbance to the development of enamel organs, affecting both the crowns and roots. Thus, it would appear that the root system is particularly susceptible to disruptive insults that might impair normal root formation as compared to the crown. A normal root system is dependent on an intact Hertwig root sheath developing from proliferation of a normal external and internal enamel epithelium. This in turn, has differentiated from a bud of epithelial cells initiated at early stage in life. Root development can also be affected in three ways; thinning and tapering of the roots producing an appearance of taurodontism, localised constriction of the roots and arrested root development.

Näsman *et al.*[18] conducted a study to compare the effects between children treated with chemotherapy protocols for malignant disease and children conditioned with 10Gy total body irradiation (TBI) prior to BMT. They found that 4.1±5.0 were affected by disturbances in enamel mineralization. In the TBI group 4.6±4.6 teeth were affected, both counts being significantly higher than those of the healthy control group: 0.7±1.4 ($P< 0.05$). White/cream coloured opacities were most commonly diagnosed in all three groups, followed by yellow/brown opacities. Twelve percent of the children treated with TBI exhibited hypoplasia, compared with 8% in the chemotherapy group. The result showed that children, who are long-term survivors of paediatric malignant diseases, exhibit a wide range of disturbances in the oral cavity. In the study the most severe disturbances are found in children treated with total body irradiation prior to BMT. The severity of these effects on the dentofacial structures were found to be related to the age of the patient at initiation of treatment and the use of cranial radiation. The abnormalities were more severe in those patients, who received radiation at an earlier age and at a higher dosage.

Viral infection in-patient who has had bone marrow transplantation is well documented.[26] The sequential occurrence of infections is linked with the dynamically changing immunological state of the bone marrow transplantation recipient during the course of BMT. The events of the BMT procedure result in a sequential occurrence of virus reactivation, which is activation of latent herpes virus (HSV1 and 2), human cytomegalovirus (HCMV), Epstein Barr (EBV), varicella zoster virus (VZV), hepatitis B (HBV) and human papillomavirus (HPV). As many as one third of all people treated for haematologic neoplasm may have non-A, non-B hepatitis (hepatitis C). These viral infections can be either primary infection, reactivation of prior infection or reinfection.[26] Therefore treatment of patient categorized as high risk must adhere to the guidelines on infection control in dental practice which serves to provide guidelines to minimize or eliminate the risk of cross infection. Hence it is important for dentist to practice universal precautions to protect both their patients and themselves. The only safe approach is to assume that all patients are potential sources of infections.[27]

Dental treatment that could be affected or modified by chemoradiation damage to developing teeth includes orthodontic tooth movement, prosthetic abutment consideration, periodontal health, space maintenance, requirements for home fluoride regimens to protect hypomineralized areas, restoration options for hypoplastic/hypomineralized teeth and endodontic procedures.

Ideally, radiographs should be taken prior to chemoradiation therapy to indicate the stage of dental development, thus allowing the clinician to assess the potential dental defect. Thus, a panoramic radiograph may be indicated as a routine part of the preoncology dental treatment plan for the child. If pre-therapy radiographs are not available, the clinician must rely on estimates of dental development at the time of chemoradiation therapy from dental/chronological development charts. Post chemoradiation therapy radiographs are essential to indicate the severity of dental damage.

Dahllöf *et al.*[28] in a questionnaire survey to 5 orthodontists regarding the outcome of 10 orthodontically treated children, who had chemoradiation therapy, reported that the result of question analysis suggested that although ideal treatments were not always achieved, orthodontic treatment did not produce any harmful side effects in children, who are long term survivors of childhood cancer.

Proper oral care before, during and after cancer therapy has been found to be effective in preventing and controlling oral complications and long term follow up of these children is also necessary to monitor the dental and orofacial growth[29]. Studies have also been done to assess the dental health of patient, who had undergone oncological treatment for malignancy[16,18,19,22,23,25] and the parameters for dental health include dental caries, periodontal disease, and salivary secretion. Purdell-Lewis *et al.*[12] found children, who were treated with chemotherapy for malignancies, had higher caries experience as compared to other studies, who found no increase caries risk as compared to control.[16,18,23,25] Welbury *et al.*[23] found no variation from normal with regards to periodontal disease in children, who were in remission from malignant disease, but Sonis *et al.*[19] found patients treated with cranial irradiation of more than 24 Gy before the age of 5 years were at greater risk to periodontal disease. Nasman *et al.*[18] compared three treatment modalities and found that children treated with bone marrow transplantation (BMT) had a significantly lower salivary secretion rate compared to the chemotherapy group and the control group.

Thus, long-term survivors of childhood cancer represent a group of children with special needs that require long-term follow-up and meticulous treatment planning as the presence of a malignancy or the use of cytotoxic drugs during tooth development could affect the developing tooth germ, leading to dental abnormalities, which, in many cases will require cosmetic dental care.[22] They can also cause malformation of the roots, which may complicate orthodontic treatment or necessitate early extraction and advanced rehabilitative dental care.

CONCLUSION

Chemotherapy given at childhood can have long-term effect on the patient. Other than physical growth retardation, various dental complications could occur which include: generalized delayed exfoliation of primary teeth, generalized delayed development and eruption of teeth, and abnormalities of roots and enamel. Caries was also noted as the main problem. Thus, even though the patient was no longer under active medical care, they should be reviewed regularly every 3 to 6 months as they are considered a high-risk group.

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REFERENCES

1 The first report of the National Cancer Registry Cancer incidence in Malaysia 2002 Lim GCC, Yahya H, Lim TO (Eds). Ministry of Health Malaysia, 2003.
2 Wallace WHB, Blacklay A, Eiser G, Davies H, Hawkins M, Levitt GA, Jenney MEM. Developing strategies for long term follow up of survivors of childhood cancer. BMJ 323: 271-4, 2001.
3 Kumar V, Cotran RS, Robbins SL. Basic pathology. Sixth edition WB Saunders Company 1997.
4 Arececi R. Progress and controversies in the treatment of pediatric acute myelogenous leukaemia. Curr Opin Hematol 9: 353-60, 2002.
5 Cousin GCS. Oral manifestation of leukaemia. Dent Update 24: 67-70, 1997.
6 Oeffinger K, Eshelman D, Gail E, Tolle M, Schneider G. Providing primary care for long-term survivors of childhood acute lymphoblastic leukaemia. J Fam Pract 49: 1113-46, 2000.
7 Goho C. Chemoradiation therapy: effect on dental development. Paed Dent 15: 6-12, 1993.
8 Razmus TF, Williamson GF. Current oral and maxillofacial imaging. WB. Saunders Company, 1996.
9 Poynton HG. The effects of radiation on teeth. Oral Surg 26: 639-46, 1968.
10 Dury DC, Roberts MW, Miser JS, Folia J. Dental root agenisis secondary to irradiation therapy in a case of rhabdomysarcoma of the middle ear. Oral Surg 57: 595-9, 1984.
11 Rosenberg SW, Kolodney H, Wong GY, Murphy ML. Altered dental root development in long-term survivors of pediatric acute lymphoblastic leukaemia; a review of 17 cases. Cancer 59: 1640-8, 1987.
12 Purdell-Lewis DJ, Stalman MS, Leeuw JA, Humphrey GB, Kalsbeek H. Long term results of chemotherapy on the developing dentition: caries risk and development aspects. Community Dent Oral Epidemiol 16: 68-71, 1988.
13 Jaffe N, Toth BB, Hoar RE, Reid HL, Sullivan MP, McNeese MD. Dental and maxillofacial abnormalities in long-term survivors of childhood cancer: effects of treatment with chemotherapy and radiation to the head and neck. Paediatrcs 73: 816-23, 1984.

14 Maguire A, Welbury RR. Long-term effects of antineoplastic chemotherapy and radiotherapy on dental development. Dent Update 23: 188-94, 1996.
15 Dahllöf G, Nasman M, Borgström A, Modéer T, Forsberg CM, Heimdahl A. Effect of chemotherapy on dental maturity in children with haematological malignancies. Paed Dent 11: 303-6, 1989.
16 Nunn JH, Welbury RR, Gordon PH, Kernahan J, Craft AW. Dental caries and dental anomalies in children treated by chemotherapy for malignant disease; a study in the north of England. Int J Paed Dent 1: 131-5, 1991.
17 Sonis AL, Tarbell N, Valachovic RW, Gelber R, Schwenn M, Sallan S. Dentofacial development in long term survivors of acute lymphoblastic leukaemia. Cancer 66: 2645-52, 1990.
18 Näsman M, Björk O, Söderhäll S, Ringdén O, Dahllöf G. Disturbances in the oral cavity in pediatric long-term survivors after different forms of antineoplastic therapy. Paed Dent 16: 217-23, 1994.
19 Sonis AL, Waber DP, Sallan S, Tarbell NJ. The oral health of long-term survivors of acute lymphoblastic leukaemia: a comparison of three treatment modalities. Eur J Cancer B Oral Oncol 31B: 250-2, 1995.
20 Clayton PE, Shalet SM, Morris-Jones PH, Price DA. Growth in children treated for acute lymphoblastic leukaemia. Lancet 1(8583): 642, 1988.
21 National Clinical guidelines recommended for use by the Scottish Intercollegiate Guidelines Network (SIGN), Royal College of Physician of Edinburgh in the SIGN website: www.sign.ac.uk
22 Maguire A, Murray JJ, Craft, AW, Kernahan J, Welbury RR. Radiological features of the long term-effects from treatment of malignant disease in childhood. Br Dent J 162: 99-102, 1987.
23 Welbury RR, Craft A, Murray JJ, Kernahan J. Dental health of survivors of malignant disease. Arch Dis Child 59: 1186-7, 1984.
24 Logan WHG, Kronfeld R. Development of the human jaws and surrounding structures from birth to the age fifteen years. JADA 379-27, 1933.
25 Maguire A, Craft, AW, Evan RGB, Amineddine H, Kernahan J, Macleod RI, Murray JJ, Welbury RR. The long term effects of treatment on the dental condition of children surviving malignant disease. Cancer 60: 2570-5, 1987.
26 Zaia JA. Viral infections associated with bone marrow transplantation. Hematology/Oncology Clinics of North America 4: 603-23, 1990.
27 Guidelines on infection control in dental practice. Dental Services Division, Ministry of Health Malaysia 1996.
28 Dahllöf G, Jönsson A, Ulmner M, Huggare J. Orthodontic treatment in long –term survivors after pediatric bone marrow transplantation. Am J Orthod Dentofacial Orthop 120: 459-65, 2001.
29 Clinical guideline on the dental management of paediatric patients receiving chemotherapy, bone marrow transplantation and /or radiation American Academy of Paediatric Dentistry Paed Dent 23: 82-4, 2001.