Oral Care Protocol for Paediatric Oncology Patients
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Part 4: Screening and preventative practices for survivors of childhood cancer; an oral health perspective

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Introduction
Survival rates for childhood cancer have seen significant increases as a result of the development of highly specific diagnostic procedures and the introduction and refinement of multimodal treatment strategies (Kaatsch 2010). Current survival rates as calculated with the period method utilising the data of prevalent cases in Australia between 1999-2008 demonstrated 1 year survival rates of 91.4%, 5 year survival of 81.2% and 20 year survival of 76.6% (Youlden et al 2013). Unfortunately increased survival rates have come at the cost of increased patient morbidity (Wogelius et al 2008). Oral complications of therapy are among the possible sources of patient morbidity. Cancer therapy can have significant late effects on the craniofacial skeleton and the oral cavity, see table 1 below. Craniofacial, skeletal and dental developmental late effects are more frequently reported to occur in patients age 5-6 years of age or younger at the time of their oncology therapy (Fischer & Epstein 2008; AAPD 2013; deFonseca 2000; Holtta et al 2002).

Table 1: Possible Orofacial Late Effects of Oncology Therapy

<table>
<thead>
<tr>
<th>Possible Orofacial Late Effects of Oncology Therapy</th>
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<tbody>
<tr>
<td>Tooth agenesis</td>
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<tr>
<td>Microdont teeth</td>
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<tr>
<td>Altered root development</td>
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<td>Developmental enamel defects</td>
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<td>Salivary gland hypofunction</td>
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<td>Chronic Graft versus host</td>
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<td>Altered craniofacial growth and development</td>
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<tr>
<td>Malocclusion</td>
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<td>Compromised aesthetics</td>
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<td>Temporomandibular disorders</td>
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<tr>
<td>Fibrotic remodelling</td>
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<tr>
<td>Increased risk of oral cancer</td>
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</table>
Craniofacial, skeletal and dental developmental problems more frequently reported to occur in patients that are less than 5-6 years of age at the time of their oncology therapy (Fischer & Epstein 2008; AAPD 2013; deFonseca 2000; Holtta et al 2002). The effects of chemotherapy and radiotherapy on dental development include tooth agenesis, complete or partial arrest of root development with thin and tapered roots, early apical closure, globular and conical crowns, enamel and dentine opacities and defects, microdontia, enlarged pulpal chambers, taurodontism and abnormal occlusion and delayed eruption is not uncommon (daFonseca 2000).

Orofacial Late Effects

Tooth Agenesis, Microdont Teeth, Altered Root Development, Developmental Defects of Enamel

Tooth agenesis as a result of chemotherapy is seen less frequently due to the short half life of most chemotherapeutic agents, unless intensive and repetitive therapy is utilised (Hong & daFonseca 2008). Chemotherapy is disruptive to proliferating cells as it disrupts DNA synthesis and replication RNA transcription and cytoplasmic transport mechanisms. Chemotherapy targets the most rapidly dividing cells systemically. Thus cells that are non-proliferative at the time of chemotherapy are not affected (daFonseca 2008). Chemotherapy tends to result in milder dental defects such as crown hypoplasia, microdontia, enlarged pulpal chambers and disturbed root development (Hong & daFonseca 2008). Research has shown increased prevalence of enamel opacities of up to 62.5% in paediatric patients with a history of chemotherapy (Hutton et al 2009). Microdont teeth have also been noted to be significantly increased. Younger age is also a clear contributing factor with all children treated for solid tumours with chemotherapy prior to the age of 3.5 years demonstrating evidence of microdont permanent teeth (Hutton et al 2009). Kaste and colleagues in their assessment of over 9000 long term paediatric oncology survivors, found children less than 5 years at the time of chemotherapy were more likely to demonstrate more than one dental defect (Kaste et al 2009).

Radiotherapy can cause disruptions to enamel and dentine formation when administered to the craniofacial area in the treatment of head and neck lesions and also during total body irradiation used in the conditioning phase of BMT. Radiotherapy affects cells in their mitotic phase but can also affect non-proliferating cells when in very high doses (daFonseca 2000). Radiation doses as low as 4Gy can result in dental defects however, the exact threshold level at which cell damage versus cell death occurs in the head and neck is not known (Hong & daFonseca 2008). Mature ameloblasts have been permanently damaged by 10 Gy of radiation, halting tooth development from the time of irradiation (Kaste et al 1994; Minicucci et al 2003). Kaste et al (2009) found that total radiation exposures of greater than 20Gy significantly increased incidence of one or more dental anomaly. High-dose radiation that is focussed on the dentoalveolar complex during the early phases of tooth development can result in the destruction of the odontogenic precursor cells leading to complete agenesis of the tooth and even halting of the growth of the craniofacial complex (Hong & daFonseca 2008; Rosenberg 1990). Radiation that occurs during the later stage of tooth development or that occurs at lower doses can result in less severe effects of microdontia, enamel hypoplasia, incomplete calcification and arrested root development (Hong & daFonseca 2008).

All children under the age of 12 years that undergo bone marrow transplantation are reported to have dental effects; the most severely affected children being those aged less than 5-6 years at the time of transplant (Holtta et al 2002). The degree to which the dentition is affected can range from mild hypomineralisation to agenesis of permanent teeth (Holtta et al 2002). Children conditioned with TBI are
reported to have more severe dental effects. Research reports that 94.9% of teeth were affected by dental late affects following conditioning with TBI compared to 37.3% in those that were not conditioned with TBI. All children treated with TBI had agenesis (6.6 teeth missing on average) compared to only 40% of patients from the non TBI group (3 teeth missing on average) (Holttia et al 2002).

**Salivary Gland Hypofunction and Xerostomia**

Chemotherapy and radiotherapy can lead to salivary gland hypofunction (Anderson et al 1981; Marks et al 1981; Wolff et al 1990; Fischer & Epstein 2008; Hong & daFonseca 2008). Changes are usually reported to be reversible following chemotherapy in paediatric patients (Hong & da Fonseca 2008). A systematic review performed by Jensen et al 2010 concluded that chemotherapy can cause salivary gland hypofunction and xerostomia which is transient (Jensen et al 2010). However the evidence was variable and often did not have adequate post treatment follow up. There is research that has shown ongoing salivary gland hypofunction and xerostomia for 0.5-7 years post chemotherapy in adult and paediatric patients (Jensen et al 2010; Wickham et al 1999; Avsar et al 2007).

Chronic salivary gland hypofunction is expected in cases of high dose head and neck irradiation that involves the salivary glands (Fischer & Epstein 2008). Salivary gland hypofunction and consequential xerostomia are reported to be the most common and persistent complaint following head and neck radiotherapy (Deboni et al 2012; Jensen et al 2010). The degree of damage to the salivary glands is related to the cumulative dose of irradiation and the volume of the salivary gland tissue that has been exposed (Jensen et al 2010). Nasopharyngeal malignancies that are treated with radiotherapy have the highest prevalence and severity of salivary gland hypofunction with consequential xerostomia (Jensen et al 2010). Following radiotherapy there is a decrease in the quantity and quality of saliva. There is potential for a decreased concentration of antimicrobial proteins, reduced remineralisation potential and decreased buffering capacity (Fischer & Epstein 2008), which can contribute to increased dental caries in patients that have undergone radiotherapy treatment (Fischer & Epstein 2008).

Following irradiation, salivary gland recovery is possible for 12-18 months dependent upon the location and dose received. However, following large dose head and neck irradiation, the healing is usually incomplete and patients can suffer from salivary gland hypofunction and associated symptoms for life (Fischer & Epstein 2008).

**Chronic Graft Versus Host Disease**

Graft versus host (GVHD) disease results when the transplanted T-lymphocytes attack the host resulting in immune-mediated injury (Krusse & Gratz 2009; da Fonseca 2000). In the chronic form GVHD is reported to present after day 80 post transplant and usually develops from 3-15 months post transplant (da Fonseca 2000; Nicolatou-Galitis et al 2001; Eggleston et al 1998). It can occur as a continuum of acute GVHD, following resolution of acute GVHD or de novo with the later resulting in the lowest level of patient morbidity (da Fonseca 2000). It presents with dermal, hepatic, gastrointestinal, ocular or oral mucosal involvement (da Fonseca 2000). It is reported to occur less frequently in younger people affecting approximately 20% of surviving children (Nicolatou-Galitis et al 2001; Zecca 2002) with estimates varying up to 33% in identical twin transplants and 64% in unrelated donors (da Fonseca 2000).

Chronic GVHD can be suspected in the patient that presents with increasing mucosal xerostomia and stomatitis 100 days or more post transplant (Krusse & Gratz 2009; Eggleston et al 1998). It is essential that the dental practitioner recognises that the oral cavity may be the first or only site of GVHD.
Table 2: Oral Manifestations of Chronic GVHD (daFonseca 2000; Nicolatuo-Galitis et al 2001):

<table>
<thead>
<tr>
<th>Mucosal atrophy</th>
<th>Loss of stippling of attached gingiva and papillae from the tongue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td></td>
</tr>
<tr>
<td>Lichenoid changes</td>
<td></td>
</tr>
<tr>
<td>Lips, labial and buccal mucosa, palate and gingiva</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Xerostomia</td>
<td></td>
</tr>
<tr>
<td>Ulceration (buccal mucosa, palate and dorsal and lateral of tongue)</td>
<td></td>
</tr>
<tr>
<td>Ulcerations may be covered with a heavy grey/yellow membrane</td>
<td></td>
</tr>
</tbody>
</table>

Oral examinations and oral biopsies have been shown to be useful in GVHD assessment between day 80-100 post transplant. Minor salivary glands demonstrate changes of ductal necrosis, inflammation and lymphocytic infiltrate, acinar cell destruction and epithelial cell necrosis when assessed. (daFonseca 2000). Oral GVHD management is focussed on palliation of symptoms.

Altered Craniofacial Growth and Development

As long term survival rates have increased, the late effects of oncology therapy on the craniofacial development have become more apparent (daFonseca 2000). The extent and severity of the effects are related to the patient’s age at the start of therapy and whether therapy included chemotherapy alone, chemotherapy in combination with TBI or head and neck irradiation. It has been demonstrated that the younger the age of the patient the more severe the effects with children less than 5-6 years more severely affected (Dahllof et al 1989; Sonis et al 1990). Factors that affect growth in children following BMT include chronic GVHD, pulmonary dysfunction, general poor health, steroid therapy, direct irradiation effects on skeletal growth and thyroid function (daFonseca 2000).

Abnormalities in the craniofacial complex are seen frequently in long term survivors that received radiation therapy for a primary tumour in the head and neck region (Hong and daFonseca 2008). Damage to the maxillary and or mandibular growth centres can result from radiotherapy and this can compromise maturation of the craniofacial complex (Fischer & Epstein 2008). They often present as asymmetries which are clinically obvious (Fischer & Epstein 2008; Hong & daFonseca 2008). If the patient is irradiated bilaterally effects may be less obvious clinically and cephalometric analysis may help with identification and monitoring (Fischer & Epstein 2008). Features such as higher radiation doses, longer radiation schedules and younger age results in patients being differentially affected (Hong & de Fonseca 2008). As mentioned above growth overall can be affected and when damage occurs to the thyroid gland and pituitary axis this also indirectly leads to a potential exacerbation of skeletal effects with overall retardation of growth. Malocclusion and complications can arise from facial asymmetry. Treatment of such defects is difficult and can involve multiple surgeries of which the success may be unpredictable due to poor healing of the irradiated tissues (Hong & daFonseca 2008).

Osteoradionecrosis

Osteoradionecrosis (ORN) remains a devastating complication among adults with a history of radiotherapy (Rosenberg, 1990) for patients who receive more than 40 Gy in the jaw area (Paulino & Casillas, 2008). ORN is not a common complication. However, it is frequently noted in the adult population following dental treatment such as extraction or surgery in adult populations. The mandible is affected more commonly than the maxilla (Otmani 2007; Paulino & Casillas, 2008). ORN is defined as an area of exposed devitalised irradiated bone that fails to heal over a period of 3–6 months in the absence of local neoplastic disease it can occur spontaneously, due to periodontal and apical disease and possibly after trauma induce by dentures, or after surgery or tooth extraction (TGI 2012).
ORN has a reported incidence of approximately 2-18% in adult populations previously treated with head and neck irradiation. Elective surgical treatments should be avoided in patients that have received high dose radiotherapy to their head and neck region. Should extractions be needed within the field of irradiation, hyperbaric oxygen therapy is recommended (Little et al 2008). A recent systematic review found 19 articles for inclusion and reported that the total incidence of osteoradionecrosis in adult patients was 7% after dental extraction. It appeared that the use of hyperbaric oxygen treatment decreased this incidence to 4% following dental extraction. The extraction of mandibular teeth within the radiation field in patients who received a radiation dose higher than 60 Gy represents the highest risk of developing osteoradionecrosis (Nabil & Samman 2011).

The high oxygen level with HBO is thought to induce fibroplasia and angiogenesis in the hypoxic, hypocellular and hypovascular tissue, thus preventing the occurrence of ORN. Intra-operatively, measures such as alveoloplasty, primary closure and limited periosteal trauma during extraction are said to be critical steps in avoiding ORN (Nabil and Samman et al 2011). Individualised hyperbaric oxygen (HBO) therapy schedules are developed as needed for patients that have received high doses of radiation to the oral region and require subsequent dental surgery.

**Increased Risk of Oral Cancer**

The literature reports that the incidence of secondary neoplasm of the oral cavity, oesophagus and thyroid gland in patients with a history of HSCT is 4-7 times increased on the general population (Kruse & Gartz 2009; Curtis et al 1997; Demarosi et al 2005; Bhatia et al 1996). Risk factors include total body irradiation, chemotherapy, male gender, virus, young age, chronic graft versus host and prior immunosuppressive therapy (Kurse & Gratz 2009). It is essential that paediatric dentists are aware of this risk. Much about the aetiology of this relationship remains unclear. However, it is essential that high risk patients such as those with cGVHD with lichenoid changes are closely monitored for the development of oral squamous cell carcinoma (Kruse & Gratz 2009).

**Ongoing Dental Management and Identification of Those Patients at Risk of Late Effects**

The AAPD 2013 recommends the following three objectives for oral care once oncology treatment is complete;

i) To maintain optimum oral health

ii) To reinforce to the patient/parents the importance of optimal oral and dental care for life; and

iii) To address and or treat dental issues that may arise as a result of the long term effects of cancer therapy

The goal of management of patients post oncology therapy is to maintain good oral health by routine maintenance and dental treatment as needed (Brennan et al 2008). The frequency of review appointments is dictated by the individual patient. It is essential that the dental issues specific to each individual patient are identified (Brennan et al 2008). Oral hygiene, diet and fluoride program (as needed) are reinforced.

As a regular recall period, 6 months is generally acceptable once a patient is in remission unless they are high caries risk and or have ongoing problems such as cGVHD, xerostomia or trismus (AAPD 2013).

Orthodontic treatment is generally not recommended to be commenced or recommenced until the patient has been disease free for 2 years and is no longer taking immunosuppressive medications. Discussion with the patients’ physician is recommended prior to initiation or recommencement of orthodontic treatment as risk of relapse, prognosis and residual effects of therapy on growth are variable (Berry et al 1983; Gaynon
et al 1997; Lawson et al 2000). There are no detailed orthodontic treatment guidelines available specific to the paediatric oncology patient in remission however methods to minimise root resorption, lighter forces, early termination of treatment, simple methods and sparing the lower jaw of treatment have been recommended in the literature (Dahllof et al 2001; AAPD 2013).

As discussed above, the risk and severity of late effects is largely dependent upon the age and stage of dental development of the patients and also on the modalities and intensities of treatment received. Below is adapted from a table used by Hong and daFonseca 2008 to describe the risk of late effects related to different types of oncology therapies.

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Chemotherapy</th>
<th>Head and neck radiotherapy including TBI</th>
<th>Autologous HSCT</th>
<th>Allogeneic HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental anomalies</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Dose and age dependent</td>
<td>Dose and age dependent</td>
<td>Dose and age dependent</td>
<td>Dose and age dependent</td>
</tr>
<tr>
<td>Anomalies in craniofacial development</td>
<td>Unlikely</td>
<td>Yes</td>
<td>Possible</td>
<td>Possible</td>
</tr>
<tr>
<td>Persistent xerostomia and hyposalivation</td>
<td>Unlikely</td>
<td>Yes</td>
<td>Unlikely</td>
<td>Not commonly</td>
</tr>
<tr>
<td></td>
<td>Dose and age dependent</td>
<td>If major salivary glands in field</td>
<td>Dose and age dependent</td>
<td>Unless complication of cGVHD</td>
</tr>
<tr>
<td>Trismus</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If masticatory muscles in field</td>
<td></td>
<td>Unless complication of cGVHD</td>
</tr>
<tr>
<td>Postradiation osteonecrosis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If &gt;60Gy to jaw</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

It is known that moderate/high intensity chemotherapy can cause dental late effects affecting the population under 6 years at the time of treatment most significantly. On the other hand bone marrow transplants and head and radiotherapy can have much more marked effects on dental development when performed on children younger than 12 years of age. This information combined with the information in the table above has been combined to develop the following late effects protocol that can be used by specialised hospital departments to identify those children in need of ongoing specialised care. See flow chart 4 and 5 below.
Oral Care Protocol for Paediatric Oncology Patients

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Flowchart 4: Late effects protocol for those patients who received moderate/high intensity chemotherapy

Flowchart 5: Late effects protocol for those patients who received head and neck radiation or a bone marrow transplant

Conclusion

There are a variety of late effects that can have devastating effects on the oral cavity of childhood cancer survivors. The specific oncology therapy regimen and the age of the child at the time of their treatment are both factors that have an influence on the type and severity of late effects that develop. Not all children are at risk of significant late oral effects. The above system has been developed to help the practitioner anticipate and identify dental late effects and advise and manage patients accordingly.
Oral Care Protocol for Paediatric Oncology Patients

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