



DENTAL CONSIDERATIONS WITH WALDENSTROM MACROGLOBULINEMIA

by Linda P. Nelson, DMD, DDS

Following an extremely active career in the field of pediatric dentistry, Dr. Nelson recently retired from the Harvard School of Dental Medicine where she was a member of the faculty from 1996- 2016 and held many administrative positions. Linda Nelson is a Trustee of the IWMF.

Dr. Linda P. Nelson

When is the best time to have major dental problems taken care of when diagnosed with symptomatic Waldenstrom macroglobulinemia (WM)? The best answer is prior to the diagnosis! Most major dental problems that are seen in patients with WM are not a direct manifestation of the disease itself but are problems resulting from untreated dental infections that have been subclinical (smoldering) and now reveal themselves as a result of immunosuppression or low blood counts that accompany high serum IgM levels. The time to have major dental procedures is not when the patient requires rapid control of symptomatic disease. Consultation (always a good idea) with the patient's oncologist, oncology nurse practitioners, dentists, dental specialists, hygienists, and dieticians can often achieve highly effective preventive and therapeutic dental care. A multidisciplinary approach is warranted because of the medical complexity of the patient with symptomatic WM and because a regimen of therapy affects dental treatment planning, prioritization, and timing of dental care.

General Dental Considerations

Dental care is an important consideration for patients with WM for multiple reasons:

1. the initial or presenting symptom of the disease is often unexplained and frequent oral bleeding or bleeding gums with no history of gum (periodontal) problems.
2. the presence of hyperviscosity (excess thickness of the blood due to high serum IgM) may be suggested by frequent, spontaneous gum and nasal bleeding,
3. patients who have excellent oral health before starting chemotherapy or immunotherapy are less likely to have complications and mouth sores (mucositis) from their drug therapy (ibrutinib, for example) than are patients in poor oral health,
4. the best time to have major dental procedures, such as implants, root canals (endodontics), extractions (removal of teeth), or gum surgery is not when patients are fatigued, have muscle aches, low serum IgG levels, low blood cell counts (neutropenia) making them less able to fight infections, or when their platelets are low (thrombocytopenia) and are less able to stop bleeding.

Oral or Nasal Bleeding may be a Symptom of WM

Although there may be frequent, uncontrolled, spontaneous bleeding along the body's entire mucosa (lining of the gastrointestinal tract), it is not as immediately obvious to the patient as it is from the nose or gums. In patients with WM the cause is a low red cell count and/or low platelet level resulting from a high serum IgM level. Bleeding gums or nosebleeds can be the initial symptoms that bring patients with WM into their doctor's office for a diagnosis. Of course, other conditions may be the cause of the spontaneous gum and/or nasal bleeds, but it is part of the hypothetical or differential diagnoses that the medical team will consider when ordering medical tests. In WM, when the IgM level is reduced by drug therapies or plasmapheresis to a safer level, the spontaneous bleeding from the gums should likewise decrease.

Rituximab

It should be noted that during treatment with rituximab about 50% of WM patients experience a transient increase in serum IgM levels – the IgM “flare” phenomenon. This flare occurs mostly during the first months of treatment but may persist for several months. If patients with baseline serum IgM level of 4000 mg/dl or greater have not had plasmapheresis prior to treatment, they may experience bleeding from their nose or gums during this period for the same reasons they had the bleeding initially.

Other adverse reactions to rituximab may be swelling of the lips, tongue, face, and throat during infusion. Severe mouth and skin reactions (Stevens-Johnson syndrome) have also been reported during treatment with rituximab. Tell your medical team right away if you experience red, swollen, peeling or blistered skin; or sores or ulcers on your skin, lips, or in your mouth.

Ibrutinib

Ibrutinib is a targeted therapy and inhibitor of an enzyme in the B-cell signaling pathway called Bruton’s tyrosine kinase (BTK). Historically there was a strong rationale to begin testing this drug in WM patients because BTK is activated by the MYD88 L265P gene mutation found in 90-95% of WM patients.

Treatment-related side effects of ibrutinib include low white cell count (neutropenia), low platelet count (thrombocytopenia), post-procedural bleeding, ulcers, sores or white spots in the mouth (mucositis), nausea and vomiting, and dry mouth (xerostomia), among others.

Because ibrutinib can temporarily lower the number of white cells in the blood, the patient is at greater risk of getting an infection. This also means that if there is an infection brewing in a tooth (root canal), bone, or gums (periodontal), it may well go from a quiescent state (subclinical) to a full-blown infection with internal or external swelling due to the drug’s side effects or the patient’s immunosuppression (low IgG). Ibrutinib can also lower the number of platelets (thrombocytopenia) and may prevent proper blood clotting.

If you are having a tooth removed, implant placed, gum (periodontal) surgery, or other surgical procedures, inform your dental and medical team. They may recommend that ibrutinib be discontinued for 3-7 days pre- and post-surgery, depending on the risk of bleeding. Generally, surgical procedures should not be done if the platelet count is below 50,000.

Acquired von Willebrand disease is a bleeding disorder that may occur with high IgM level. Testing for von Willebrand activity is recommended in WM patients with a history of bleeding prior to starting ibrutinib therapy. Patients with von Willebrand disease may require pre-treatment with medications, such as desmopressin, prior to dental treatment that carries high bleeding potential.

See below for mouth sores associated with ibrutinib.

Oral Bleeds, Mouth Sores, Change in Taste, Dry Mouth, Nausea, Vomiting

Although rarely serious, **oral bleeds** can be of concern to the patient and family. Oral bleeding may be mild (e.g., small red spots (petechiae) located on the lips, posterior palate, or floor of the mouth) or severe (e.g., persistent gum (gingival) hemorrhage or bleeding from herpes simplex virus ulcers) if the patient has very low platelet counts (thrombocytopenia).

Mouth sores (mucositis, esophagitis) can range in severity from a red, sore mouth and gums to very painful open sores, causing a patient to be unable to eat normally. Normal oral mucosa (the inside lining of your lips and cheeks) is estimated to undergo a complete replacement every 9-16 days.

Ibrutinib can cause ulcerative mucositis that emerges approximately 7-10 days after initiation of the drug. The mucosa that lines the inside of the lips and cheeks, the tongue, floor of the mouth, and soft palate (the part of the palate that is back towards the throat) are more affected than the gums and front part of the palate.

Methotrexate also has a high propensity to damage the mucosa and create mouth sores. Most medical teams will prescribe oral corticosteroids, such as dexamethasone, for their anti-inflammatory properties. By reducing the body's natural defensive response, dexamethasone reduces swelling and irritation from the mouth sores.

There is some evidence that using 3% hydrogen peroxide rinses diluted 1:1 with water to remove the dried blood associated with the mouth sores may be helpful; however, this approach should only be used for 1-2 days because more extended use may impair timely healing of the mucosal lesions associated with the bleeding. Keeping well hydrated and eating ice chips and ice water prior to meals can alleviate some of the pain while eating. Try to avoid mouth rinses with alcohol, as these can make the mouth sores even more painful. Mouth sores heal on their own in 2-4 weeks after stopping the drug when uncomplicated by infection. Continuing to perform good oral hygiene can speed the recovery along. There is anecdotal evidence that suggests that patients who experience mucositis with a specific medication during the first cycle will develop comparable mucositis during subsequent courses of that regimen.

Patients sometimes complain of a **metallic taste or other taste changes** during treatment. Sometimes these can be due to a nutritional problem and referral to a nutritionist may be appropriate, but in the interim, overpowering the metallic taste may help. Sugar free lemon drops or mints or chewing strongly flavored sugar free gum may provide relief. Adding extra flavoring to food, such as marinades, herbs, vinegar, or pickled vegetables may overpower the metallic taste, as well.

Dry mouth (xerostomia) is another side effect of ibrutinib and other chemotherapeutic drugs that is often transient and can be treated. Plasma cells in the salivary glands of the mouth produce IgA for the saliva, and IgG is contributed to the saliva from the serum. The IgA binds to the inner lining of the mouth (mucosa) to form a protective layer that may be lost, contributing to mouth sores and dry mouth symptoms. Hyposalivation (reduction in saliva) can further aggravate the inflamed mouth sores, increasing the risk of infection and make eating and swallowing difficult. There can also be thickening of the saliva due to changes in the salivary glands themselves. For relief, sip water, as needed, to alleviate mouth dryness. Saliva substitutes or artificial saliva preparations (e.g., oral rinses or gels containing hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, polyglycerylmethacrylate, mucin, or xanthan gum) may relieve the discomfort of xerostomia by temporarily wetting the oral mucosa. Rinsing with a solution of 1/2 teaspoon baking soda (and/or 1/4 or 1/2 teaspoon of table salt) in 1 cup of warm water several times a day helps clean and lubricate the oral tissues. Chewing sugar free gum or sucking on sugar free lozenges helps to stimulate salivary flow.

Nausea and vomiting over a prolonged period of time can etch and eventually wear away the enamel of teeth making them exquisitely sensitive to cold and putting them at risk for decay. The medical team can prescribe anti-nausea (antiemetic) medications to help manage the queasiness. Avoiding triggers, such as heavy or greasy or fatty foods, spicy or acidic foods (lemons, tomatoes, and oranges) may help. Antacids (milk of magnesia, calcium tablets, Tums), saltine crackers, or sugar free ginger ale may also lessen the nausea. Sodium bicarbonate toothpastes and rinses help counter the acidity produced with vomiting.

Dental Management during Therapy for Patients with WM

Routine oral hygiene is important for reducing the incidence and severity of oral and dental problems. The National Cancer Institute recommends tooth brushing 2-3 times a day with a soft nylon bristled brush, rinsing frequently. More frequent brushing may be necessary to remove food and plaque if xerostomia (dry mouth) is present and there is reduced salivary flow. Using a fluoridated toothpaste is recommended, especially if the patient lives in a non-fluoridated community. Using non-mint flavored toothpaste may be better tolerated than mint flavored products when a mucositis is present. Rinsing the toothbrush in hot water every 15-30 seconds during brushing will soften the bristles and reduce the risk for trauma. Brushes should be air-dried between uses. Ultrasonic brushes may be substituted for manual brushes if the patient has been trained by the dental team in their use.

For younger patients with aggressive WM for whom other treatments are no longer working, allogenic (donor generated) stem cell transplantation may be an option as part of a clinical trial, if the patient's own stem cells (autologous) are not available. Although not commonly used for WM, allogenic stem cell transplantation produces patients who are at increased risk for graft-versus-host disease (GVHD). This condition, where the patient's immune system is taken over by that of the donor, may have severe oral manifestations. The use of non-mint flavored toothpaste may be better tolerated, as these patients are most at risk for severe mouth sores.

If possible, floss once a day before bed. Avoid rinses containing alcohol. Poorly fitting dentures or other appliances should not be worn during times of low platelet counts, if bleeding is a problem. Leave dentures and other appliances out of the mouth when sleeping and during periods of severe mouth sores. Prevent dryness of the lips from mouth breathing or dry mouth with lanolin-based creams and ointments (lanolin-based products are more moisturizing and lubricating than petroleum-based oils and waxes).

Dental brushing and flossing represent simple, cost-effective approaches to bacterial dental plaque control. This strategy is designed to reduce risk of oral soft tissue infection during therapy. Spontaneous gum (gingival) oozing may occur when platelet counts drop below 20,000, especially when there is preexisting gum inflammation (gingivitis) or gum and bone disease (periodontitis). Even normal function or routine oral hygiene (brushing and flossing) can induce gum oozing in the face of preexisting gingivitis and periodontitis. Oncology teams at some centers promote their use, while teams at other centers have patients discontinue brushing and flossing when peripheral blood components decrease below defined thresholds (e.g., platelets < 30,000). There is no comprehensive evidence regarding the optimal approach. Many centers adopt the strategy that the benefits of properly performed dental brushing and flossing in reducing risk of oral/dental infection outweigh the risks.

Patients may experience temporomandibular dysfunction pain involving muscles used for chewing (mastication), temporomandibular joints, or teeth. This condition is not unique to WM or cancer patients per se, and it correlates with stress and dysfunctional habits including grinding the teeth (bruxism) and clenching of the jaws. Stress and sleep dysfunction appear to be the most frequent etiologic factors. Judicious use of muscle relaxants or anxiety-reducing agents plus physical therapy (moist heat applications, massage, and gentle stretching) is the standard approach for management. For patients with a tendency for clenching or grinding teeth during sleep, the use of customized, removable occlusal splint appliances that cover the teeth while sleeping may be of value.

Bisphosphonates

Although not specific to WM, we would be remiss if there were not a discussion of bisphosphonates. Bisphosphonates are a class of drugs that prevent bone loss. Patients should understand that although bisphosphonates are effective, these drugs also carry risk to their dental health. Bisphosphonate treatment can cause a rare but serious side effect called "osteonecrosis of the jaw (ONJ)." ONJ causes part of the jaw bone to die, which can lead to pain, open sores, and higher risk of tooth loss and infection. Patients should have a dental check-up before starting treatment with this class of drugs and address any dental problems before treatment begins. Doctors will stop the bisphosphonate treatment if ONJ occurs. The occurrence of ONJ is based on cases reported in the literature, and occurrence ranges from between 1% and 10% for patients receiving the intravenous formulation (pamidronate and zoledronic acid) to less than 1% for patients taking oral bisphosphonates. NCI's PDQ cancer information summary about bisphosphonates and ONJ states the risks succinctly: dental extractions, ill-fitting dentures, intravenous bisphosphonate, time on medication, and multiple myeloma. Some clinicians believe that discontinuing the drug for patients scheduled for dental surgical procedures may be beneficial, although this belief is not supported by scientific study. It is recommended that such a drug holiday be maintained until clinical evidence of healing is observed. However, controversy surrounds this issue, and further research is needed.

Conclusion

With any treatment for WM it is imperative that the patient tell the medical team about any dental infection (tooth, gum or bone) that the patient has before initiating therapy. Most of the drug therapies will lower the body's ability to fight infection. When asked about infections, many patients forget to report about their teeth, leading to management problems down the line. The oral cavity is highly susceptible to direct and indirect effects of drug therapies. This risk results from multiple factors, including high rates of cellular turnover for the lining of the mouth, a diverse and complex microflora of bacteria, viruses, and fungi, and trauma to the oral tissues during normal oral function.

For Further Information: PDQ® Supportive and Palliative Care Editorial Board. PDQ Oral Complications of Chemotherapy and Head/ Neck Radiation. Bethesda, MD: National Cancer Institute. Updated. Available at: <http://www.cancer.gov/about-cancer/treatment/side-effects/mouth-throat/oral-complications-hp-pdq>. Accessed March 31, 2017. [PMID: 26389320]

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