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Review Article

Evaluation, Prediction and Treatment of Radiation-Induced Normal Tissue Damage in Head and Neck Cancer

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Abstract

Locally advanced head and neck squamous cell cancer (HNSCC) requires a multidisciplinary approach and frequently concurrent chemoradiation (CRT) as a definitive or adjuvant treatment. Oral mucositis (OM) affects 80% of patients receiving radiation treatment and about half of the patients receiving CRT experience severe grade 3-4 mucositis. Severe mucositis results in high hospitalization rates and treatment interruptions, which can negatively affect treatment outcomes. The local tumor control rate may be reduced by 0.5 to 1% for each day of unplanned interruption in radiation treatment. Severe late toxicity occurs in about 43% of patients receiving CRT. Careful selection of patients for concurrent chemotherapy with attention to detailed assessment and aggressive supportive care is paramount to minimizing treatment related complications. Here we discuss aspects specific to management of mucositis, radiation dermatitis, nutritional and dysphagia assessment, and early interventions to avoid long term toxicity in the subgroup of patients receiving CRT. Investigational and alternate strategies to systemic treatment with cisplatin that could impact radiation induced normal tissue damage are discussed as well.

Abbreviations: HNSCC: Head and Neck Squamous Cell Cancer; OM: Oral Mucositis; WHO: World Health Organization; CTCAE: Common Toxicity Criteria Adverse Events; HPV: Human Papilloma Virus; QOL: Quality of Life

Introduction

About 50-60% of patients with head and neck cancer present with a locally advanced stage [1]. The treatment usually includes multidisciplinary approach involving addition of chemotherapy, which has been shown to improve overall survival by about 8% at 5 years and a higher increase in locoregional control [2-4].The intensive treatment with concurrent radiation and chemotherapy comes at the expense of increased treatment related acute and long-term toxicity [5,6]. Hence, to balance the potentially improved oncological outcomes with increased toxicity, careful selection of patients for intensive treatment should be undertaken in terms of disease risk factors and comorbidities. Meticulous supportive care and early recognition of toxicities with potential chemotherapy dose modification or dose holding if needed are key to successful treatment completion. The goal should be to minimize treatment interruption as unplanned radiation treatment interruption is associated with worse local control [7,8]. Here we discuss the commonly encountered toxicities in patients receiving CRT with cisplatin, with a focus on current management of mucositis. We explore the potential changing landscape of systemic treatments for locally advanced HNSCC and its impact on toxicities associated with concurrent radiation.

Mucositis: pathophysiology, risk factors and time course

Oral mucositis or damage to the mucosal tract from radiation for head and neck cancer, remains one of the most challenging side effects of CRT. OM starts as painful erythema that frequently progresses to ulceration and has multitude of consequences ranging from pain, dysphagia, malnutrition, dehydration, aspiration, predisposition to infections, hospital admission and possibly treatment interruption. As anticipated OM is associated with significant patient distress and effect on quality of life. The pathophysiology of mucositis is a complex interplay of direct mucosal injury, cell death, production of

reactive oxygen species, activation of pro inflammatory cascade and finally healing. A five-step model of initiation, upregulation, signal amplification, ulceration and healing has been proposed [9,10]. Direct mucosal injury from chemotherapy and radiation results in DNA damage and generation of reactive oxygen species starting the initiation phase. Subsequently, the cells damaged by radiation and chemotherapy may release endogenous damage associated pattern molecules (CRAMPs), which then bind to specific receptors and contribute to the initiation of the second stage. This then leads to the activation of the innate immune response and a number of biological events including the activation of nuclear factor Kappa-B (NF-kB) pathway. The activation of NF-kB leads to the expression genes associated with the production of pro-inflammatory cytokines [such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)], cytokine modulators, stress responders (such as cyclooxegenase-2 (COX-2), inducible nitric oxide (NO)-synthase, superoxide dismutase), and cell adhesion molecules [11]. In the fourth stage, patients develop symptomatic deep ulcerations and are more prone to infection. Bacteria colonizing the ulcers release molecules stimulating infiltration macrophages, which leads to further mucosal damage. The final stage is characterized by healing.

World health organization (WHO) mucositis scale and Common Toxicity Criteria Adverse Events (CTCAE) are the most commonly used scales in clinical practice [12,13]. The WHO scale combines clinical exam findings of erythema, ulceration and patient's functional ability to eat. The CTCAE combines pain and ability to eat. The first symptom of oral mucositis appears at week 1-2 of treatment which corresponds to 10-15 Gy of cumulative radiation dose. This follows a linear and well documented course with progression through subsequent weeks of treatment. Recovery usually starts about 2-4 weeks after treatment completion[10]. The extent of mucosal injury is directly related to mucosal volume irradiated, anatomic sub-site, treatment intensity including fractionation regimens, use of systemic treatment and pre-treatment patient characteristics like smoking, oral hygiene, and possibly human papilloma virus (HPV) status [14,15]. Patients treated with CRT experience more severe mucositis and are prone to complications of dehydration, acute kidney injury especially in the setting of cisplatin use. Trotti et al. reported an incidence of 43% of grade 3-4 mucositis in patients receiving concurrent CRT[6]. The incidence of treatment modification or interruption was 19% with CRT compared to 9% with RT alone [6]. Higher rates of hospitalization are also reported with CRT (6%) compared to 2% with RT alone [16]. In a cross-sectional study chemotherapy was reported to increase the risk of severe mucositis by 3.3 over RT alone (95% CI, 1.4-8.0) [17]. In a retrospective analysis on 164 patients, chemotherapy was found to increase the risk of mucosal Grade 3 toxicity, 4 times over radiation therapy alone, and the authors concluded that it is equivalent to an extra 6.2 Gy to 21 cc of oral mucosa over a 7-week course [18]. Careful selection of patients for concurrent CRT especially with the growing elderly population becomes important. Alternative systemic regimens to standard cisplatin-based chemotherapy have been explored for cisplatin ineligible patients or as a way of de-intensifying treatment and improving tolerability. HPV positive oropharyngeal cancer presents in a different age, socioeconomic and comorbid group. A larger portion of HPV positive patients are expected to be long term survivors and the effect on their quality of life (QOL) may be different. There were initial suggestions that treatment modality may not affect QOL in HPV positive patients [15]. In a retrospective study on 177 patients, the QOL measures in speech (p=0.0009), swallowing (P=0.021) and chewing (P=0.0004) at 1 year were also better in HPV positive patients compared to p16-negative patients [15]. On the other hand, a subgroup analysis of 200 oropharyngeal patients from a phase 3 trial of patients treated with CRT, reported better functional assessment scores at baseline for p16 positive patients compared to those of p16 negative, but a more dramatic decline in these scores at two months for p16 positive patients [19].

Mucositis: management and specific agents

Several agents have been investigated but convincing evidence from phase 3 trials is lacking. Most agents have failed to demonstrate improvement in outcomes of CRT compliance, reduction in opioid use to justify the costs in Phase 3 trials. Clinical outcomes relevant to mucositis, such as oral pain duration, severity, narcotic use, dietary alteration, dysphagia, weight loss and dehydration are not universally reported in clinical trials complicating the end points for investigation of these agents. Supersaturated calcium phosphate oral rinse, caphosol that increases the lubrication and integrity of the mucosa in the oral cavity through its high concentration of calcium and phosphate ions, failed to show a reduction in severe oral mucositis [20,21]. Palifermin, a recombinant keratinocyte growth factor stimulates proliferation of epithelial cells including that of the oral and gastrointestinal tract. In a randomized controlled study, Palifermin reduced the numerical incidence of severe OM compared to placebo in LAHNSCC receiving CRT, the results were not statistically significant [22]. It is not approved for use outside of the hematopoietic stem cell transplant setting. Low level laser treatment has anti-inflammatory, wound healing effect and has shown to decrease the incidence, duration and severity of mucositis. In a meta-analysis that included 57 trials with 5261 patients, low-level laser additional to standard oral care was an effective prophylactic treatment for reducing severe radiotherapy-induced oral mucositis compared to standard oral care alone [23]. In a randomized trial on 94 patients, low level laser treatment was found to be associated with lower morbidity and was cost effective when compared to standard of care after accounting for feeding tube placement and hospitalization for mucositis in the two groups [24]. Ongoing trials are looking to establish feasibility, minimal effective dose and frequency of low-level laser treatment [25,26]. There are some promising agents in clinical trials for prevention and treatment of mucositis. The formation of reactive oxygen species including super oxide play a key role in the initiation cascade resulting in radiation induced mucositis. GC4419, a superoxide dismutase mimetic rapidly and specifically converts super oxide to hydrogen peroxide and arrests the initiation of this cascade. Phase

IIb randomized double blind trial with GC4419 showed significant reduction in severe OM duration (P = .024; median, 1.5 v 19 days), incidence (43% v 65%; P = .009) and severity (grade 4 incidence, 16% v 30%; P = .045) [27]. A multicenter phase III trial with GC4419 is actively recruiting patients at this time [28]. Selective ongoing trials for mucositis are summarized in Table 1.

Table 1: Ongoing clinical trials in USA with agents for mucositis.

Clinical Trial Identifier	Agent/Intervention	Mechanism of Action	Trial Design
NCT03689712	GC4419	Antioxidant/superoxide dismutase mimetic	Phase 3 placebo controlled
NCT03480971	Tempol	Antioxidant	Phase 2 placebo controlled
NCT03461354	Mucolox	Mucosal protectant; adhesive polymer	Phase 2 single blinded, sodium bicarbonate comparator arm
NCT04648020	Clonidine Hydrochloride	Muco-adhesive buccal tablet	Phase 2b/3 placebo controlled
NCT03843554	Oral mucosal and Dental Prophylaxis Protocol	Periodontal surface debridement and alteration of microbiome	Phase 2 randomized controlled
NCT03972527	Photo modulation, low level laser	Anti-inflammatory, wound healing	Phase 2 double blinded, placebo controlled

Supportive care: Mucositis, dysphagia, dehydration, nutrition

In the absence of specific agents approved for management of mucositis, treatment remains supportive. Patient related factors that contribute to mucositis include poor dental hygiene, smoking and alcohol intake. Salt and soda rinse to maintain oral hygiene should be encouraged [29]. Medicated mouthwash can increase irritation and should be avoided in general. Use of soft toothbrush, avoidance of trauma from ill-fitting dentures or acidic, spicy food is encouraged. Caloric intake assessment, weights, dysphagia and odynophagia should be assessed on a regular basis [30]. Patients receiving comprehensive radiation for oral cavity and oropharyngeal cancer are at higher risk of mucositis impacting caloric intake and in the presence of other risk factors (like presence of pre-existing dysphagia, co morbidities, weight loss more than 10% body weight in 6 months prior to treatment) need to be assessed for prophylactic feeding tube [31]. Mode and timing of enteral nutrition continues to be a topic of debate with varying institutional practices. Patients who need enteral nutrition should be encouraged to continue oral intake as oral intake interruption even for short intervals has been associated with long term dysphagia [32]. Although prophylactic feeding tubes may provide continuous caloric intake, their impact on treatment outcomes and interruption, long term dysphagia remains controversial [33,34]. Patients require frequent oral exams, nutritional and caloric assessments and evaluation for swallowing. Oral mucosa should be examined for thrush and fungal infection treated with nystation or oral fluconazole.

Pain management starts with topical agents including magic mouthwash which a compound prescription and the composition varies from one pharmacy to another. Topical lidocaine, along with benadryl and maalox with or without antifungal nystatin are the usual constituents. Topical morphine 2% is also part of certain formulations. Oral care is encouraged with bland rinses like salt and baking soda 4-6 times a day. Medicated or antimicrobial mouthwashes do not improve time to development or severity of mucositis [35]. Topical morphine and topical lidocaine are usually effective in initial pain control [36]. Gabapentin is started at the start of radiation at 300mg three times a day and gradually increased to 900mg three times a day [37]. This has been shown to decrease the use of narcotics. Accompanying nausea, vomiting and constipation needs to be managed. Increased oral hydration should be encouraged to help xerostomia and manage thick secretions. Dysguesia or loss of taste also presents a significant challenge for oral intake. Management of radiation dermatitis starts with good moisturizing lotion containing aloe vera or hyaluronic acid. Protective nonadherent gel-based dressings and silver sulfadiazine creams are used for moist desquamation.

In patients undergoing CRT, week 5-7 requires close monitoring of toxicities to prevent treatment interruption. Assessments include percentage weight loss, pain control, renal function that can guide decisions on chemotherapy dose reduction or dose holding with the goals of avoiding any radiation interruption. Unplanned treatment break has been reported to decrease local tumor control rate by 0.5 to 1% for each day of interruption [38,39]. Unplanned treatment interruption and prolongation of treatment time from ulcerative mucositis has also been shown to decrease overall survival [8]. Careful supportive care can minimize hospitalization, cost of care and pain discomfort. Management of patients is multidisciplinary with close follow up by dietician, speech and swallow pathologist, pretreatment dental evaluation, attention to hydration status, oral care, and pain management. Smoking cessation should be strongly encouraged, and compliance frequently assessed to improve disease control outcomes and risk for oral mucositis. Elderly population constitutes a growing subgroup at higher risk for complications including severe mucositis but does seem to benefit from addition of chemotherapy in the appropriate setting [40,41]. In addition to calorie assessment, adequate fluid intake and supportive hydration play a key role in managing patients at high risk for toxicities as they approach week 5 of treatment. Urine specific gravity has been suggested as a means of recognizing the need for hydration early by our group and can be used as an adjunct to assessment

of other clinical parameters [42]. Follow up assessments should be more frequent as the patients approach week 4 of treatment or earlier depending on comorbidities and side effects. Intravenous hydration depending on infusion resources, distance from patient and patient preference should be considered until patients are able to successfully maintain oral intake. Recovery from toxicities is slow and does not start until about 2-4 weeks after treatment conclusion. Reassessment after treatment conclusion to identify and intervene in patients with potential decline plays a key role in successful management of patients.

Role of chemotherapeutic agent

Cisplatin bolus dose of 100mg/m^2 every three weeks or 40mg/m^2 every week, remains the standard of care. Other agents in patients who are cisplatin ineligible include: carboplatin/5FU, carboplatin and paclitaxel, cetuximab. Due to toxicities associated with bolus cisplatin, weekly low dose cisplatin is widely used in practice and is increasingly adopted as a standard of care arm in clinical trials. In a large population based retrospective study including 2901 patients, high dose every 3-weekly cisplatin, was not associated with improved overall survival (hazard ratio= 0.94, 95% confidence interval=0.80 to 1.04) compared to weekly low dose cisplatin and was associated with an increased risk of acute kidney injury, neutropenia and hearing loss [43]. A prospective randomized trial from India compared bolus 100mg/m2 cisplatin with weekly 30mg/m2 Cisplatin with 92% patients being in the adjuvant setting. 2-year loco-regional control rate was 58.5% in weekly arm and 73.1% in bolus cisplatin group (p = .014; hazard ratio (HR), 1.76 (95% CI, 1.11 to 2.79), no differences in OS between the two groups was observed [44]. Acute toxicities of grade 3 or higher occurred in 71.6% of patients in the once-a-week arm and in 84.6% of patients in the once-every-3-weeks arm (P = .006) [44]. The weekly dose used in the trial of 30mg/m2 is lower than the usual dose used in United States of 40mg/m2 of weekly cisplatin. In a phase II/III non inferiority clinical trial comparing 100mg/m2 every three-week cisplatin with weekly low dose cisplatin of 40mg/m2 with concurrent radiation in the adjuvant setting, the low dose weekly cisplatin was found to be non-inferior (3-year OS was 59.1% vs 71.6% with a HR of 0.69 (99.1% CI, 0.374-1.273 [<1.32], one-sided p for non-inferiority = 0.00272 < 0.00433) and was associated with lower grade 3 neutropenia, hearing loss and acute kidney injury [45].

The Bonner trial showed the addition of cetuximab to radiation improved the median overall survival from 29.3 months to 49 months for locally advanced head and neck cancer [46]. Of note, cetuximab was associated with acneiform rash and infusion reactions but the incidence of other grade 3 toxicities including mucositis was not increased. The search for systemic options with lower toxicity and absence of comparison to cisplatin lead to widespread adoption of cetuximab with radiation in community practice. However, RTOG 1016 phase III non inferiority trial comparing standard cisplatin to cetuximab with concurrent radiation in HPV positive patients failed to meet the non-inferiority boundary. Five years overall survival was 77.9% (95% CI 73.4-82.5) in the cetuximab group versus 84.6% (80.6-88.6) in the cisplatin group. Although the acute toxicity profiles differed, the proportions of acute moderate to severe toxicity (77.4%, 95% CI 73.0-81.5 vs 81.7%, 77.5-85.3; p=0.1586) and late moderate to severe toxicity (16.5%, 95% CI 12.9-20.7 vs 20.4%, 16.4-24.8; p=0.1904) were similar between the cetuximab and cisplatin groups [47]. A parallel European multi-center trial with primary outcome of overall severe (grade 3-5) toxicity events at 24 months from the end of treatment, showed no benefit with cetuximab in terms of reduced toxicity, but also showed worse tumor control [48]. Cetuximab concurrently with RT was also compared with weekly cisplatin 40mg/m2 concurrently with RT in locoregionally advanced HNSCC and found to inferior with higher incidence of locoregional failures at 3 years was 23% (95% CI, 16% to 31%) compared with 9% (95% CI, 4% to 14%, P = .0036) in the cetuximab versus the cisplatin group [49]. Bolus cisplatin remains the current standard chemotherapy with potential mounting evidence for low dose weekly cisplatin especially in the adjuvant setting with better tolerability profile.

Emerging and alternate approaches to standard platinum and radiation

Trials are underway for tailoring treatment for HPV patients based on disease risk groups with efforts to evaluate lower gross tumor dose, lower systemic dose, and role of immunotherapy concurrently with radiation. An individualized approach based on clinical and pathological risk factors as envisioned by ECOG 3311 might help reduce long term side effects while maintaining treatment outcomes of loco-regional control and overall survival [50]. A phase II ECOG 1308 trial on HPV positive patients, clinical complete response to induction chemotherapy (IC) was explored as a predictor of reduced radiation dose to 54 Gy with weekly cetuximab. At 12 months, significantly fewer patients treated with 54 Gy of radiation had difficulty swallowing solids (40% v 89%; P = .011) or had impaired nutrition (10% v 44%; P = .025). Patients treated with IC and reduced-dose radiation with low-volume disease (e.g., T1-T3, N1-N2b) and less than 10 pack-years of cigarette smoking had high rate of disease control, with a 2-year PFS of 96% (95% CI, 76% to 99%) and overall survival of 96% (95% CI, 76% to 99%) [51]. Larger phase III trials like HN005 for low-risk HPV patients are exploring reducing radiation dose to 60 Gray with cisplatin or nivolumab [52].

For the subgroup of cisplatin ineligible patients, investigations and clinical trials continue to study agents that decrease treatment related toxicity without compromising treatment efficacy. A phase II trial comparing cetuximab to pembrolizumab with RT in cisplatin ineligible patients, did not show improvement in loco-regional control with at 15 months (59% with Cetuximab RT and 60% with Pembrolizumab RT, p=0.91). Acute toxicity (mainly dermatitis in radiation field, mucositis, and cutaneous rash) was lower in Pembrolizumab arm than Cetuximab arm 74% vs 92% patients with at least one grade ≥ 3 acute adverse events (p=0.006) [53]. Cisplatin ineligible patients also generally require additional supportive care due to comorbidities. On the other hand, outcomes for locally advanced p16 negative patients remain poor and

identification of agents that improve efficacy without increasing treatment related toxicity remains elusive. RTOG 0522 comparing addition of cetuximab to cisplatin and RT, resulted in treatment interruption in 26% of patients compared to 15% and more grade 3, 4 mucositis: 43 vs 33% [54]. 3 years PFS, OS, loco-regional failure and late toxicity were similar between the two arms. Debio 1143 is an orally available antagonist of inhibitor of apoptosis proteins with the potential to enhance the anti-tumor activity of cisplatin and radiotherapy. A phase II randomized trial comparing the addition of Debio 1143 to cisplatin and radiation showed improvement in loco-regional control in patients with HPV negative head and neck cancers (54 vs 33%; odds ratio 2.69 [95% CI 1.13-6.42], p=0.026). The study showed some increment in grade 3-4 mucositis from 21% to 31% [55]. The development of new treatment paradigms and combination approaches with radiation should also focus on optimizing normal tissue protection to improve treatment completion and compliance in addition to improving short and long-term quality of life outcomes.

Conclusion

CRT is associated with high rates of acute toxicity in locally advanced HNSCC. Individualized treatment approaches could potentially improve quality of life while maintaining efficacy and oncological outcomes for patients. New, cost-effective agents for mucositis are urgently needed to improve treatment toleration, quality of life and potentially allow for more intensive treatment in groups with poorer outcomes. At this time, aggressive multidisciplinary supportive care with attention to comorbidities, nutrition, dysphagia, oral care, hydration status and pain management remain paramount to successful treatment of this patient population as new treatment paradigms emerge. Continuous efforts are needed to individualize treatment with novel approaches, treatment de-escalation and radiation plans with possible sparing of tissues. Identification of better supportive care agents for mucositis could help minimize toxicity and treatment breaks and could lead to improved outcomes for higher risk patients.

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