Chapter 5

Head and Neck Cancer in Patients with Fanconi Anemia

Introduction

Head and neck squamous cell carcinoma (HNSCC) is significantly more common in patients with Fanconi anemia (FA) than in the general population. This chapter provides an overview of HNSCC in patients with FA. Focus areas include early surveillance, risk factors, diagnosis, and currently available treatment options. Head and neck cancers are diagnosed at a younger age (20-50 years) in patients with FA and often at an advanced stage. The cornerstone treatment for FA patients with HNSCC is surgery; however, outcomes are poor if the diagnosis is at an advanced stage. Patients with FA also have significant toxicity issues from systemic chemotherapies used to treat HNSCC in the general population. The precise risk factors associated with HNSCC for patients with FA have yet to be defined, although studies have shown that DNA repair defects associated with the disease, increased age, and graft-versus-host disease (GvHD) after hematopoietic cell transplant (HCT) correlate with increased risk for HNSCC development. Causative well-defined risk factors in the general population, such as tobacco and alcohol use, should be avoided by patients with FA. It is recommended that early surveillance by oral examination begin at a young age.

Head and Neck Cancer in the General Population

Head and neck cancers encompass a wide variety of tumors that typically begin in the squamous cells that line the mucosal surfaces of the oral cavity, nasal cavity, pharynx, and larynx. These tumors often are referred to as head and neck squamous cell carcinoma (HNSCC). Approximately 30,000 individuals are diagnosed with head and neck cancer in the United States annually, and about 30% of these patients die from their disease. Increasingly, HNSCC is an international health problem, representing the fifth most common cancer type and cause of cancer-related death worldwide [1].

The vast majority of HNSCC cases (more than 90%) develop following exposure to carcinogens, including tobacco and alcohol [2, 3], betel nut [4], Epstein-Barr Virus (EBV), and sexually transmitted viral pathogens such as human papilloma virus (HPV) [5]. Head and neck cancers are prototypic tobacco-related cancers. The risk for the development of HNSCC and the subsequent risk for the development of second primary cancers in the upper aerodigestive tract is directly attributable to the duration and intensity of tobacco exposure. Tobacco-related cancers also can occur in non-smokers as a result of environmental smoke exposure. Chronic consumption of alcohol is estimated to increase the risk for HNSCC by two- to three-fold in a dose-dependent manner. Moreover, individuals who use both tobacco and alcohol have up to 10-20 times higher risk for HNSCC than people who do not use tobacco or alcohol. Approximately 5% of HNSCC develop in individuals who do not smoke or consume alcohol. Emerging evidence suggests that HPV may play a role in the development of HNSCC, with HPV detected in more than 70-80% of cases of oropharyngeal cancer.

Head and Neck Cancer in Patients with Fanconi Anemia

Head and neck squamous cell carcinoma (HNSCC) is the most common solid tumor in patients with FA. The incidence of HNSCC in FA patients is 500- to 700-fold higher than in the general population [6-9]. The main cause of death in adulthood for patients with FA is HNSCC and the risk increases with age. In some cases, diagnosis of HNSCC tumors precedes the diagnosis of FA [10]; therefore, FA testing should be considered in patients younger than age 40 who develop HNSCC, especially if they have atypical findings such as borderline anemia or an atypical response to cytotoxic treatment.

Compared with the general population, the age of onset, distribution, and course of HNSCC is significantly different in patients with FA. Patients with FA tend to be diagnosed with HNSCC between the ages of 20-50 years [10], whereas individuals in the general population tend to be diagnosed between the ages of 60-70 years. Patients with FA also

have a higher proportion of HNSCC in the oral cavity (approximately 65%), the vast majority of which involve the tongue, compared with the general population. Furthermore, a much higher proportion of HNSCC in patients with FA is diagnosed in advanced stages compared with the general population. Despite aggressive treatment, the outcome of HNSCC in FA patients is significantly poorer than that in the general population. Moreover, even after cure of the primary HNSCC, patients with FA are more likely than the general population to develop second primary cancers (more than 60% versus ~30%, respectively) [10]. The anatomic distribution of second primary cancers also is significantly different in patients with FA compared with the general population. Whereas patients with HNSCC in the general population tend to develop second primary cancers in the lung and esophagus, patients with FA develop second primary cancers in the head and neck region, genitourinary tract, and skin. Interestingly, the pattern of second primary cancers in patients with FA resembles that observed in HPV-associated HNSCC in the general population [11].

Risk Factors Associated with Head and Neck Cancer in Patients with Fanconi Anemia

Most individuals with FA are now living into adulthood, due to significant improvements in bone marrow transplant outcomes. With increased age, these patients are experiencing a significant escalation in the incidence of cancer, which now represents the major cause of death in the FA adult population. Age alone is a significant risk factor for HNSCC for patients with FA. They are diagnosed with HNSCC earlier than the general population (20-50 years vs. 60-70 years) and the risk increases significantly with age. Cumulative genomic instability from DNA repair defects that are a hallmark of FA also contributes significantly to this age-related risk [12].

Patients with FA have the highest risk for HNSCC amongst all patients with inherited genetic syndromes (e.g., Li-Fraumeni syndrome and Bloom's syndrome). Unlike individuals with an inherited mutation in the retinoblastoma gene (*RB*), nearly all of whom develop tumors of the retina, not all patients with FA develop HNSCC. Like the association between radiation exposure and the development of high-grade sarcomas in patients with an inherited *RB* mutation, a co-factor(s) is likely required for FA patients to develop HNSCC. The precise cause(s) of and co-factor(s) for the increased risk of HNSCC in patients with FA have yet to be defined. The type of FA mutation and severity of manifestations have not been clearly associated with the development of HNSCC. A 2004 study [13] suggests that bone marrow transplantation increases the risk for HNSCC development in patients with FA, and primarily attributed the increased risk to the development of acute and/or chronic graft-versus-host disease (GvHD). However, high numbers of patients with FA who have never undergone HCT also develop HNSCC [14]. An association between GvHD and HNSCC also has been suggested in patients without FA [15]. Tobacco and alcohol consumption are less commonly reported in patients with FA than in the general population; nonetheless,

both remain major risk factors for the development of HNSCC in patients with FA. Most studies support a role for HPV in gynecological malignancies, but its precise contributions to HNSCC in patients with FA remain controversial. Some studies [16, 17] suggest that HPV may be a major contributor to HNSCC development in patients with FA, whereas other studies [18, 19] dispute these results. Laboratory studies show that mutations in genes that cause FA increase susceptibility to HPV-induced carcinogenesis [20, 21]. Overall, the scientific literature suggests that multiple factors contribute to the development of HNSCC in patients with FA, although the precise contributions of individual factors remain to be defined.

Prevention of Head and Neck Cancer in Patients with Fanconi Anemia

Abstaining from Alcohol and Tobacco

The causal link between tobacco and alcohol exposure and the development of HNSCC is well-established. The use of tobacco and tobacco products should be discouraged categorically, including exposure to secondhand smoke. Further, marijuana and e-cigarette use also have been associated with the development of HNSCC in the general population [22]; therefore, FA patients are encouraged to abstain from use of these agents. While it is best to abstain from alcohol use, individuals who consume alcohol should restrict their intake to no more than one drink equivalent per month. The chronic use of alcohol-containing mouthwashes also should be discouraged (see Chapter 6).

Maintenance of Oral Hygiene

Several reports suggest that poor oral hygiene and chronic, repeated physical trauma to the oral cavity may promote the development of HNSCC [23-25], although the evidence is not yet conclusive. Therefore, maintenance of proper oral hygiene and routine dental evaluations are recommended. The use of oral appliances, braces, and dental X-rays do not need to be restricted in patients with FA given the lack of evidence to suggest a causal association with HNSCC. This subject is discussed in Chapter 6.

Human Papilloma Virus Vaccination

The role of human papilloma virus (HPV) in HNSCC development in patients with FA is controversial [16, 17, 19, 26, 27] and more studies are needed. Despite the controversy, it is recommended that both male and female patients with FA receive an HPV vaccination at an early age [28, 29]. See Chapter 7 for detailed vaccination recommendations for female patients with FA.

Surveillance of Head and Neck Cancer in Patients with Fanconi Anemia

The high incidence of HNSCC combined with the poor outcome of this disease in patients with FA underscore the need for careful HNSCC surveillance. Surveillance should begin at age 10, which is based on literature reports of the earliest age of HNSCC diagnosis [8, 10]. The oral cavities of individuals with FA often contain multiple lesions. Distinguishing suspicious lesions from those that are non-cancerous requires the input of a health care provider with significant experience in the evaluation and management of HNSCC for FA patients. Qualified professionals may have dental, oral surgery, otolaryngology, or general surgery backgrounds supplemented with specialized training in detecting and/or treating HNSCC. Routine oral cancer screening by a general dentist can supplement but should not replace thorough HNSCC screening.

Oral Examination

Thorough head and neck examination in patients with FA should occur every six months. The sites at risk for development of HNSCC include all areas of the upper aerodigestive tract. Therefore, all mucosal surfaces of the head and neck region should be examined thoroughly. The oral cavity, the most common site for HNSCC in patients with FA, and the proximal oropharynx can be effectively evaluated through the mouth by visual examination and palpation. Examination of the distal oropharynx, nasopharynx, larynx, and hypopharynx requires the use of either a transoral mirror or a flexible fiberoptic laryngoscope. Although patients with FA have a higher rate of SCC in the cervical esophagus than the general population [30], the routine use of esophagoscopy for screening is not advocated. Symptom-based evaluation for esophageal cancer needs to be considered. Any patient with odynophagia, dysphagia, or other localizing symptoms merits evaluation with a barium swallow study and/or esophagoscopy.

Importance of Brush Biopsy for Patients with Fanconi Anemia

The oral cavities of patients with FA often have multiple leukoplakia-like lesions that are typically not malignant. In the past, all suspicious lesions were diagnosed through incisional tissue biopsy only. Early surveillance of tumor development in the head and neck region of individuals with FA is essential; however, conducting numerous incisional biopsies on suspicious lesions is invasive and painful. Patients with FA therefore require alternative and effective early surveillance strategies that do not cause extensive tissue damage. Fourteen years ago, a medical team from Germany initiated a study to see if a non-invasive brush biopsy procedure could accurately determine pre-malignant and malignant tissue in a large cohort of patients with FA. This study, published in 2020, showed that in 713 patients with FA worldwide, careful examination of the oral cavity followed by brush biopsy and cytology identified pre-malignant and malignant lesions with high sensitivity (97.7%) and specificity (84.5%). The addition of DNA ploidy analysis to brush biopsy samples examined by cytology increased the sensitivity and specificity to

100% and 92.2%, respectively [31]. This is a highly significant finding, as 63% of lesions in the study were diagnosed as pre-malignant or early-stage cancer and were curable through surgery.

It is important to point out that once suspicious lesions are identified as precancerous or cancerous by a brush biopsy, they should be biopsied with an incisional biopsy immediately. Suspicious lesions not found pre-cancerous or cancerous by brush biopsy should be closely monitored. Stability or shrinkage in size of the lesion can be used as an indicator to continue observation. Growth or changes in characteristics of the lesion (i.e., thickening or erythroplakia) require further attention.

Treatment of Head and Neck Cancer in Patients with Fanconi Anemia

Surgery, radiation, and chemotherapy—either alone or in combination—are used to treat HNSCC in the general population. As a general rule, early-stage disease is treated either with surgery or with radiation therapy, whereas advanced-stage disease requires multi-modality therapy with surgery followed by radiation with or without chemotherapy or concomitant treatment with chemoradiation therapy. While all of these approaches can be used in the general population, significant negative side-effects limit the use of chemotherapy and radiation therapy in patients with FA. Therefore, several modifications are required in the management of HNSCC in patients with FA.

Treatment Team

Optimal treatment of HNSCC requires a treatment team that includes not only surgeons (cancer and reconstructive specialists), radiation oncologists, and medical oncologists, but also specialized dentists, oral surgeons, speech and language pathologists, nurses, as well as many other professionals. This team should work in close collaboration with other FA specialists to provide comprehensive care.

Treatment Approach to Head and Neck Cancer in Patients with Fanconi Anemia

The following factors complicate the management of HNSCC in FA patients, making surgery the preferred therapeutic modality in patients with FA:

- The tumors of FA patients tend to be very aggressive and often are present in advanced stages.
- The non-cancerous cells of FA patients are more sensitive to treatments that crosslink DNA, such as the chemotherapeutic drug, cisplatin, and external beam radiation—two mainstays of HNSCC treatment for the general population.
- HNSCC cells in FA patients are not as sensitive as non-cancerous cells to DNA-crosslinking agents. Therefore, HNSCC in FA patients does not respond to sub-therapeutic doses of radiation. Therefore, surgery is the preferred therapeutic modality in FA patients.

Recommendations for Surgical Treatment of Head and Neck Cancer in Patients with Fanconi Anemia

In contrast to the other treatment modalities, surgical therapy for HNSCC in FA patients is well tolerated and can result in durable local control for small tumors without lymph node metastases [32]. Patients with FA exhibit no significant increase in the incidence of complications following surgery, including wound infections or long-term negative side effects associated with surgical scarring. Accordingly, the consensus opinion is that surgery should be considered the primary curative modality in all FA patients who develop HNSCC.

A successful outcome following head and neck surgery requires a multidisciplinary preoperative assessment and optimization of the patient, intraoperative management, and postoperative care. To minimize the risks associated with surgery, FA patients should be optimized medically by a hematologist who is experienced in the management of patients with FA. Depending on the extent of surgery and the anticipated outcomes, a pain management specialist and a mental health professional should be consulted prior to surgery to help the patient cope with any negative after-effects.

Surgery for HNSCC in patients with FA should follow the same parameters that have been established for the general population. In general, a wide complete excision of the primary tumor should be performed with adequate margins. The exact type and extent of surgical resection should be dictated by the primary site, size, and extent of the tumor. Large cancers that involve multiple subsites of the head and neck should be excised via an open approach as in the general population. However, smaller accessible tumors can be resected trans-orally using robotic or laser instruments. In general, tumors of the oral cavity and pharynx should be excised with at least 1-cm margins. The margins for laryngeal tumors need not be as comprehensive, due to the unique biology of laryngeal cancers and anatomy of the larynx.

Management of the neck also follows principles established for the management of HNSCC in the general population. In general, cancers that are classified clinically as N0 disease with high risk for occult metastasis or small volume N1 disease may be managed with a selective neck dissection, whereas modified neck dissection or even radical neck dissection may be required for more advanced regional disease. A recent study in patients without FA showed that elective nodal dissections in patients with oral cavity cancers with an N0 neck are associated with a significant improvement in overall survival [33]. Therefore, it is recommended that elective nodal dissection be included as part of management in FA patients who have oral cancer as well.

Reconstruction of the primary site defect should follow the guidelines established for reconstruction in patients with HNSCC in the general population and should not be limited based on the presence of FA. Several case reports have described the successful use of free flap reconstruction in FA patients [34-36]. Therefore, the use of free flaps for reconstruction should be considered as indicated, without restrictions. The specific details of surgical management are discussed in other references [37, 38].

Radiation Therapy of Head and Neck Cancer in Patients with Fanconi Anemia

Radiation treatment is associated with severe negative after-effects in patients with FA, and many patients cannot complete a full course of radiation. The risk of dying from the negative after-effects of radiation is as high as 50%. Death may be due to local effects, but systemic effects such as bone marrow failure are also major contributors. Those who survive radiation treatment face severe side effects, including xerostomia, dysphagia, esophageal stenosis, laryngeal edema, and wound breakdown. Therefore, radiation therapy should be used only in FA patients for whom it is absolutely required for disease control.

When radiation therapy is to be utilized, FA patients must be monitored closely for signs of severe toxicity. It is important to keep in mind that tumor cells in FA patients do not have increased susceptibility to the effects of radiation (unlike the tumor cells in most individuals in the general population). Therefore, treatment with radiation should be planned for the same doses used in the management of patients without FA. Radiosensitivity of normal tissues in FA patients is a concern as there have been several case reports of severe mucositis occurring in the oral cavity of FA patients after doses of 10–20 Gy with conventional field sizes encompassing the entire oral cavity. These clinical presentations have usually been associated with conventional fractionation of 1.8–2.0 Gy per day, five days a week, to a target volume that included the entire oral cavity and oropharynx.

An approach has been designed in which a small field of 5 cm x 5 cm is treated for one week (five fractions) at reduced fraction size of 0.5 Gy per day, with daily examination for mucositis and daily peripheral blood counts. Both patients with FA and animal models of FA [39-41] with radiosensitivity have demonstrated significant abscopal bone marrow suppression and leukopenia. Patients tolerating the first week of reduced field and reduced fraction size then can be moved up to a second week of same reduced field size, but now with conventional fractionation of 1.8–2.0 Gy per day. Daily measurements of mucositis by physical exam and peripheral blood counts should be continued. Patients who tolerate this therapy then can move on to the entire clinical target volume with reduced fraction size of 0.5 Gy per day. Subsequently, in the absence of significant mucositis or leukopenia, patients may move on to complete radiotherapy with conventional fraction size and full target volume to the usual post-operative radiotherapy dose of 55–60 Gy. Post-operative radiotherapy for oral cavity cancers is usually indicated if there are positive resection margins and/or positive regional lymph nodes.

Systemic Therapies for Head and Neck Cancer

Systemic therapy using cross-linking agents and other targeted therapies is an integral component of the management for locally advanced, recurrent and/or metastatic HNSCC in the general population. Patients with FA cannot be safely treated with DNA cross-linking

agents due to high toxicity. Other non-cytotoxic targeted therapies may be viable options, but more research is needed to understand their effects on patients with FA.

Platinum-Based Chemotherapy in the General Population

In patients in the general population with surgically resected HNSCC, cisplatin (100 mg/m^2 intravenously once every 21 days) administered concurrently with post-operative radiation therapy has been demonstrated to improve locoregional control and overall survival in randomized studies [42, 43]. A pooled analysis of two phase III clinical trials demonstrated that patients with positive margins and/or extracapsular nodal spread benefited the most from the addition of chemotherapy to post-operative radiation therapy [44]. Based on these results, treatment guidelines currently recommend adjuvant cisplatin-based concurrent chemoradiation therapy for patients with these high-risk adverse features.

In patients with locally advanced disease who are treated non-surgically with curative intent, the integration of platinum-based chemotherapy concurrently with radiation therapy has been demonstrated to improve locoregional control and overall survival in prospective clinical trials and meta-analysis, compared with radiation therapy alone. These studies demonstrated an absolute 5-year survival benefit of approximately 6.5% [45, 46]. As a result, concurrent platinum-based chemoradiation therapy has become a standard option for non-surgical management of locally advanced HNSCC. However, the addition of cytotoxic chemotherapy to radiation therapy has been associated with an increased incidence of adverse events, including mucositis, dermatitis, skin toxicities, and the need for feeding tube placement [45].

Epidermal Growth Factor Receptor Inhibition in the General Population

Cetuximab (Erbitux) is a monoclonal antibody that inhibits the epidermal growth factor receptor (EGFR) and is used for the treatment of patients with locally advanced HNSCC. Cetuximab has been shown to improve locoregional control and survival when added to definitive radiation therapy in patients with oropharyngeal, laryngeal, and hypopharyngeal tumors in a randomized phase III clinical trial [47]. Based on these results, cetuximab has been approved by regulatory agencies throughout the world to be used in this setting. Cetuximab has a more favorable side effect profile than cytotoxic chemotherapy. Clinically relevant cetuximab-induced adverse events include skin rash, hypomagnesemia, grade 3-5 hypersensitivity reaction (in approximately 3% of patients), and a small increase in the incidence of radiotherapy-induced mucositis. Blood toxicity is not usually observed with concurrent cetuximab and radiation therapy. Concurrent cetuximab and radiation therapy recently has been directly compared to concurrent cisplatin and radiation therapy in two randomized studies of patients with HPV-related, locally advanced oropharynx cancers treated non-surgically. These studies have shown inferior locoregional control for the cetuximab-treated patients [48, 49]. As such, concurrent cisplatin with radiation therapy is still considered the standard of care for most

patients with HPV-related and non-HPV-related locally advanced HNSCC treated without surgery. Studies evaluating the role of cetuximab in the post-operative setting are ongoing.

Systemic Therapy for Recurrent or Metastatic Disease in the General Population

For patients with recurrent and/or metastatic disease, the cornerstone of treatment is systemic therapy with single agents (cisplatin, taxanes, 5-fluorouracil, or methotrexate), or platinum-based doublet regimens (the combination of a platinum-based drug with other chemotherapy agents) to maintain quality of life and prolong survival. Cetuximab has activity as single agent, and also has been shown to improve survival when added to first-line platinum/5-fluorouracil in a randomized phase III trial [50]. More recently, immunotherapy has emerged as a novel strategy to treat recurrent and/or metastatic disease. Immunotherapy has a different mechanism of action than chemotherapy. It stimulates the patient's own immune system to recognize and eliminate cancer cells. As such, side effects related to immunotherapy are different and usually less severe than chemotherapy, and mostly consist of auto-immune reactions resulting from normal cell injury by the activated immune system. Immunotherapy also benefits a relatively small proportion of patients. However, when effective, immunotherapy may control the disease for longer periods of time when compared to chemotherapy and/or cetuximab. The anti-programmed death-1 (PD-1) immunotherapy drugs nivolumab or pembrolizumab have been shown to improve survival compared to standard therapies in patients who have failed platinum-based treatments [51, 52]. In treatment-naïve patients with recurrent and/or metastatic disease, pembrolizumab alone (in selected patients) or pembrolizumab added to chemotherapy also have been shown to improve survival over the standard-of-care regimen of chemotherapy plus cetuximab.

Systemic Therapies for Head and Neck Cancer in Patients with Fanconi Anemia

The use of chemotherapy—particularly DNA-damaging agents—in FA patients is challenging, especially as it pertains to bone marrow failure and increased risk for normal tissue injury. The issue is further complicated by the lack of prospective trials, or even large retrospective series evaluating the safety and efficacy of cytotoxic agents in this patient population. Table 1 summarizes the published experience with the use of cytotoxic chemotherapy in FA patients for treatment of multiple tumor types (the majority of which are HNSCC). Notwithstanding possible publication bias, the limited data demonstrate that standard doses and schedules of chemotherapy do not seem to be feasible in patients with FA. Furthermore, cytotoxic chemotherapy at both standard and low doses is associated with severe, and in many cases fatal, toxicities and poor treatment outcomes.

The use of biologic agents in FA patients is an attractive alternative to cytotoxic chemotherapy, given the more favorable side effect profile of biologic agents. Nonetheless, cetuximab (the only targeted agent approved for HNSCC) has been used only anecdotally in FA patients and seems to be better tolerated than cytotoxic chemotherapy (Table 1), but efficacy in the FA setting is unknown. The use of anti-PD-1 inhibitors in FA

patients could be an alternative to cytotoxic therapy for management of recurrent and/or metastatic disease, but experience in FA patients also has been limited. Challenges regarding the use of this modality in FA patients include risk of activation of graft-versus-host disease (GvHD) in post-transplant patients [53], and possible lower efficacy compared to the general population, given the presence of immune dysfunction in FA individuals. These concerns, however, remain to be characterized through clinical observations.

Systemic therapies serve only as an adjunct to the cornerstone treatment—adequate surgery and/or radiation therapy—for patients without FA who have locally advanced disease. In patients with FA, the highest chance for long-term disease-free survival is achieved with adequate surgery (and/or possibly radiation therapy). Because of the high incidence of complications related to cytotoxic agents in patients with FA, the risks of integrating cytotoxic chemotherapy to the treatment regimen outweigh the potential benefits in most situations. Therefore, the use of cytotoxic agents in FA patients who have locally advanced or recurrent and/or metastatic head and neck cancers is strongly discouraged. For selected cases in which chemotherapy and/or biologic therapy or immunotherapy are to be considered, it is recommended that treatment is delivered in centers with extensive experience managing head and neck cancers and FA.

Table 1. Systemic therapies for HNSCC in patients with Fanconi anemia.

Tumor type	N	Chemotherapy	Cycles	Outcome
SCC tonsil [54]	1 ¶	Cisplatin (40 mg/m2)	X1	Fatal myelotoxicity
SCC hypopharynx [55]	1 ¶	Cisplatin (100 mg/m2)	X1	Fatal myelotoxicity
SCC esophagus [56]	1 ‡	Cisplatin (33 mg/m2) 5-FU (1000 mg/m2)	X1	Severe diarrhea and myelotoxicity Partial response allowing surgery
SCC tongue [57]	1 ‡	Cisplatin (8 mg) 5-FU (60 mg)	X1	Severe toxicity No tumor response
SCC lung [58]	1 ‡	Carboplatin (AUC 3 d1) Gemcitabine (1250 mg/m2 d1,8)	X2	Pneumonitis Partial response allowing surgery
SCC head and neck [8]	3 (2 ¶ + 1 ‡)	N/A	N/A	All died with disease
SCC vulva [59]	1 ¶	Cisplatin (40 mg/m2)	X1	Fatal fungal sepsis
SCC oral tongue [60]	1¶	Cetuximab	X8	Neutropenia, mucositis, cholestasis
SCC head and neck [32]	1	Carboplatin and paclitaxel	X2	Pancytopenia, colitis, hepatotoxicity
	1¶‡	Cetuximab	Several	Severe toxicity with radiation therapy, well tolerated with tumor response as single agent
	1¶	Cetuximab	Several	Well tolerated
	1	Cetuximab ¶ and nivolumab‡	Several, X3	Tolerated cetuximab well, had nivolumab-induced encephalitis
	1	Cetuximab ¶, paclitaxel (20-80 mg/m2/week)‡, tremelimumab‡, durvalumab‡	Several	Tolerated treatment well, died of disease
SCC head and neck [10]	3¶	Cetuximab	Several	Cytopenia in 1 patient
	3	Conventional chemotherapy	N/A	Severe complications in 1 patient

Chemotherapy was given as a single modality (‡) or concurrently with radiation therapy (¶). Abbreviations: AUC, area under the curve; N, number of patients treated with chemotherapy in each report; N/A, not available; SCC, squamous cell carcinomas.

Rehabilitation and Lifestyle Modification Post-Treatment of Head and Neck Cancer

The treatment of HNSCC can be debilitating. Rehabilitation should be initiated, as needed, to optimize the patient's functional, psychological, and vocational outcomes. The negative aftereffects of surgical tumor removal on speech and swallowing require intervention by physical and rehabilitation specialists (e.g., neck and shoulder exercises, speech and swallowing therapy, etc.). In addition, paralyzed vocal cords and stricture or obstruction of the pharynx also require intervention. Cosmetic restoration of the face is crucial to psychological rehabilitation. Following radiation therapy, patients may require management of xerostomia, dental care, and prevention of fibrosis-related complications such as trismus. Patients should be placed on long-term care specifically with respect to dental management. Monitoring of dentition should be maintained and prevention measures for caries initiated, including the use of fluoride treatments in all patients. Following chemotherapy, patients may require management of kidney function, hearing, and damage to peripheral nerves.

Summary

Patients with FA have an increased risk for developing aggressive head and neck squamous cell carcinoma (HNSCC), especially of the oral cavity. Until new therapeutic and preventative measures are available, strict abstinence from tobacco and alcohol, avoidance of second-hand smoke, maintenance of oral hygiene, and aggressive routine screening are the most immediate ways to reduce the development and morbidity of HNSCC in FA patients. Early and frequent head and neck examinations, including careful oral cavity evaluations and flexible fiberoptic laryngoscopy, are important surveillance measures. Appropriate surgical resection remains the mainstay of treatment for patients with FA, because radiation and chemotherapy are poorly tolerated. If radiation and chemotherapy are required for advanced tumors, they should be used with caution and by physicians who have experience in identifying, preventing, and treating associated complications.

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