Successful use of a therapeutic trial of graduated volume and dose escalation for postoperative head and neck radiotherapy in a Fanconi anemia patient

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Abstract
Background: Patients with the heritable disease, Fanconi anemia (FA), have a 500-fold risk of developing head and neck squamous cell carcinomas (HNSCC). However, the use of conventional cytotoxic agents including radiation therapy and cisplatin-based chemotherapy is contraindicated in patients with FA due to underlying DNA repair defects.

Methods/Results: We present a young FA patient with recurrent HNSCC and high-risk pathologic features treated with a therapeutic trial of chemoradiation. This novel strategy employs a gentle radiation dose and volume escalation with concurrent pembrolizumab. The patient completed the entire course of therapy with no treatment delays or interruptions.

Conclusions: The FA patient population has a clear need for adjuvant treatment regimens given their predilection for HNSCC. A therapeutic trial may allow FA and other radiosensitive patients to trial radiation with the option to terminate treatment before any severe side effects occur and for some to complete a full course of treatment.

KEYWORDS
Fanconi anemia, pembrolizumab, radiation therapy, squamous cell carcinoma, therapeutic trial

1 | INTRODUCTION/BACKGROUND

Fanconi anemia (FA) is a complex and heterogeneous clinical condition resulting from germ line mutations in the Fanc family of genes involved in DNA repair mechanisms. FA is a rare disease that is estimated to occur once in every 100 000 to 250 000 births. The first member of the FA family was described in 1996 and labeled Fanc-A. Since that time, the number of genes contributing to FA has grown to 22 all of which are autosomal recessive except for Fanc-B, which is X-linked recessive, and Fanc-R, which is autosomal dominant. The protein products from Fanc genes assemble into FA core, signaling and repair complexes that ultimately result in repair of DNA interstrand cross-links and DNA double-strand breaks. The most commonly observed mutant is Fanc-A representing 60% to 70% of FA cases, followed by Fanc-C and Fanc-G each comprising 10% to 15% with the other 16 genes comprising the remaining percentage of cases. The diagnosis carries with it a dramatic 28% likelihood of developing solid tumors by 40 years of age and a 500-fold increased risk of developing head and neck squamous cell carcinomas (HNSCC) relative to the general population.
population. As these patients survive their bone marrow failure, HNSCC is becoming more prevalent, and management approaches are lacking. Treatment approaches are largely individualized and complex. Surgeons must consider the potential of possible recurrence balanced with potential toxicities of a wide resection. Medical oncologists must be cognizant of potential reactions to systemic therapies, a classic example of which is cisplatin, due to impaired interstrand cross-link repair in FA. Radiation oncologists must be aware of toxic reactions to radiation therapy (RT) resulting from impaired repair of DNA double-strand breaks in FA patients.

Until recently, the life expectancy for FA was usually the second to third decade of life with the cause of death largely due to bone marrow failure. However, with the advent of improved disease specific bone marrow transplant (BMT) with less toxic induction agents such as fludarabine or partial body irradiation, patients with FA increasingly survive into middle age but become subject to an array of diseases related to their underlying DNA instability. HNSCC is the most common type of solid tumor diagnosed in FA patients, representing 24% of all diagnoses. Ironically, BMT increases the risk of HNSCC by a factor of 4.4 and reduces the median age of onset from 33 to 18 years of age. As BMT secondary to bone marrow failure is required in 90% of FA patients by the age of 40, the incidence of HNSCC continues to climb. As such, there is a need for optimizing management of HNSCC in this population.

Treatment for the typical HNSCC patients without FA can be complex and is approached with upfront surgery followed by adjuvant treatment with postoperative RT, with or without chemotherapy. In FA patients with HNSCC, treatment is complicated by concerns largely unique to FA, including (a) the potential for severe sensitivity reactions to radiation and (b) increased risk for secondary malignancies when cancer therapies target interstrand cross-links and double strand breaks. Increased toxicity from RT in FA is driven by the combination of the treatment intervention itself (disruption to DNA structure) and the inherent defects in DNA damage repair mechanisms in FA. As expected, FA patients experience a significant increase in the likelihood and severity of mucositis and skin toxicity.

FA patients have a predisposition to severe cytopenias following RT. Some studies have suggested that RT of FA cells in mice triggers increases in transcriptional growth factor beta (TGF-β), which in turn induces bone marrow suppression. Another contributing factor could be the radiation of leukocytes as they circulate through the treatment field. The accelerated breakdown of protective barriers in the oral cavity and skin synergizes with neutropenia to increase the risk of sepsis, reported as high as 41% in one series. In aggregate, the available literature suggests that approximately 75% experience high-grade mucositis, 50% require percutaneous endoscopic gastrostomy tube placement and as many as 50% of FA patients treated with RT die within 1 year. This compares with 50% overall survival at 3 years in HNSCC patients without FA treated with surgery and postoperative RT. The concern for RT toxicity frequently results in suboptimal therapeutic doses resulting in local recurrence free survival of 14% at a median follow-up of 13 months compared with 3-year disease-free survival of 54% for a typical HNSCC patient.

Combination of surgery, chemotherapy, and RT are all commonly used to treat HNSCC; however, the latter two modalities carry an excessive risk of morbidity and mortality in FA patients. Unfortunately, in many cases, complete surgical management is not possible and the use of carefully selected systemic agents and/or cautious application of RT in the adjuvant setting is required to offer better disease control. There is a clear need to stratify patients into groups that cannot tolerate RT and those who may be able to reach a sufficient dose to achieve local control. The concept of a therapeutic trial has previously been described in palliation of myeloid metaplasia in 1977 and suggested for FA, but has never been attempted in this population. In this case report, we demonstrate how a therapeutic trial in which the RT dose is carefully increased over time proved to be a rational choice that balanced the risk of serious side effects with the known benefits of adjuvant treatment.

2 | CASE

Our patient was a 27 year old, otherwise healthy, female who was originally diagnosed with FA at the age of 4 with pancytopenia on laboratory testing prior to planned hand surgery. The diagnosis was confirmed by peripheral blood chromosome breakage analysis at that time and later followed by DNA confirmation of a mutation in Fanc-G (also known as XRCC 9), which is a member of the FA core complex and has been shown to impair homologous recombination. Past medical history was notable for the absence of reported smoking or use of smokeless tobacco and active participation in a malignancy screening program per FA management guidelines with a negative screen several months prior to diagnosis. In addition, due to a stabilizing reversion in her bone marrow to wild type in one clonal population, no BMT had been required. She was originally diagnosed with cT1N0M0 stage 1 squamous cell carcinoma (SCC) of the left buccal mucosa. She underwent a wide local excision and gross tissue pathology revealed a mass measuring 1.2 cm in largest diameter.
with 1.4 mm maximal depth of invasion. Histopathology showed a well-differentiated, p16-negative SCC and surgical resection margins were negative with the closest being 1.5 mm to the medial/inferior margin with no evidence of lymphovascular space invasion (LVSI) or perineural invasion (PNI).

After multidisciplinary discussion, given her FA and risk of greater toxicity following standard adjuvant therapy, it was elected to observe closely rather than offer adjuvant therapy. Two biopsies of the gingiva near the operative bed were performed at 4 and 7 months postsurgery and were found negative for recurrence. However, at 8 months, she presented with an enlarging, painful left-sided neck mass, concerning for regional recurrence of SCC. Computed tomography (CT) scan of the neck with contrast demonstrated a cystic/necrotic mass associated with two necrotic level 1B lymph nodes measuring 1.3 cm by 2.4 cm and one enlarging level 3 lymph node measuring 9 mm with internal cystic changes. Positron emission tomography/computed tomography (PET/CT) demonstrated avidity in the neck consistent with regional recurrence, without evidence of distant metastatic disease. She underwent salvage surgery that included a modified radical neck dissection requiring a partial mandibulectomy and sacrifice of her marginal mandibular nerve to obtain clear margins around the pathologic lymph node in level 1B. Pathology was significant for a moderately differentiated, p16-negative SCC involving multiple lymph nodes in level 1B that measured maximally 3.2 cm with evidence of masseter muscle invasion, positive anterior margin, and LVSI and PNI. Additionally, further lymph nodes removed during the dissection revealed 2 of 8 nodes positive with SCC, with the largest measuring 3.4 cm with extracapsular extension (ECE) and LVSI.

Given the presence of multiple aggressive pathologic features, adjuvant therapy after salvage surgery was considered. The options discussed included continued active clinical surveillance, systemic therapy, immunotherapy, and RT. The decision was made to proceed with concurrent chemoradiotherapy. Cisplatin remains the standard-of-care adjuvant therapy for patients with pathological positive margins and ECE. However, cisplatin causes crosstalks in DNA with subsequent DNA damage. Thus, systemic administration of cisplatin in a patient with FA could be potentially fatal as FA patients are known to have hypersensitivity to DNA crosslinkers. Therefore, given recent approval for programmed death-1 (PD-1) inhibition in the recurrent/metastatic HNSCC setting and several small trials in which the combination of pembrolizumab and RT were found to be safe with signal of improved efficacy over RT alone, we decided to proceed with pembrolizumab and RT concurrently followed by adjuvant pembrolizumab.

Radiation was planned as a therapeutic trial to minimize RT-related toxicity in the head and neck area with close monitoring. During treatment, history and physical examination were performed daily with photographic documentation to monitor for acute local toxicity. Daily blood counts were also monitored for cytopenias resulting from an abscopal effect on the bone marrow.

The therapeutic radiation escalation occurred in four phases. Initial treatment volumes included a small field covering the primary resection site. This was agreed upon by both the radiation oncologist and the ENT as the highest area of concern for recurrence, and radiation beams were strategically arranged to treat this area while intentionally exposing mucosal tissue easily visible on physical exam in the beam path. This approximately 5 × 5 cm (as seen on skin rendering “small” field was irradiated first with a low (0.5 Gy) and then standard (2 Gy) dose per day for 5 days each. A traditional head and neck field as would have treated someone without a diagnosis of FA was also designed and planned. As the patient experienced no toxicity with the small radiation field, she was then treated to 0.5 Gy daily for 5 days to the full treatment volumes with intensity-modulated radiation therapy (IMRT), and then, as no concerning exam or laboratory findings were noted, she was escalated to the conventional head and neck dosing of 2 Gy per day for 30 fractions (Figure 1). Each new dose/volume escalation was delivered Monday to Friday to ensure the entire segment could be delivered without interruption. Radiation treatment began 25 days postsurgery. The first dose of pembrolizumab was administered 6 days prior to the beginning RT and was given every 21 days concurrent with and after the completion of RT.

Escalation to conventional field size and fractions took 3 weeks in total. Given the differences in volumes and doses, and the difficulty of accurately calculating the cumulative biologic dose delivered in the first 3 weeks, these treatments were not considered when planning the complete postoperative course of 60 Gy in 30 fractions to the traditional volume. This approach insured, if completed, the delivery of a more than an adequate adjuvant dose while maintaining the option to terminate RT if unacceptable toxicities arose during treatment. Any CTCAE v5 grade 4 toxicities were set as predetermined criteria for termination of RT.

The patient completed the entire therapeutic trial with 3 weeks of RT escalation as planned followed by 6 weeks of standard postoperative RT with concurrent pembrolizumab. There were no treatment delays or interruptions, and in total she completed RT in 67 days. On exam, she developed CTCAE grade 1 radiation dermatitis...
and grade 2 mucositis, oropharyngeal pain, and dry mouth with no grade 3 or 4 events noted. Clinical photographs demonstrating mucosal reaction over the course of her treatment were obtained (Figure 2). Initial development of fibrosis was also noted. She developed moderate trismus during RT, which improved with recommended mouth opening exercises.

Her blood counts remained acceptable over the course of therapy. However, platelet and absolute lymphocyte counts showed significant decline over time with $R^2$ (correlation coefficient) values of 0.92 and 0.89, respectively. RBC and absolute neutrophil count were stable both with $R^2$ values of 0.002. WBC was more variable than other metrics but also remained relatively stable during treatment with a mean of 3.6, range of 2.2 to 5.5, and $R^2$ value of 0.46.

PET/CT obtained 3 months following the completion of RT demonstrated an area of maximum SUV of 9.5
involving the gingiva along the left maxillary molars. Exam revealed granulation tissue (Figure 3). Biopsies of this site were obtained on two separate occasions immediately following the PET/CT and were negative. Repeat imaging 7 months following the completion of RT continued to demonstrate avidity of the left maxillary gingiva and a third biopsy of the same area noted recurrence of a well- to moderately differentiated SCC. This recurrence was located outside of the previous surgical beds and at the margin of her RT field. PET/CT was fused to her radiation planning CT and demonstrated that the recurrence occurred at the margin of the full dose head and neck field (Figure 3) and in retrospect received a maximal dose of 57 Gy at the posterior lateral edge closest to the treatment field and the entire lesion was covered by the 48 Gy isodose line. Additionally, the recurrence site received no radiation dose during the first 2 weeks of the therapeutic trial and minimal dose in the third. This resulted in the area remaining essentially untreated by RT until 46 days postsurgery.

Following diagnosis of her second recurrence another salvage surgical resection was planned to include a marginal mandibulectomy and infrastructure maxillectomy, followed by anterolateral thigh reconstruction to close the palate. Pathology demonstrated moderately differentiated SCC with no LVSI, no PNI, and closest margin 7 mm in the posterior soft palate tissue. CARIS testing was performed and demonstrated a low tumor mutational burden and significant combined positive score of 25, indicating benefit for pembrolizumab so it was continued following surgery. The patient continues to be followed closely every 3 months and is now 4 months out from surgery for her recurrence following RT.

Institutional approval and written informed consent from the patient was obtained for publication of the case and clinical photographs.

3 CONCLUSION/DISCUSSION

Due to the nature of their DNA repair defect, patients with Fanconi anemia have a high likelihood of developing malignancies. In particular, they are at risk for HNSCC during their lifetime. Therefore, the standard of care has been to apply aggressive surgical management and avoid any intervention, such as radiation, that would be expected to aggravate further this underlying predisposition to both acute toxicity and secondary mutations. First-line chemotherapy, cisplatin, has also been avoided due to its expected exacerbation of DNA repair impairment. However, as the life expectancy of patients with FA increases, the risk benefit of these treatments, as suggested by the clinical course of our patient, needs to be periodically revisited. Clearly, as seen in this case, even early and aggressive resection exclusively may not prevent recurrence or the development of additional primary tumors.

There is a clear heterogeneity in the FA population regarding tolerance of RT with some patients doing poorly at even low doses and others with normal tolerance of full treatment.9,10 Variable responses to RT are likely due to different underlying FA mutations in
the reported patient population. This non-uniform response of FA cells to RT has also been observed in human-derived Fanc-C, two different Fanc-G and Fanc-D2 cell lines in the in vitro setting. Relevant to this case, an in vitro study of Fanc-G demonstrated a decrease in repair of DNA double-strand breaks compared to controls when cells were exposed to radiation during S and G2 phases but not other phases of the cell cycle. Individual gene mutations resulting in different DNA repair deficiencies, a patient's transplant status, and other clinical features may, in theory, contribute to the observed heterogeneous response to RT.

In this case, the patient had developed a rare revertant cross-over event, which generated a clonal expansion of a wild-type hematopoietic progenitor cell. This cell line likely helped stabilize her disease and avoid the need for BMT. We hypothesize that this near normal clonal population may also have contributed to the stability of her blood counts during treatment; however, it would not have helped with local toxicity as her somatic cells still retain the Fanc-G mutation. Some early studies suggest peripheral blood leukocytes could be used to predict hematologic radiosensitivity in vitro, but not mucosal or skin toxicity. Increased cataloging of specific mutations, unique clinical details, and treatment responses in FA patients will broaden our understanding of which patients may benefit from specific treatment modalities.

In summary, FA patients are a uniquely challenging population to treat with RT due to their defective DNA damage repair mechanisms predisposing them to excessive radiation-induced toxicities. However, there appears to be heterogeneity within the population as some individuals are able to tolerate RT while others are not. The clinical course of our patient involving a closely monitored progressive increase in radiation as tolerated may be one viable approach when forced to consider adjuvant radiation. This approach allows patients that do not develop significant toxicity to potentially benefit from the additional local control benefit afforded by standard doses of RT. In addition, reporting outcome of these therapeutic trials may allow for further elucidation of the factors that contribute to RT tolerance in the FA population. Future clinical trials will be required to refine target volumes and timeline to maximize the efficacy. The role of pembrolizumab in the head and neck cancer setting continues to evolve, but in this case no significant side effects were noted from the immune therapy.

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