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# Squamous cell carcinoma development in Fanconi anemia patients who underwent hematopoietic stem cell transplantation

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## Abstract

We examined SCC development of 24 FA patients, who received HSCT from HLA-matched relatives. In our BMT center, we applied low-dose CY + LFI + ATG (n:13) as conditioning regimen for FA patients between 1992 and 1999, and CY + BU + ATG (n:11) between 1999 and 2002. The aim of this study was to investigate SCC development after HSCT and examine features of the follow-up patients. The 10-year overall survival (OS) of the group with LFI + regimen was 43%, whereas the group without LFI regimen was 60%. There was a statistically significant relationship between infections (viral/bacterial) and overall survival (Fisher's Exact test $P < .001$). Five out of 13 long-term (>1 year) surviving patients developed SCC in the HNSCC (n:4) and esophagus (n:2) region (a patient with oral SCC developed a second primary esophageal SCC). The SCC rate in our FA patients was 38%, four of the SCC patients were transplanted with irradiation used conditioning regimens, three of them had acuteGvHD (Grade II-III), only one developed chronic GvHD. The interval between HSCT and SCC diagnosis was median 13 (range 6-18) years, the age for the development of cancer was median 21 (range 15-32) years. Survival after SCC was low, median 6 months (range 6-12), due to delayed SCC diagnosis, tumor progression under therapy and treatment-related toxicities of the usually reduced RT and/or CT.

KEYWORDS

Fanconi anemia, GvHD, hematopoietic stem cell transplantation, squamous cell carcinoma

## 1 | INTRODUCTION

FA is a genetically and phenotypically heterogeneous autosomal recessive, dominant or X-linked disorder, characterized by congenital abnormalities, bone marrow failure, and increased risk for cancer.[1,2] FA is diagnosed by detecting of increased chromosome breakage and on cytogenetically analyzing of lymphocytes with DEB and MMC[3,4] and is also confirmed by detecting germline mutations occurring in the DNA repair genes of the FA/BRCA pathway.[5,6]

**Abbreviations:** AA, Aplastic anemia; ATG, Anti-thymocyte globulin; BM, Bone Marrow; BMT, Bone Marrow Transplantation; BRCA, Breast Cancer Gene; BU, Busulfan; CMV, Cytomegalovirus; CsA, Cyclosporine A; CT, Chemotherapy; CY, Cyclophosphamide; DEB, Diepoxibutane; FA, Fanconi anemia; FISH, Fluorescence in situ Hybridization; GvHD, Graft-versus-Host Disease; HLA, Human Leukocyte Antigen; HNSCC, The Head Neck Squamous Cell Carcinoma; HSCT, Hematopoietic Stem Cell Transplantation; IvIG, Intravenous Gamma Globulin; LFI, Limited Field Irradiation; MMC, Mitomycin C; MTX, Methotrexate; RRT, Regimen-Related Toxicity; RT, Radiotherapy; SCC, Squamous Cell Carcinoma; SPSS, Statistical Package for the Social Sciences; TAI, Thoraco-abdominal irradiation; TRM, Treatment-Related Mortality.

  

HSCT is the standard treatment for FA patients with BM failure. Various conditioning regimens were used over time for FA patients, to reduced RRT, to reduced the risks of malignancy, GVHD and other late adverse effects with enhanced survival after HSCT.[7-11] Malignancy is a late complication of HSCT for FA patients with inherently underlying genomic instability defects, the risk of malignancy is 48- to 500-fold higher for FA patients than the non-FA population.[12-14]

In this study, we investigated the SCC development, its features, the relationship between GvHD and two different conditioning regimens of our pediatric FA patients who were transplanted from an HLA-identical-family member.

## 2 | METHODS

### 2.1 | Patients

Twenty-four FA (12 boys and 12 girls) patients with a median age of 8 years (range 6-14) underwent HLA-matched related donor HSCT between 1992 and 2002 at Istanbul University Faculty of Istanbul Medicine, Our Children Leukemia Foundation BMT Center. The diagnosis of FA was confirmed by the presence of multiple chromosome breaks, enhanced by incubation with cross-linking agents (DEB and MMC testing), and also, all donors were determined to be DEB-MMC negative before HSCT.[4] At the time of HSCT, all patients had evidence of AA, none of the patients had dysplasia or leukemic transformation. All patients received stem cells from HLA fully matched family members (21 sibling donors, 3 maternal donors). Consanguinity was detected in 14 FA patients' families.

### 2.2 | Preparative regimen

Pretransplant conditioning regimens were divided into two main categories in accordance with the CY dose and radiation schedule. Between 1992 and 1999, 13 patients received LFI 500cGy, low-dose CY20 mg/kg, and ATG10 mg/kg/d (Fresenius) for 4 days. Between 1999 and 2002, 11 patients received CY40 mg/kg and BU6 mg/kg and ATG 10 mg/kg/d (Fresenius) for 4 days. Bone marrow served as the source of stem cells in all patients, and the total nucleated cell dose infused for FA recipients was median $3.14 \times 10^8$/kg (range 1.6-11.2). All patients received GVHD prophylaxis with CsA and MTX. Time to engraftment was calculated as the interval from transplantation to the first of 3 consecutive days with an absolute neutrophil count of $0.5 \times 10^9$/L. Engraftment was confirmed by BM aspiration along with cytogenetic studies (FISH, HLA) and ABO typing.

### 2.3 | Supportive care

Blood component transfusion was administered when required. Fluconazole, acyclovir, IvIG, and trimethoprim-sulfamethoxazole were administered after HSCT. Irradiated and leukocyte-depleted red blood cell and platelet transfusions were performed on the patients.

### 2.4 | Statistical methods

The probabilities of OS were plotted using the Kaplan-Meier method. The significance was estimated by log-rank test (Mantel-Cox) and logistic regression analysis. Data were analyzed using the SPSS 21.00 version. The significance was estimated by log-rank test or Fisher's exact test.

## 3 | RESULTS

The time to engraftment was median 12 days (range 10-18).

### 3.1 | Infections

Two patients who had graft failure after the first HSCT received a second HSCT from the same donor; however, no engraftment developed, and the patients died due to aplasia and infections.

Two other patients died with bacterial sepsis (Klebsiella pneumoniae and Pseudomonas aeruginosa species). One patient died with acute respiratory distress syndrome and high fever. Before transplantation, the FA patients were 15/24 CMV seropositive, the donors were 12/24 CMV seropositive, post-transplant 6 patients developed CMV infections; 2 CMV antigenemia, 4 symptomatic CMV disease and died with CMV ensephalitis n = 1, hepatitis n = 1, interstitial pneumonitis n = 2. As a result of the follow-ups, 9 patients died (<7 months post-transplantation) due to infections. We found a statistically significant relationship between infections (viral/bacterial) and overall survival (Fisher's Exact test $P < .001$). Infections of the patients remain an important risk factors for early mortality.

### 3.2 | TRM

Two TRM occurred. One patient developed CNS toxicity (confusional status, seizure, coma, and hypertension), one patient experienced lung and heart toxicity and died of pulmonary, heart failure, and infections. The most frequent toxicity was gastro-intestinal toxicity (19/24), and the rarest toxicity was renal toxicity (1/24). Three patients developed hemorrhagic cystitis, and no veno-occlusive disease was observed. One patient died at home 5 months after the transplantation due to an unknown cause.

### 3.3 | GVHD

Nine patients out of 24 (37%) developed acute GVHD (5 patients had grade II, and 4 patients had grade III), only one patient developed

chronic GVHD. The patient with cGvHD received azathioprine and steroid treatment, developed HNSCC after 5 years. After HSCT, the number of the long-term surviving patients was 13.

### 3.4 | Late mortality

A male patient aged 19 years developed transverse myelitis 13 years after HSCT. He did not respond to various treatments including steroids, ivIg, and plasmapheresis. He died 5 months later, because of continuous increase in neurological symptoms and development of pulmonary embolus. A female 11-year-old patient who lived in countryside died 40 months after HSCT due to an unknown reason, after she reported acute abdomen.

### 3.5 | Malignancy

Five out of 13 long-term (>1 year) surviving patients (3 male, 1 female) developed SCC, 4 HNSCC (one of them also developed a second primary SCC on the esophagus) and 1 esophagus SCC. The location of HNSCC was the oral cavity, the retromolar trigone. The classification of the tumor node metastasis (T/N/M), location of the cancer, the treatment, and outcome of the patients is summarized in Table 1. The histological characteristics of the SCCs were well differentiated (n:3) and moderately differentiated (n:2). None of the patients used tobacco or alcohol, but their oral hygiene was quite poor. Since patients ignored cancer symptoms and applied in the advanced stage, 3/4(75%) of the HNSCCs have progressed to locally advanced disease by the time of diagnosis. Surgical tumor resection was performed as the primary treatment to HNSCC (excluding one patient who was regarded as inoperable).

Post-operative RT and/or modified doses of CT (low-dose cisplatin 30-40 mg/m$^2$ every 21 days, 5-Fluorouracil 1 g/m$^2$/per cycle) were given; the total RT dose ranged from 3230cGy to 4590cGy (150-170cGy per dosis). CT of three SCC patients was discontinued due to toxicity; myelosuppression (n:2), severe mucositis (n:3), and sepsis (n:1). Accordingly, only one esophagus SCC patient completed the RT dose. Three HNSCC patients and one esophagus SCC patient developed a rapid recurrence of tumor after discontinuation of treatment and died. The most frequent toxicities during RT were high-grade mucositis (n:4), dysphagia (n:2), local edema (n:2), wound site breakdown (n:1), retrosternal pain (n:1), and radiation pneumonitis (n:1).

The patient with second primary tumor (esophagus SCC) developed stenosis in the esophagus 2 months after RT. After endoscopy and dilation procedures, a stent was inserted on her esophagus. However, the patient developed esophageal-bronchial perforation after 3 months, which was followed by pneumonia and mediastinitis, and she eventually died.

A female 26-year-old patient underwent pap smear test for routine cancer screening. Epithelial cell abnormality (low-grade squamous intra-epithelial lesion) was found on the cervicovaginal smear. Extensive tissue biopsy was recommended, and the diagnosis was CIN I and II Yi premalignant lesion. She refused gynecological follow-up. Three years later, she got pregnant and gave a birth to a healthy infant.

The cancer rate in our long-term surviving patients was 38% (5/13). The median age for development of cancer was 21 (range

**TABLE 1** Post-transplant Malignancies of FA Patients; (T/N/M) Classification, Cancer Location, Treatment, and Outcome

| Patients diagnosis, Symptoms | T/N/M (Stage), Location | Treatment | Outcome |
|---|---|---|---|
| HNSCC; mass in the oral cavity, ulceration, pain | Stage III T3 N1 M0 oral cavity, right retromolar trigone | Primary tm + radical neck dissection; second tm resection RT(4250cGy) | Died after 6 mo; with Tm progression, RT toxicity |
| HNSCC; mass in oral cavity and on the mandible | Stage III T3 N1 M0 oral cavity, left retromolar trigone | Primary tm + radical neck dissection; second tm resection RT(3230cGy)+ CT | Died after 6 mo; with tm progression, RT + CT toxicity |
| HNSCC; mass in oral cavity and on the mandible, ulceration, pain | Stage IV A T3N3 M0 oral cavity, left retromolar trigone, infra-auricular, | Inoperable RT(3400cGy) + CT | Died after 6 mo; with tm progression, RT + CT toxicity |
| (a)-HNSCC; buccal swelling, leukoplakia | Stage I T1 N0 M0 oral cavity, right retromolar trigone | Primary tm resection | Died 10 mo after esophagus SCC; RT toxicity esophagus stenosis. |
| (b)-Second primary tm: Esophagus SCC; retrosternal pain | stage IIA T2 N0 M0 Middle third of esophagus | RT(4590cGy), esophagus stent emplacement | After stent bronchial perforation, pneumonia mediastinitis |
| Esophagus SCC; dysphagia | Stage IIIA T3N1M0 Upper third of esophagus | Esophagectomy, colonic interposition CT | Died after 6 mo with tm recurrence, CT toxicity, sepsis |

Abbreviations: CT, Chemotherapy; HNSCC, Head and Neck Squamous Cell Carcinoma; M, Metastasis; N, Node; RT, radiation therapy; SCC, squamous cell carcinomas; T, Tumor.

15-32) years. The interval between HSCT and cancer diagnosis was median 13 (6-18) years. The 10-year of OS of the group with LFI was 43%, whereas the group without LFI was 60%. There is no statistically significant difference in OS between the irradiated (the median OS ± SE %95CI = 72 ± 74.833 [0-218.673]) and non-irradiated groups (the median OS ± SE %95CI = 156 ± 173.122 [0-495.32]), Log-Rank (Mantel-Cox) ($\chi^2$ = 0.207) $P$ = .649. SCC were in a limited proportion of patients, four of them were transplanted with irradiation used conditioning regimens. Three of the SCC patients had acuteGvHD (GradeII-III), only one developed chronic GvHD. Survival after SCC was low, median 6 months (range 6-12), the patients died of tumor progression, RT and CT toxicity or complications. Currently, 6 FA patients are alive, one of the patients developed hepatocellular carcinoma and the tumor was completely removed surgically; all patients are still in good condition.

## 4 | DISCUSSION

HSCT is the standard treatment of choice for FA patients with BM failure or hematological malignancy. Until 1990, survival of FA patients undergoing HSCT was poor due to RRT, GVHD and infections. Gluckman et al proposed the use of low-dose CY and a single fraction of TAI (500 cGy) conditioning regimen, leading to markedly to reduced RRT with enhanced survival after related sibling donor HSCT[8]. Later, the use of low-dose CY and LFI became the standard HCT preparative regimen for FA patients with related donors.[15] However; GVHD still remains a major problem and malignancy is seen as a late complication of HSCT. Various groups had modified the Gluckman regimen by attempting to eliminate the need for irradiation in the preparative regimens for FA patients.[9,16]

Pasquini R. et al conducted a study comparing the irradiation and non-irradiation regimes of 148 FA patients transplanted from related donors. According to their study, hematopoietic recovery, acute and chronic GVHD and mortality were similar after two regimens.[17] They reported that infections, organ failure, and GVHD are the leading causes of death within the first 2 years after transplantation. Also, the pretransplantation CMV serostatus of the donor and/or recipient were an important risk factor for post-transplant outcome.[17] According to our study, we also found a statistically significant relationship between infections (viral/bacterial) and overall survival (Fisher's Exact test $P$ < .001).

HNSCC was previously described to be the most significant long-term complication after HSCT in FA patients.[18-21] Rosenberg et al demonstrated that transplanted FA patients have increased risk and earlier occurrence of HNSCC compared with non-transplanted FA patients and confirmed the strong association between GVHD and late malignancies.[18] It has been demonstrated that approximately 40% of FA patients develop cancer (especially solid tumors) after HSCT.[19]

We observed similar results in our FA patients, the cancer rate in our long-term surviving patients was 38% and HNSCC was the most common cancer (n:4) after HSCT. Because our HNSCC patients ignored to symptoms and went to the hospital in the advanced stage of the disease, they reduced their chance of more successful treatment. The FA patients with SCC died early due to tumor progression under therapy and also with severe treatment-related toxicities of the usually reduced RT and/or CT. Survival after SCC was low, median 6 months (range 6-12).

Early diagnosis and treatment of cancers are critical for increased survival in FA patients, so it is recommended to maintain proper oral hygiene and undergo programmed dental examinations.[7,21-23] For that reason, we give importance to the prevention and early diagnosis of HNSCCs in our FA patients and we started to do regular screenings of the oral cavity and oropharynx with a team of dentists every 6 months.

Esophagus localized SCC is a relatively rare tumor.[24] We observed 2 esophagus SCC cases after 18 and 19 years of HSCT, who died due to therapy complications. Hosoya et al referred a FA patient with esophageal SCC 10 years after HSCT; who demonstrated a complete response after neoadjuvant therapy and a subtotal esophagectomy.[25]

Masserot et al described 13 cases of HNSCC in FA patients who underwent HSCT. All patients were given irradiation-based conditioning before HSCT, and all developed extensive cGVHD.[26] The proposed risk factors for SCC include the use of irradiation and the development of cGVHD.[19,21] Rosenberg et al reported that severe aGVHD and extensive cGVHD were significant risk factors for SSC post-transplant as well.[18] Since the number of SCC patients is unsufficient, we did not compare the relationship between cancer development and irradiation or GVHD.

## 5 | CONCLUSION

Cancer development especially SCC is a late complication in FA patients after HSCT. SCC survival is low because of delayed diagnosis, tumor progression under therapy, and treatment-related toxicities of the usually reduced RT and/or CT. Prevention, early diagnosis, and new conservative therapeutic strategies are crucial in management of cancers, and they may improve the survival in FA patients with SCC.

## AUTHORS' CONTRIBUTIONS

Sema Anak, Professor: Is responsible of Bone Marrow Transplantation Center and the patients, actively working in the Bone Marrow Transplantation Center; Nevin Yalman, Professor: Served as the major writer of this article, actively working for Bone Marrow Transplantation Center, especially about Fanconi Anemia, bone marrow deficiencies, and immune deficiencies; concluded the follow-up procedures of patients until 2020; organized mouth and dental care and treatments for the patients; consulted cancer-developing patients with necessary clinics; and guided them for surgery and medical treatments; Hülya Bilgen, Doctor: Actively works in the Bone Marrow Transplantation Center; Elif Sepet, dentist faculty member, Professor: Concluded all mouth and dental treatments for Fanconi Anemia patients; Ayhan Deviren, Professor: Did DEP and

MMC tests for all Fanconi Anemia patients and their families and helped the diagnosis; Başak Gürtekin: Produced all statistics studies for the article; Fatih Tunca, Professor: Concluded esophagus, stomach, and intestine surgical consultations and operations of Fanconi Anemia patients; Bora Başaran: Concluded oral and esophagus lesion consultations, biopsy, and surgical treatments of Fanconi Anemia patients.

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