# Fanconi Anemia: 29 Years Experience in a Single Center

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**ABSTRACT**

Hematopoietic stem cell transplantation, which is the only curative therapy for marrow failure experienced by Fanconi anemia, was not available for all patients due to lacking in adequate transplantation centers in Turkey in the past years. For this reason, although androgens side effects are well known, they have been widely used for Fanconi anemia. Here we reported the clinical characteristics and outcome of 42 Fanconi anemia cases in 29-year period in a single center. The median follow up period was 67.5 months (range: 1 -111 months) after diagnosis. Treatment modalities were as follows: Androgens with low dose corticosteroids (n= 34) (anti lymphocyte globulin were used in three of 34 patients, and five of 34 underwent to hematopoietic stem cell transplantation), high dose methylprednisolone (n= 1), hematopoietic stem cell transplantation (n= 1), supportive treatment (n= 2), no treatment required (n= 4). The uses of androgens in our patients were as follows: Oxymethalone and prednisolone (n= 21), testosterone and prednisolone (n= 8), testosterone, prednisolone, and anti lymphocyte globulin (n= 3), oxymethalone, testosterone, and prednisolone (n= 2) were given to 34 patients. In our series, one patient developed acute myeloid leukemia. None of our patients developed liver tumors and peliosis hepatitis was diagnosed in one patient. We used androgens with low dose corticosteroids. Only six (14.3%) patients underwent hematopoietic stem cell transplantation. Eight (19%) patients were lost to follow up, and 11 patients (26.2%) died.

**Keywords:** Fanconi anemia, Androgens, Adrenal cortex, Leukemia

**ÖZET**

**Fankoni Anemisi: Tek Merkezin 29 Yıllık Deneyimi**

Fankoni anemisinde tek küratif tedavi yöntemi olan kök hücre nakli, geçmiş yıllarda Türkiye'de nakil merkezlerinin yetersizliği nedeni ile tüm hastalara tedavi seçeneği olarak sunulamıyordu. Bu nedenle, androjenler yan etkileri bilinmesine rağmen Fanconi anemisinin tedavisinde yaygın olarak kullanılmışlardır. Bu makalede bir merkezin 29 yıl içerisinde izlediği 42 Fanconi anemili hastanın klinik özellikleri ve sonuçları tartışılmıştır. Hastaların tanıdan sonraki ortanca izlem süresinin 67.5 ay olduğu saptandı (aralık:1-111 ay). Kırk iki hastanın 34'üne androjenlerle birlikte düşük doz kortikosteroid (bu 34 hastanın üçüne birlikte antilenfosit globulin verilmiş, beşine kök hücre nakli uygulanmıştır), bir hastaya yüksek doz metilprednizolon, bir hastaya sadece kök hücre nakli, iki hastaya destek tedavisi verilmiş, dört hastanın ise hiçbir tedavi gereksinimi olmamıştır. Hastalarımızda androjen kullanımının ayrıntısı şöyledir: Oksimetalon ve prednizolon (n= 21), testosteron ve prednizolon (n= 8), testosterone, prednizolon ve antilenfosit globulin (n= 3), oksimetalon, testosteron ve prednizolon (n= 2) olmak üzere toplam 34 hastaya androjen verilmiştir. Bizim serimizde, bir hastada akut myeloid lösemi gelişti. Hiçbir hastamızda karaciğer tümörü görülmezken bir hastada peliosis hepatitis saptandi. Androjen kullanan hastalarımızın hepsinde düşük dozda kortikosteroid kullandık. Sadece altı (14.3%) hastamıza kök hücre nakli uygulanabildi. Sekiz (19%) hasta izlemden çıktı, 11 (26.2%) hasta izlem sırasında öldü.

**Anahtar Kelimeler:** Fanconi anemisi, Androjen, Adrenal korteks, Lösemi

## INTRODUCTION

Fanconi anemia (FA) is a rare autosomal (all complementation groups except FA-B group) or X-linked (FA-B group) recessive disease, clinically characterized by multiple congenital abnormalities, bone marrow failure, and cancer susceptibility. The clinical course of FA has been extensively reviewed.[1-3] The prevalence of FA is estimated to be 1 to 5 per million, and heterozygous carrier frequency is estimated to be one in 300.[1,4] The heterozygous frequency of FA is estimated around one in 250 Turkish subjects.[5] Treatment of FA is based on androgen therapy and hematopoietic stem cell transplantation (HSCT).[2] Hematopoietic stem cell transplantation is the only curative therapy for marrow failure experienced by FA patients. However, particularly in the past years HSCT was not available for all patients due to lacking in adequate transplantation centers in Turkey. In this situation, although androgens side effects are well known, they have been widely used for Fanconi anemia in Turkey. We believe in importance of reporting clinical characteristics and outcome of FA patients in 29-year period in our center.

## PATIENTS AND METHODS

Forty-two FA cases who were admitted to our Pediatric Hematology Department during the period from 1980 to 2009 were evaluated retrospectively. The symptoms at admission, congenital malformations, hematological findings, treatment, and outcomes of FA patients were evaluated. The diagnosis of FA was based on the characteristic hypersensitivity of FA cells to the cross- linking agents mitomycin C (MMC), or diepoxybutane (DEB). Liver enzymes was checked every three months and ultrasonography of hepatic system was done annually.

**Table 1.** Admission symptoms

| Symptom | n= 42 | % |
|---|---|---|
| Pallor | 19 | 45.2 |
| Epistaxis-bruising | 17 | 40.5 |
| Failure to thrive | 11 | 26.2 |
| Fanconi in sibling | 2 | 4.8 |
| Fever | 2 | 4.8 |
| Seizures | 1 | 2.4 |
| Deafness | 1 | 2.4 |

**Table 2.** Phenotypic Abnormalities

| Abnormality | n= 42 | % |
|---|---|---|
| Skin signs<br>Hypopigmentation<br>Hyperpigmentation<br>Cafe au lait spots | 40 | 95.2 |
| Microcephaly | 31 | 73.8 |
| Growth retardation | 24 | 57.1 |
| Thumb and radius | 20 | 47.6 |
| Microophtalmia | 17 | 40.5 |
| Skeletal system | 15 | 35.7 |
| Urinary system | 15 | 35.7 |
| Genitalia | 11 | 26.2 |
| Ear | 6 | 14.3 |
| Strabismus | 5 | 11.9 |
| Deafness | 4 | 9.5 |
| Cardiovasculary system | 4 | 9.5 |
| Pytosis | 2 | 4.8 |

## RESULTS

Forty-two (25 male, 17 female) FA cases were evelauated, aged between 2.5 and 11.6 with a mean of 6 ± 2.5 years. The median follow up period was 67.5 months (Range: 1 -111 months) after diagno-

**Table 3.** Hematological findings

| Parameter | Mean | ±SD | (Range) |
|---|---|---|---|
| Hemoglobin (g/dl) | 9.4 | ±2.01 | (7-10.6) |
| White blood cell count ($mm^3$) | 4,800 | 2171.3 | (1.100-7.300) |
| Platelet count ($mm^3$) | 76,000 | 100090.8 | (27.000-352.000) |

**Figure 1.** Photograph of a 10-year-old boy with Fanconi anemia showing the absence of radius and thumb on the right, hypo-plastic thumb on the left hand and hypo-genitalimus

sis. The symptoms, phenotypic and hematological abnormalities of the patients' at admission were shown at Table 1- 3 respectively. Bone marrow biopsy revealed aplasia (26.2%) and hypoplasia (73.8%). The photograph of a 10-year-old boy with FA showing the absence of radius and thumb on the right, hypo-plastic thumb on the left hand and hypo-genitalimus was shown at Figure 1. Hemoglobin F levels were found to be increased in patients with a range 4-47% (median: 12.5%). Cytogenetic analysis were performed and revealed marked spontaneous and induced chromosomal breaks and fragmentation with DEB or MMC in all of our patients. Structural abnormalities in chromosome culture; chromatid breaks and fragmentation (Figure 2) and typical 'endoreduplication' (Figure 3) were indicated. Treatment modalities were as follows: Androgens with low dose corticosteroids (n= 34)(anti lymphocyte globulin were used in three of 34 patients, and five of 34 underwent to hematopoietic stem cell transplantation), high dose methylprednisolone (n= 1), hematopoietic stem cell transplantation (n= 1), supportive treatment (n= 2), no treatment required (n= 4). The uses of androgens in our patients were as follows: Oxymethalone and prednisolone (n= 21), testosterone and prednisolone (n= 8), testosterone, prednisolone, and anti lymphocyte globulin (n= 3), oxymethalone, testosterone, and prednisolone (n= 2) were given to 34 patients. We used androgens with low dose corticosteroid. Eight (19%) of oxymethalone and prednisolone therapy group became refractory to drugs. Treatment modalities and outcomes were shown at

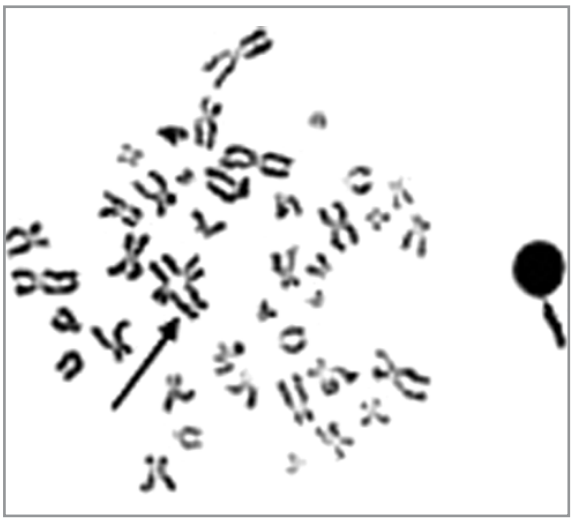

**Figure 2.** Chromosomal structure abnormalities in a child with Fanconi anemia; arrow indicates chromatid breaks and fragmentation

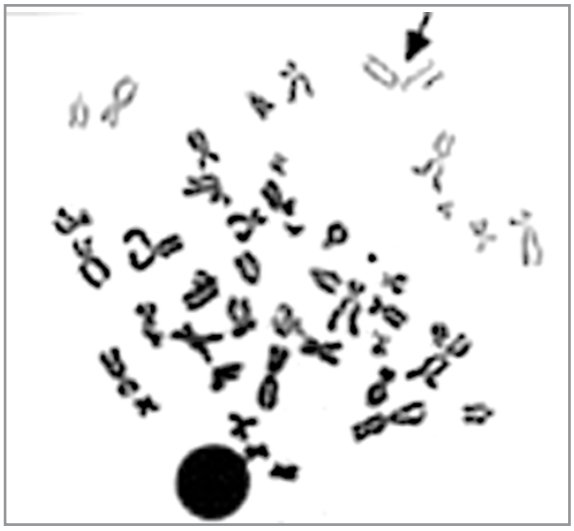

**Figure 3.** Structural abnormalities in chromosome culture; arrow indicates typical 'endoreduplication'

**Table 4.** Treatment modalities and outcomes

| TREATMENT | PATIENT | | OUTCOME | | | | | |
|---|---|---|---|---|---|---|---|---|
| | n | % | Alive | | Lost to follow-up | | Died | |
| | | | n: 42 | % | n: 42 | % | n: 42 | % |
| Oxymethalone+Prednisolone | 16 | 38.1 | 12 | 28.6 | 1 | 2.4 | 3 | 7.1 |
| Testosterone+Prednisolone | 8 | 19 | - | - | 5 | 11.9 | 3 | 7.1 |
| Testosterone+Prednisolone +ALG[1] | 3 | 7.1 | 2 | 4.8 | - | - | 1 | 2.4 |
| Oxymethalone+ Testosterone +Prednisolone | 2 | 4.8 | - | - | 1 | 2.4 | 1 | 2.4 |
| High dose methylprednisolone | 1 | 2.4 | - | - | 1 | 2.4 | - | - |
| HSCT[2] | 1 | 2.4 | 1 | 2.4 | - | - | - | - |
| Oxymethalone +Prednisolone +HSCT | 5 | 11.9 | 4 | 9.6 | - | - | 1 | 2.4 |
| Supportive treatment | 2 | 4.8 | - | - | - | - | 2 | 4.8 |
| No treatment required | 4 | 9.6 | 4 | 9.6 | - | - | - | - |
| TOTAL | 42 | 100 | 23 | 54.8 | 8 | 19 | 11 | 26.2 |

1: Anti lymphocyte globulin 2: Hematopoietic stem cell transplantation

Table 4. In our series, one patient developed acute myeloid leukemia. None of our patients developed liver tumors.

## DISCUSSION

Fanconi anemia has considerably high prevelance because of the frequent consanguineous marriages in Turkey. The treatment of FA is largely directed to the complications of bone marrow failure. Fanconi anemia patients respond to androgen therapy, although long-term androgenic exposure may result in complications and liver diseases. Additionally, patients may become refractory to these treatments in the follow-up period the follow-up period. In our series, 19% (n= 8) of oxymethalone and prednisolone therapy group became refractory to drugs. Several studies and case reports have shown a direct connection between androgen use and development of liver tumors in both FA and non-FA patients. Almost all reported cases of liver tumors in FA patients are either hepatocellular carcinomas or hepatic adenomas.[6] The type of hepatic neoplasm is associated with the type of androgen. Hepatocellular carcinoma was found more frequent in patients who received oxymetholone or methyltestosterone than in those who took danazol.[7] In our series, we did not experience liver tumors in our follow up period. Although some reports suggest that the use of androgens alone is as effective as the use of androgens combined with corticosteroids, the general recommendation was that combination therapy be administered in the past years.[2] Corticosteroids are believed that they reverse anabolic side effects of androgens. It was reported that growth retardation effect of corticosteroids may be a counterbalance to growth acceleration due to the androgens.[8] We used oxymethalone and/or testosterone in combination with prednisolone (5-10 mg/ every other day). None of our patients developed liver tumors. Liver tumors, including hepatocellular carcinoma and liver cell adenoma, represented 2.8% of the tumors recorded in a comprehensive review of the tumors reported since 1927 in patients with FA.[9] Altay et al reported hepatocellular carcinoma in one (1.9%) of 52 FA patients.[5]

The most frequently reported neoplasms associated with FA are myeloid leukemias, liver tumors, head and neck carcinomas and gynecological malignancies.[6,10] In our series, one patient developed AML (3.1%). Several transplant centers recommend androgens not be given to any FA patients unless no suitable donor is available. Accepted consensus in the treatment of FA is matched allogeneic HSCT before transfusion requirement.[11] The outcome of HSCT has improved due to progress in conditioning regimens.[12] In a previous study, we reported that fludarabine based regimens have proven to be a significant advance.[13] Fanconi anemia patients, who survive bone marrow diseases, perhaps by HSCT, remain prone to malignancies, usually in the second or third decade of life. The use of chemotherapy and radiation in the treatment of FA patients with cancer is limited, due to the underlying cellular sensitivity of FA cells to these genotoxic agents.

In conclusion, the management of FA patients with an aplastic bone marrow and without an HLA-matched sibling donor is challenging in the developing countries where the unrelated transplantation is not available. For these patients medical treatment approaches such as androgen therapy are needed. Close monitoring during the therapy is a key to the optimal care of these patients.

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