Frequency and Natural History of Inherited Bone Marrow Failure Syndromes:

the Israeli Inherited Bone Marrow Failure Registry

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Running title: Israeli Inherited Bone Marrow Failure Registry

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ABSTRACT

Background: Inherited bone marrow failure syndromes are rare genetic disorders characterized by bone marrow failure, congenital anomalies, and cancer predisposition. Available single diseases registries provide reliable information regarding natural history, efficacy and side effects of treatments and contributed to the discovery of the causative genes. However, these registries, could not shed light on the true incidence of the various syndromes. We, therefore, established an Israeli national registry in order to investigate the relative frequency of each of these syndromes and their complications.

Design and Methods: Patients were registered by their hematologists in all 16 medical centers in Israel. We included patients with Fanconi anemia, severe congenital neutropenia, Diamond-Blackfan anemia, congenital amegakaryocytic thrombocytopenia, dyskeratosis congenital, Shwachman-Diamond syndrome, and thrombocytopenia with absent radii.

Results: One hundred and twenty-seven patients diagnosed between 1966 and 2007 were registered. Fifty-two percent were found to have Fanconi anemia, 17% severe congenital neutropenia, 14% Diamond-Blackfan anemia, 6% congenital amegakaryocytic thrombocytopenia, 5% dyskeratosis congenita, 2% Shwachman-Diamond syndrome, and 2% thrombocytopenia with absent radii. No specific diagnosis was identified in only 2 patients. Of the thirty patients (24%) developing severe bone marrow failure, 80% had Fanconi anemia. Seven of 9 patients with leukemia had Fanconi anemia, as did all 6 with solid tumors. Thirty-four patients succumbed to their disease; 25 (74%) had Fanconi anemia and 6 (17%) had severe congenital neutropenia.
Conclusions: This is the first comprehensive population-based study evaluating the incidence and complications of the different inherited bone marrow failure syndromes. By far the most common disease was Fanconi anemia, followed by severe congenital neutropenia and Diamond-Blackfan anemia. Fanconi anemia carried the worst prognosis, with severe bone marrow failure and cancer susceptibility. Diamond-Blackfan anemia had the best prognosis. The data presented provide a rational basis for prevention programs, and longitudinal surveillance of inherited bone marrow failure syndromes complications.
INTRODUCTION

Inherited bone marrow failure syndromes are a group of rare genetic disorders characterized by bone marrow failure, congenital anomalies, and cancer predisposition.\(^1\) The inherited bone marrow failure syndromes include disorders associated with pancytopenia: Fanconi anemia and dyskeratosis congenita, as well as disorders with predominantly, but not exclusively, single lineage cytopenias: Diamond-Blackfan anemia, severe congenital neutropenia, Shwachman-Diamond syndrome, congenital amegakaryocytic thrombocytopenia, and thrombocytopenia with absent radii.\(^2-7\)

Single disease registries, which have been established worldwide since the 1980s, are dedicated to patients diagnosed with Fanconi anemia, Diamond-Blackfan anemia, or dyskeratosis congenita\(^5,8,9\) The Severe Congenital Neutropenia International Registry differs, since it collects data on all patients with neutropenia treated with granulocyte colony stimulating factor (G-CSF).\(^10\) These registries provide more reliable information than case series regarding clinical presentation, natural history, and response to therapy. Analysis of the data collected in the registries made it possible to evaluate the efficacy and side effects of treatments and contributed to the discovery of the causative genes.\(^5,8-10\) However, these registries, being disease-specific or treatment-specific, cannot shed light on the true incidence of the various syndromes.

We established a retrospective population-based national registry of inherited bone marrow failures in Israel. Using this registry, we calculated the relative frequency of each of the inherited bone marrow failure syndromes, the birth rate of Fanconi anemia, and the frequency of complications. Using previously described
methods, we performed quantitative analysis of the risks of adverse events in Fanconi anemia. (11-13)
DESIGN AND METHODS

Registry

Patients were registered from all 16 pediatric hematology-oncology centers in Israel. Referral to the registry was made by the treating physician. Recruitment included both living and deceased patients diagnosed between 1966 and 2007. The studies were approved by the research ethics committee of the Rabin Medical Center approved the study, as well as by the ethics committees in each of the participating centers. Since this was a chart review study, individualized consent forms were not required.

The data collecting form used is a modification of the one developed by Alter et al. and was used for the North American Survey of Fanconi anemia (NAS) and in an expanded version for the ongoing National Cancer Institute inherited bone marrow failure syndromes Study (www.marrowfailure.cancer.gov). Our questionnaire included data regarding: (i) demographics; (ii) laboratory tests supporting the diagnosis, including molecular diagnosis; (iii) physical examination; (iv) hematological information: complete blood counts (CBC) at diagnosis, at onset of pancytopenia, and at the last follow-up; (v) treatment: medical, supportive, and stem cell transplantation (SCT) dates and SCT complications; (vi) malignancy, including types of cancer and date/age at onset.

A research nurse (RZ) or a physician (DN) filled out the questionnaire after a review of the patients’ charts at each center. The diagnosis of each patient was approved by a senior investigator (HT), based on the best available current diagnostic criteria for each disease. Only questionnaires that included sufficient data were


included. Each questionnaire was individually entered into a Microsoft Excel spreadsheet.

Inclusion criteria

**Fanconi anemia**: individuals demonstrating an appropriate clinical picture supported by the abnormal chromosomal breakage test\(^2\); and if available by mutation in one of the genes.\(^{14}\)

**Dyskeratosis congenita**: individuals exhibiting the typical clinical features\(^{15}\) supported when available by the presence of a mutation in the *DCK1, TERT* or *TERC* genes.\(^{16}\)

**Diamond-Blackfan anemia**: individuals fulfilling the classic diagnostic criteria,\(^4,17\) supported if available by increased erythrocyte adenosine deaminase (eADA) activity and/or by mutation in the *RSP19, RPS24, RPS17, RPL5, RPL11* or *RPL35A* genes.\(^{18}\)

**Shwachman-Diamond syndrome**: individuals exhibiting neutropenia associated with exocrine pancreatic insufficiency, and, if possible, by mutation in the *SBDS* gene.\(^6\)

**Severe Congenital Neutropenia**: individuals with an appropriate clinical picture and, if available, by mutations in *ELA2, HAX1, G6PC3* or *WAS* genes.\(^{19}\)

**Congenital amegakaryocytic thrombocytopenia**: individuals who presented with early-onset thrombocytopenia, typical BM findings, and mutations in the thrombopoietin receptor (*cMPL*) gene.\(^7\)

**Thrombocytopenia with absent radii**: individuals with typical clinical manifestations.\(^7\)

**Bone marrow failure-not otherwise specified**: individuals who presented with marrow failure and were suspected to have inherited bone marrow failure by the combination of young age at presentation, low birth weight, macrocytosis and high
levels of hemoglobin F. However no specific diagnosis could be reached as there was normal chromosomal breakage test, normal telomeres length as well as no mutations in SBDS or c-MPL genes.

Hematological criteria

As previously suggested severe BMF was defined as associated with pancytopenia, necessitating SCT or causing death (12). Diagnosis of myelodysplastic syndrome (MDS) was made by the presence of chromosomal aberration and/or 5-20% blasts in bone marrow. Since MDS does not always develop into leukemia, MDS data were analyzed separately from leukemia.

The Fanconi anemia birth rate and calculations

We estimated the Fanconi anemia birth rate using two approaches. The first was an indirect method that assumed recessive inheritance and external estimates of the frequency of any Fanconi anemia allele among Jews (1/90) (20) and non-Jews (1/300). (21) The second was a direct approach that divided the numbers of cases enrolled in the registry according to birth year by the corresponding numbers of live births in Jews and non-Jews, respectively. (22)

Statistical Methods

The follow-up period for living patients was calculated by using the date of the last follow-up at the treating medical center, minus the date of diagnosis. If the date of the last follow-up was not available, we used the date when the questionnaire was filled out. Deceased patients were censored at the time of death. Descriptive data are presented as percentages, medians, and ranges. Analyses were performed using the Microsoft Excel-XP program.

A competing risks approach to estimate cause-specific hazard functions and cumulative incidence curves for bone marrow failure, acute myeloid leukemia, and
solid tumors was performed as previously described.(11-13) For each specific type of
cancer the observed number of cancer cases occurring prior to transplant was
compared with the expected number (O/E ratio) based on the experience of the United
States Surveillance, Epidemiology and End Results Program (SEER 9).(23) For
Fanconi anemia we also studied the association between the risk of severe bone
marrow failure and leukemia and the previously identified five-item congenital
abnormality scale with possible values ranging from 0 through 5.(13) Survival was
described using the Kaplan-Meier method.
RESULTS
Demographics

One hundred and fifty-nine living and deceased patients were registered between August 1st, 2005 and January 31st, 2008. Sixteen patients (10%) were omitted because there was not enough data to support the proposed diagnosis or to allow statistical analysis (most did not have a complete blood count; 8 were suspected to have Fanconi anemia, 5 severe congenital neutropenia, and 3 Diamond-Blackfan anemia). Another 16 were only known by name; they were mostly family members of included patients for whom no questionnaire was filled out and they were probably lost in follow-up. The final review includes 127 patients (80%), of whom 65 were males (51%) and 62 females (49%). The earliest birth year was 1958. Demographic data are presented in Table 1.

At the time of analysis, 89 patients (70%) were alive, 34 (27%) were dead, and 4 additional patients (all Fanconi anemia) were lost in follow-up. The youngest living patient was a 3-month-old patient with Diamond-Blackfan anemia and the oldest was a 42-year-old patient with Fanconi anemia. The median age at diagnosis was 2.2 years (range: birth to 26.5 years). The median follow-up period at the primary medical center before inclusion in the registry was 5.8 years (range: 0-39.1 years). Seventy-two (56%) patients were of Jewish origin and 55 (44%) were of Arabic origin.

Relative frequencies of the different disorders

The relative frequency of each disease is presented in Table 1. Sixty-six (52%) patients were found to have Fanconi anemia, 21 (17%) severe congenital neutropenia, 18 (14%) Diamond-Blackfan anemia, 8 (6%) congenital amegakaryocytic thrombocytopenia, 6 (5%) dyskeratosis congenita, 3 (2%) Shwachman-Diamond syndrome, and 3 (2%) thrombocytopenia with absent radii. It should be noted that two patients (one with dyskeratosis congenita and the other with
Shwachman-Diamond syndrome) were initially diagnosed as having acquired aplastic anemia, the correct diagnosis was reached however, 2 and 3 years following the initial diagnosis with the appearance of dysplastic nails and exocrine pancreatic insufficiency respectively. In 2 patients (2%), although an inherited bone marrow failure syndromes was suspected, no specific diagnosis could be reached. They presented at an early age (1 and 3 years of age), to consanguineous families, they were small for gestational age and had macrocytosis as well as, high hemoglobin F levels. Normal chromosomal breakage test, normal telomeres length as well as no mutations in \textit{SBDS} or c-MPL genes precluded precise diagnosis. Both are growing well with moderate pancytopenia 5-7 years following diagnosis.

**Consanguinity and molecular diagnosis**

Ninety-eight families were included in the registry. Consanguinity was recorded in 50 patients (40%, Table 1). Fifty-six patients (44%) had other affected family members; most of them were included in the registry. Eighty-six patients (68%) underwent molecular genetic testing, and pathogenic mutations were identified in 62 patients (72% of those examined) (Table 2).

**Birth rates**

The birth rate was calculated for the most common disease, Fanconi anemia. An indirect estimate of the birth rate was obtained, assuming that the frequency of any Fanconi anemia allele is 1/90 for Jews \(^{(20)}\) and 1/300 for other Israelis \(^{(21)}\); census data indicated that approximately three-quarters of live-born children are Jews. For these values, a standard formula for recessive inheritance yielded an estimated Fanconi anemia birth rate of 2.38 per 100,000 live births in Israel. A direct estimate was obtained from the registry based on Fanconi anemia cases ascertained during the
In the 1990s. This period was chosen because cases born in earlier years might have been missed, whereas some cases born since 2000 might not yet have been diagnosed. For the 1990s, a direct estimate of the birth rate was 2.22 per 100,000 live births, with a 95% confidence interval of 1.5 to 3.4 per 100,000, based on the Poisson distribution. Hence, the two approaches yielded similar values. These values are significantly higher than the figure of 0.28 per 100,000 based on the worldwide carrier frequency estimate of 1/300.

**Overall adverse events**

Adverse events evaluated included severe bone marrow failure, malignancy, and mortality. Complication details are presented in Table 3.

**Severe bone marrow failure**

Thirty patients (24%) developed severe bone marrow failure (as defined in reference (12), at a median age of 8 years (range: 0.5-30 years, Table 2). The majority of these patients (26 of the 30, 87%) had Fanconi anemia; 3 had congenital amegakaryocytic thrombocytopenia and 1 had dyskeratosis congenita. The cumulative incidence of bone marrow failure in Fanconi anemia to age 32 was 70% (Fig 1A). The cause-specific hazard of bone marrow failure in Fanconi anemia patients peaked at 10.5%/year at age 10 years (95% CI: 6.7 – 14.1%/year) (Fig 1B). As previously found for Fanconi anemia (12), abnormal radii and a five-item congenital abnormality score (CABS) were together significantly associated with the risk of bone marrow failure (p = 0.009); the relative hazard for bone marrow failure increased by 1.6 for every 1-unit-increase in the CABS score (95% CI: 1.1-2.2) (data not shown).

**Malignancy**

Fifteen patients (15, 12%) were diagnosed with malignancy: 9 with leukemia and 6 with solid tumors (Table 3). The majority of patients developing malignancy
had Fanconi anemia (13/15), 1 had severe congenital neutropenia, and 1 had
congenital amegakaryocytic thrombocytopenia. For Fanconi anemia, the O/E ratio for
cancer was 71 for all cancers, similar to results from other Fanconi anemia registries
(11, 13). The cumulative incidence by age of development of cancer in Fanconi
anemia, severe congenital neutropenia, and congenital amegakaryocytic
thrombocytopenia is depicted in Fig 2. The probability of developing cancer by the
age of 25 was 30% in Fanconi anemia and 18% for severe congenital neutropenia (Fig
2) and 10% for congenital amegakaryocytic thrombocytopenia. No malignancy was
recorded in Diamond-Blackfan anemia, dyskeratosis congenita, Shwachman-Diamond
syndrome, or thrombocytopenia with absent radii.

Of the 9 leukemia patients, 7 had acute myeloid leukemia (AML) (6 Fanconi
anemia, 1 severe congenital neutropenia), and 2 acute lymphatic leukemia (ALL) (1
Fanconi anemia, and 1 congenital amegakaryocytic thrombocytopenia). For Fanconi
anemia the median age at diagnosis of leukemia was 10 years (range: 6 weeks-20
years). The cumulative incidence in Fanconi anemia of leukemia by age 30 was 13%.
The hazard of leukemia was stable at 0.9%/year (95% CI: 0.42 – 1.85%/year). The
CABS was also found to be significantly associated with the risk of developing acute
leukemia (p=0.05) in Fanconi anemia and every 1-unit-increase in the CABS
increased the relative hazard for leukemia by 2.1 (95% CI: 1.0-4.2). (data not shown).

All 6 patients who developed solid tumors had Fanconi anemia. The
cumulative incidence to age 32 was 17% for solid tumors. The median age at
diagnosis of a solid tumor was 30.7 years (range: 29.7-32 years). Most of the solid
tumors were squamous cell carcinoma of the head and neck, esophagus, cervix, and
vulva. In only one patient the malignant disease developed following SCT.
Significantly elevated O/E ratios for cancers were identified for head and neck
squamous cell carcinoma (986-fold), tumors of larynx (13,238-fold), vulva (3,701-fold), cervix (244-fold), and breast (88-fold).

For severe congenital neutropenia the estimated cumulative incidence of AML was high, 34% at age 30.

Fifteen (15, 11.8%) patients had MDS (11, 3 severe congenital neutropenia, and 1 congenital amegakaryocytic thrombocytopenia) at the median age of 9 years (0.5-29.5). The hazard rate for MDS in Fanconi anemia was stable at 1.4%/year (95% CI: 0.76 – 2.49%/year) (Figure 1B). The O/E ratio for MDS in Fanconi anemia was >11,000-fold.

Mortality

Thirty-four patients (27%) succumbed to their disease before inclusion in the registry (Table 3). The median age at the time of death was 10.6 years (range: 0.25-35.8 years). The mortality was due to: (i) direct complication of the disease in 5 patients (1 Shwachman-Diamond syndrome, 2 dyskeratosis congenita, 2 severe congenital neutropenia); (ii) complications of treatment in 12 patients: 11 patients succumbed to complications of SCT (8 Fanconi anemia, 3 severe congenital neutropenia), and 1 Fanconi anemia patient died of hepatic peliosis secondary to long-standing androgen treatment. (iii) 15 patients died of malignancy, either hematological or solid, primary or as a consequence of treatment (14 Fanconi anemia, 1 severe congenital neutropenia). The Kaplan-Meier survival curves for Fanconi anemia, severe congenital neutropenia, Diamond-Blackfan anemia, and congenital amegakaryocytic thrombocytopenia are depicted in Figure 3. The survival of Fanconi anemia patients was 35% at the age of 30 and that of severe congenital neutropenia 45% at the age of 20.
DISCUSSION

Accurate epidemiologic data regarding inherited bone marrow failure syndromes have been difficult to obtain and are often incomplete. The frequencies of the specific inherited bone marrow failure syndromes categories were estimated mainly from case series. Our Israeli inherited bone marrow failure syndromes registry is the first population-based national study focused on the inherited bone marrow failure syndromes, including all the major rare syndromes, and it is supported in 47% of cases by molecular testing. This report is based on 127 patients with inherited bone marrow failure syndromes diagnosed in Israel between 1966 and 2007. Studying their records enabled us to determine the relative frequency of each of these disorders, to calculate the Fanconi anemia birth rate, and to evaluate the relative frequency of complications.

By far, the most common inherited bone marrow failure syndromes was Fanconi anemia, with 66 patients (52%), followed by severe congenital neutropenia (17%) and Diamond-Blackfan anemia (14%). Congenital amegakaryocytic thrombocytopenia and dyskeratosis congenita were much less common, with 6% and 5% of patients, respectively, whereas Shwachman-Diamond syndrome and thrombocytopenia with absent radii were each found in 2% of patients (Table 1). Only in 2 of our patients (2%) with an apparent inherited bone marrow failure syndromes were we unable to identify a specific diagnosis. The long follow-up for some of our patients and the use of molecular diagnosis may have helped provide the low number of undiagnosed inherited bone marrow failure patients in our registry.

The relatively high proportion of Fanconi anemia patients in our cohort is partially caused by the high rate of consanguinity (52% of Fanconi anemia patients, Table 1), since Fanconi anemia is primarily an autosomal recessive disorder. Indeed,
direct population-based calculation of the Fanconi anemia birth rate, done for the first time, yielded a figure of 2.2:100,000 live births (95% confidence interval of 1.5 to 3.4 per 100,000), which is 7-fold higher than expected from the world-wide carrier frequency of 1:300. \(^{(21)}\) The majority of our Fanconi anemia patients were either of Sephardic-Jewish extract (38%) or Israeli-Arabs (45%) and indeed, in both communities consanguinity was present (Table 2). Although the carrier frequency in Ashkenazi Jews is 1 in 90, that group was a minority in our Fanconi anemia families.

The most common disease in our cohort, Fanconi anemia, was also associated with the highest rate of complications and carried the worst prognosis. Severe BMF as previously defined by Rosenberg et al. (12), developed in 30 patients with inherited bone marrow failure syndromes, 26 of whom (87%) had Fanconi anemia. As has been documented previously, Fanconi anemia is a cancer-prone disease. \(^{(11)}\) Cancer developed in 15 of our patients, 13 of whom (87%) had Fanconi anemia. Seven of the 9 patients (78%) who developed leukemia had Fanconi anemia, and all patients with solid tumors (6) had Fanconi anemia. The cumulative incidence (Kaplan-Meier method) of cancer in Fanconi anemia was 30% by the age of 30 (Figure 2) and unstable thereafter due to small numbers. The median survival rate was 35% by the same age (Figure 3).

Despite the relatively small number of Fanconi anemia patients in our registry, compared with two independent and larger Fanconi anemia cohorts from other parts of the world, including the NAS and the German Fanconi Anemia Registry (GEFA), \(^{(11, 13)}\) complications were qualitatively and quantitatively similar in all three studies. The cause-specific hazards of bone marrow failure, AML, and solid tumors (Figure 1), the specific tumors occurring in excess and the ratios of O/E numbers of cancers were comparable. Additionally, as previously described in the NAS and the GEFA, \(^{(12, 13)}\) a
high five-item congenital abnormality score was associated with an increased BMF rate and cancer risk. The similarity between our results and those from the NAS and the GEFA supports the validity of our data.

Severe congenital neutropenia was also associated with a low actuarial median survival rate (45% at the age of 20, Figure 3). In contrast, Diamond-Blackfan anemia seemed to have a relatively better prognosis, since none of the patients in our cohort developed any major complications. For patients with dyskeratosis congenita, Shwachman-Diamond syndrome, congenital amegakaryocytic thrombocytopenia, and thrombocytopenia with absent radii, the number of patients is too small to draw any conclusions regarding their relative severity. Dyskeratosis congenita has also recently been documented as a cancer-prone disease,(24) and the absence of such complications in our patients is probably due to the small number of patients.

This is the first national inherited bone marrow failure syndromes registry capturing the majority of such patients in the country, having a low number of undiagnosed patients (2%), and a relatively long follow-up period (median 5.8, ranging up to 39 years). However, this study has several limitations. The registry originated in a small country and, therefore, included small numbers of patients. A high consanguinity rate may have led to an over-representation of autosomal recessive diseases. Referral bias was also present, since the data were obtained from pediatric hematology units. We may thus have underestimated patients treated primarily by an adult hematologist, and those who first presented with MDS, AML, or a solid tumor. Underestimation may also be due to under-diagnosis of patients who were never seen at the collaborating centers, or for whom data were incomplete, as well as patients who did not meet diagnostic criteria for any of the known syndromes.
In summary, our data suggest that is the most common form of inherited bone
marrow failure syndromes in Israel, followed by severe congenital neutropenia and
Diamond-Blackfan anemia. The Fanconi anemia population-based calculated birth
rate was higher than expected, probably due to consanguinity. Fanconi anemia was
associated with the worst prognosis, with a high percentage of patients developing
severe BMF and cancer. Diamond-Blackfan anemia patients had the best prognosis.
The data presented provide a rational basis for prevention programs, as well as
longitudinal surveillance of inherited bone marrow failure syndromes complications.
Table 1: Demographic data of patients in the Israeli Inherited Bone Marrow Failure Registry (IS-IBMFR, N=127)

<table>
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<th>No. of patients</th>
<th>FA</th>
<th>SCN</th>
<th>DBA</th>
<th>CAMT</th>
<th>DC</th>
<th>SDS</th>
<th>TAR</th>
<th>NOS</th>
<th>All</th>
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<tr>
<td>Total (%)</td>
<td>66 (52)</td>
<td>21 (17)</td>
<td>18 (14)</td>
<td>8 (6)</td>
<td>6 (5)</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>2 (2)</td>
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<td>Number of families</td>
<td>46</td>
<td>17</td>
<td>18</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
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<td>Male: Female</td>
<td>33:33</td>
<td>11:10</td>
<td>8:10</td>
<td>3:5</td>
<td>5:1</td>
<td>2:1</td>
<td>1:2</td>
<td>2:0</td>
<td>65:62</td>
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<tr>
<td>Consanguinity (%)</td>
<td>34 (68)</td>
<td>8 (16)</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>--</td>
<td>--</td>
<td>2 (4)</td>
<td>50 (40)</td>
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<tr>
<td>Age at diagnosis, yrs, median (range)</td>
<td>6.25 (0-26.5)</td>
<td>0.08 (0-0.65)</td>
<td>0.2 (0-2.4)</td>
<td>0.6 (0-1)</td>
<td>8.9 (1-20.8)</td>
<td>1 (0-2.4)</td>
<td>0</td>
<td>0.8 (0-1)</td>
<td>2.2 (0-26.5)</td>
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<tr>
<td>Age at follow-up, yrs, median (range)</td>
<td>6.2 (0-39.1)</td>
<td>6.8 (0.8-32)</td>
<td>7.3 (0.25-27.25)</td>
<td>4.3 (2.25-11.8)</td>
<td>5.4 (0.2-11.8)</td>
<td>4.25 (1.6-9.7)</td>
<td>3 (0.2-3.2)</td>
<td>2.7 (1.5-3.9)</td>
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<td>Person-years</td>
<td>547</td>
<td>170.5</td>
<td>132.3</td>
<td>42.2</td>
<td>36.3</td>
<td>15.5</td>
<td>6.3</td>
<td>6.25</td>
<td>956.2</td>
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FA-Fanconi anemia; DC-dyskeratosis congenital; DBA-Diamond-Blackfan anemia; SCN-severe congenital neutropenia; SDS-Shwachman-Diamond syndrome; CAMT-congenital amegakaryocytic thrombocytopenia; TAR-thrombocytopenia with absent radii; *NOS-not otherwise specified; in brackets % of total number with an IBMFS; Person-years: the total sum of the number of years from diagnosis; ‡ Data on 1 patient are missing; § Data on 2 patients are missing.
Table 2 Israeli Inherited Bone Marrow Failure Registry Genetic Analysis (N=62)

<table>
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<th></th>
<th>DBA</th>
<th>Gene</th>
<th>Mutation</th>
<th>Phenotype</th>
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<td>RPS19</td>
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<td>Altered splicing</td>
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<td>Mixed Jewish</td>
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<td>p.Arg62Gln</td>
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<td>Altered splicing</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>N1</td>
<td>c.185G&gt;A</td>
<td>p.Arg62Gln</td>
<td>Sephardic (2), Mixed (1)</td>
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<tr>
<td>11</td>
<td>ND</td>
<td>c.443+1G&gt;A</td>
<td>Altered splicing</td>
<td>Ashkenazi (2), Sephardic (3), Mixed (2), Arab (4)</td>
<td></td>
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<tr>
<td>2</td>
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<td>p.Arg901Trp</td>
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<td>c.183-184 TA&gt;CT</td>
<td>In frame stop-codon</td>
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</tr>
<tr>
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<td>Altered splicing</td>
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Table 2 Israeli Inherited Bone Marrow Failure Registry Genetic Analysis (N=62)

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<th>Affected gene</th>
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<th>Mutation 2</th>
<th>Effect 1</th>
<th>Effect 2</th>
<th>Ethnicity</th>
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<td>FA</td>
<td>FANCA</td>
<td>c.3785_3787del3</td>
<td>c.3785_3787del3</td>
<td>Absence of AA</td>
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<td>Arab</td>
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<td>7</td>
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<td>c.2172_2173insG</td>
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<td>Frame shift</td>
<td>Moroccan Jewish</td>
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<tr>
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<td>c.2172_2173insG</td>
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<td>Frame shift</td>
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<td>Moroccan Jewish</td>
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</tr>
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<td>c.890_893del</td>
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<td>p.Ser858Arg</td>
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<td>Nonsense</td>
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<td>Ashkenazi (3), Sephardic (9), Arab (12)</td>
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<td>26</td>
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<td>c.709C&gt;T</td>
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Table 3: Adverse events affecting patients in the Israeli Inherited Bone Marrow Failure Registry (IS-IBMFR, N=127)

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<tr>
<th>No. of Patients and ages</th>
<th>FA</th>
<th>SCN</th>
<th>DBA</th>
<th>CAMT</th>
<th>DC</th>
<th>SDS</th>
<th>TAR</th>
<th>NOS*</th>
<th>ALL</th>
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<tbody>
<tr>
<td>Total (%)</td>
<td>66 (52)</td>
<td>21 (17)</td>
<td>18 (14)</td>
<td>8 (6)</td>
<td>6 (5)</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td>127 (100)</td>
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<tr>
<td>Deceased</td>
<td>25 (38)</td>
<td>6 (29)</td>
<td>--</td>
<td>--</td>
<td>2 (33)</td>
<td>1 (33)</td>
<td>--</td>
<td>--</td>
<td>34 (27)</td>
</tr>
<tr>
<td>Age at death, yrs, median (range)</td>
<td>11 (3.3-35.8)</td>
<td>3.8 (0.25-18.2)</td>
<td>--</td>
<td>--</td>
<td>16.7 (5.2-28.1)</td>
<td>6.7</td>
<td>--</td>
<td>--</td>
<td>10.6 (0.25-36)</td>
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<tr>
<td>Severe BMF</td>
<td>26 (39)</td>
<td>--</td>
<td>--</td>
<td>3 (38)</td>
<td>1 (17)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>30 (24)</td>
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<tr>
<td>Age at severe BMF, yrs, median (range)</td>
<td>10 (4-30)*</td>
<td>--</td>
<td>--</td>
<td>3 (0.5-3)</td>
<td>2</td>
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<td>--</td>
<td>8 (0.5-30)*</td>
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<td>SCT</td>
<td>30 (45)</td>
<td>6 (29)</td>
<td>1 (6)</td>
<td>5 (63)</td>
<td>1 (17)</td>
<td>--</td>
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<td>43 (34)</td>
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<td>Age at transplant, yrs, median (range)</td>
<td>9.5 (0.4-30.8)</td>
<td>10.5 (0.2-30.5)</td>
<td>3.1</td>
<td>2.7 (0.6-3.25)</td>
<td>1.9</td>
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<td>--</td>
<td>--</td>
<td>8.7 (0.2-30.8)</td>
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<tr>
<td>All malignancies (% of all)</td>
<td>13 (19.7)</td>
<td>1 (4.8)</td>
<td>--</td>
<td>1 (12.5)</td>
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<td>--</td>
<td>--</td>
<td>15 (11.8)</td>
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<tr>
<td>Leukemia (% of all)</td>
<td>7 (11)</td>
<td>1 (4)</td>
<td>--</td>
<td>1 (12.5)</td>
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<td>--</td>
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<td>9 (7)</td>
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<td>Age at leukemia, yrs, median (range)</td>
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<td>31</td>
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<tr>
<td>MDS (% of all)</td>
<td>11 (16)</td>
<td>3 (14)</td>
<td>--</td>
<td>1 (12.5)</td>
<td>--</td>
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<td>--</td>
<td>--</td>
<td>15 (11.8)</td>
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<td>Age at MDS, yrs, median (range)</td>
<td>16 (0.5-29.5)</td>
<td>6 (6-13)</td>
<td>2.5</td>
<td>2.5</td>
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<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
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<tr>
<td>Solid tumors</td>
<td>6 (9)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>6 (5)</td>
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</tr>
<tr>
<td>Age at solid tumor, yrs, median (range)</td>
<td>30.7 (29.7-32)*</td>
<td>--</td>
<td>--</td>
<td>--</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>30.7 (29.7-32)*</td>
</tr>
</tbody>
</table>
FA-Fanconi anemia; DC-Dyskeratosis congenita; DBA Diamond-Blackfan anemia ; SCN-severe congenital neutropenia; SDS-Shwachman-Diamond syndrome; CAMT-congenital amegakaryocytic thrombocytopenia; TAR-thrombocytopenia with absent radii; *NOS-not otherwise specified; severe BMF-severe bone marrow failure as defined in reference (12); SCT-stem cell transplantation; yrs-years; ALL-acute lymphoblastic leukemia; AML-acute myeloblastic leukemia; MDS myelodysplastic syndrome; in brackets the percentage of total number with an IBMFS; * Data on 1 patient are missing; † 2 patients had both MDS and a solid tumor; ‡ Data on 2 patients are missing;
Legends to Figures

Figure 1: **Cumulative incidence by age of adverse events and adverse event rates in IS-IBMFR with Fanconi anemia.** A. Cumulative incidence of the first adverse event, severe bone marrow failure (as in reference (12), leukemia, and solid tumor (ST), using a competing risk analysis. B. Annual cause-specific hazard rates of severe BMF, leukemia, myelodysplastic syndrome (MDS), and ST. The shaded areas represent the 95% point-wise confidence intervals.

Figure 2: **Cumulative incidence by age of development of cancer in IS-IBMFR patients**
FA-Fanconi anemia, SCN-severe congenital neutropenia, and CAMT-congenital amegakaryocytic thrombocytopenia. The shaded areas represent the 95% point-wise confidence intervals.

Figure 3: **Cumulative survival of IS-IBMFR patients calculated using the method of Kaplan and Meier.** FA-Fanconi anemia (n=66); SCN-severe congenital neutropenia (n=21); DBA-Diamond- Blackfan anemia (n=18), and CAMT-congenital amegakaryocytic thrombocytopenia (n=8). The shaded areas represent the 95% point-wise confidence intervals.
APPENDIX

Additional physicians participating in recruiting the patients:

Sheba Medical Center: D. Waldman, A. Avidgor, and M. Koren

Soroka Medical Center: I. Levi

Sha'arei Tzedek Medical Center: H. Miskin

Kaplan Medical Center: D. Shtager

Soraski Medical Center: R. Dvir

Meir Medical Center: B. Wollach

Carmel Medical Center: E. Shved

Western Galilee Medical Center: A. Kuperman

Assaf Harofe Medical Center: I. Quentzel

Edith Wolfson Medical Center: A. Lotan
Authorship and Disclosures

HT was the principal investigator and takes primary responsibility for this paper. HT, JI, SA, PS, SV, MB, CK, ABB, JK, AK, CL, and IY recruited the patients. DN and RZ reviewed most patients' charts and filled out the questionnaires. DN transferred the files to the database and participated in the statistical analysis. DN and HT wrote the paper. BPA provided the basic protocol and survey instruments for adaptation, helped to analyze data and write the report and PSR helped to analyze data and write the report. The authors reported no potential conflict of interest.
REFERENCES


