Long-term risk of cancer development in adult patients with idiopathic aplastic anemia after treatment with anti-thymocyte globulin

Idiopathic aplastic anemia (AA) is considered to be an immune-mediated bone marrow disease characterized by a pancytopenia and a hypocellular bone marrow. AA responds to immune suppressive treatment (IST) in the majority of patients. Current literature shows an increased incidence of malignant bone marrow disorders, such as myelodysplastic syndrome or acute myeloid leukemia, after treatment with anti-thymocyte globulin (ATG)-based IST in AA.[1-3] Moreover, an increased incidence of solid malignancies is reported after this treatment.[1-3] However, there are no follow up data on secondary cancer incidence beyond 15 years after first-line therapy. Only one study compared cancer incidence to the occurrence of malignancies in the general population.[3] Furthermore, a substantial fraction of AA patients is treated with hematopoietic stem cell transplantation (HSCT) after failure of ATG-based IST. HSCT itself is associated with an increased risk of secondary malignancies.[4] Nevertheless, the development of cancer before and after HSCT as second-line treatment was not separated in any published study on AA patients who received first-line IST. To address these issues, we analyzed a cohort of adult patients with idiopathic AA treated with ATG-based IST as first-line therapy between 1980 and 2014 at our centre. Cancer probabilities were calculated with cumulative incidence curves, in which HSCT during follow up and death without developing a malignancy were considered competing risks.[5] The incidence of cancer following ATG-based IST was compared to the incidence of malignancies in the general Dutch population, matched for age, sex and calendar year, by means of the standardized incidence ratio (SIR). Malignancy rates in the general Dutch population were based on the Dutch cancer registration.[6] Risk factors hypothesized to affect the risk of cancer development (disease severity and addition of cyclosporine to upfront ATG treatment) were evaluated in a multivariate analysis with a Cox proportional hazards model for the cause-specific hazard and were adjusted for age at treatment initiation.

A total of 93 idiopathic AA patients were included in this analysis. Patient characteristics are shown in Table 1. Patients with a known congenital form of bone marrow failure or patients who had a Myelodysplastic Syndrome (MDS), based on the criteria which were applicable at the time of diagnosis, were excluded. The median length of follow up for all patients was 12 years (range: 1 month - 32 years). Eleven patients (12%) were lost to follow up after a median follow-up of 5 years (range: 2 months – 13 years). Fourteen patients (15%) received a HSCT as second-line treatment. A total of 35 deaths were reported, resulting in an estimated overall survival rate of 45% after 30 years (Figure 1, 95% confidence interval (CI): 32-63%). Compared with the mortality rates of the general Dutch population matched for age, sex and calendar year, the overall survival rate of our cohort was significantly lower. During follow up 18 patients developed a malignancy; 4 patients had a myeloid malignancy and 14 patients developed various other types of cancer: non-Hodgkin lymphoma (n=2), breast cancer (n=3), colon carcinoma (n=2), and single cases of esophageal carcinoma, stomach cancer, non-small-cell lung carcinoma, astrocytoma, urothelial cell carcinoma, vulvar carcinoma, and a metastasized tumor of unknown origin. The cumulative incidences of malignancies after 10, 20, and 30 years with HSCT and death as competing risks were 8% (95% CI: 2-13%), 19% (11-28%) and 29% (17-42%), respectively (Figure 1). Cumulative incidences for myeloid malignancies were 3% (95% CI: 0-6%), 6% (0-11%) and 6% (0-11%), respectively, and for non-myeloid malignancies 5% (95% CI: 0-10%), 14% (6-22%) and 24% (12-35%) after 10, 20, and 30 years, respectively. In a landmark analysis starting at 2 years after treatment, the cumulative incidences of malignancies after 10, 20, and 30 years with HSCT and death as competing risks were 15% (95% CI: 6-24%), 27% (15-39%) and 37% (22-52%), respectively. The cumulative incidence of malignancies was significantly increased in comparison with the general Dutch population, with a SIR of 3.0 (95% CI: 1.8-4.6) (Table 2). Analyzed separately, both myeloid and non-myeloid malignancies showed an increased SIR of 46.7 (95% CI: 35.2-103.6) and 2.4 (1.3-3.8), respectively. Age at treatment initiation was a significant risk factor for malignant diseases (Hazard ratio (HR) 1.47 per 10 years age increase, P=0.02). Disease severity - non-severe *versus* severe - was not associated with cancer development (HR 1.18, P=0.69). The addition of cyclosporine to upfront ATG was not a significant risk factor; however, a hazard ratio of 1.98 may suggest an increased cancer risk in patients receiving additional cyclosporine (95% CI: 0.70-5.65).

In conclusion, we demonstrate an increased risk of both myeloid and non-myeloid malignancies after first-line IST compared with the general population. The cumulative incidence of myeloid malignancies of 3% after 10 years and 6% after 30 years appears to be lower than in previous studies that reported a cumulative risk of between 8% and 16% after 10 years and 26% after 15 years.[1,3,7] The variable rates of myeloid malignancies which have been reported could have been caused by the inclusion of patients with hypoplastic MDS which was interpreted as AA. No myeloid malignancies developed during the first 5 years following IST in our cohort, sug-

Table 1. Patient characteristics.

Patients included	93
Median age in years (range)	33 (14-76)
Male sex, n (%)	51 (55%)
Disease severity, n (%) (n=92)	Non-severe: 36 (39%) (Very) severe: 56 (61%)
Source of anti-thymocyte globulin, n (%) (n=88)	Horse (Lymphoglobulin): 80 (91%) Rabbit (Thymoglobulin): 8 (9%)
Cyclosporine, n (%)	41 (44%)

Table 2. Standardized incidence ratios of malignancies in cohort compared with the sex- and age-matched cancer rates in the general Dutch population. Patients were censored at HSCT.

	Observed cases	Expected cases	Standardized incidence ratio (95% CI)
All malignancies	18	6.0	3.0 (1.8-4.6)
Myeloid malignancies	4	0.086	46.7 (35.2-103.6)
Non-myeloid malignancies	14	5.9	2.4 (1.3-3.8)

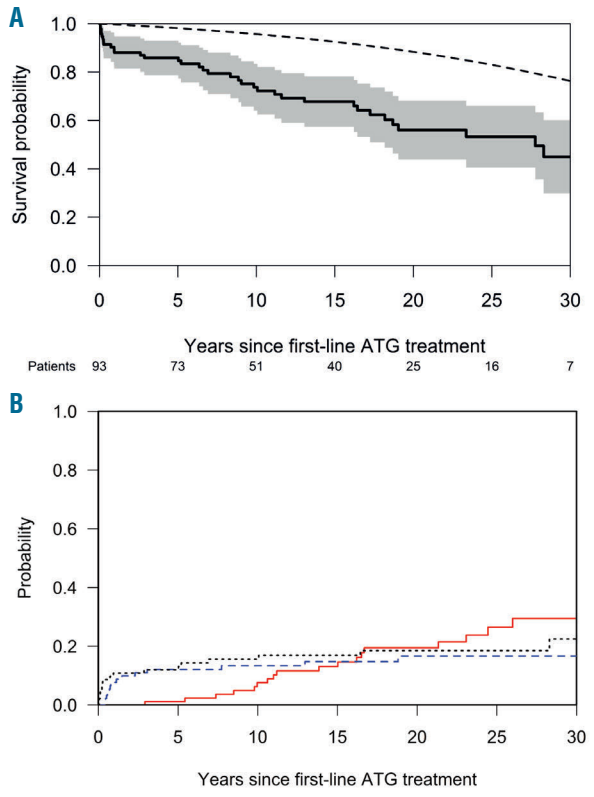

Figure 1. Survival and cancer probability in patients with idiopathic AA treated with ATG-based immune suppressive therapy. (A): overall survival of patients with idiopathic AA receiving upfront ATG-based IST from the first day of treatment (solid line) with 95% confidence intervals compared with the overall survival of the general Dutch population matched for sex, age and calendar year (dotted line). (B): cumulative incidence probabilities of malignancies (red line), hematopoietic stem cell transplantation (blue line) and death without malignancy or HSCT (black line) after first-line ATG treatment using a competing risks analysis. ATG: anti-thymocyte globulin.

gesting that the inadvertent inclusion of patients with hypoplastic MDS in our study was negligible. The absence of children in our cohort could be another explanation for the lower incidence of myeloid malignancies, as AA in children can be a feature of congenital abnormalities associated with the early development of malignancies. The cumulative risk of developing a non-myeloid malignancy was 5% after 10 years and 24% after 30 years. This cumulative incidence was heightened as compared to the general Dutch population. Two earlier studies showed an incidence of solid tumors in patients who were treated with ATG of 11% after 10 and 11 years.[1-2] A multicenter registry study reported a 10-year cumulative risk of only 2%.[3] The increased probability of the development of non-myeloid malignancies in AA patients compared with the general population could be related to IST, similar to that found after solid organ transplantations.[8] In our study, a possible yet non-significant trend towards higher cancer rates was noted in patients receiving upfront cyclosporine in addition to ATG. We consider the risk of confounding by indication of patients receiving cyclosporine unlikely, since treatment with additional cyclosporine was based on changes to guidelines in 1991. Another cause of the increased cancer risk in this patient group could be that the idiopathic AA is caused by an underlying condition, such as a germline telomerase mutation, leading to both bone marrow failure and cancer development. A direct comparison of cancer risks after IST and HSCT for idiopathic AA is currently not possible since randomized studies have not been performed. Follow-up studies in adult patients after HSCT for a variety of hematologic diseases show an increased risk of malignancies during long-term follow-up compared to the age- and sex-matched population.[4] In a study concerning late effects after HSCT for AA in children with a median follow-up time of 22 years, 13% of the patients developed a malignancy.[9] After excluding the cases with squamous cell carcinoma, 9% of patients developed cancer, which is higher than the expected cancer risk in the matched general population. As radiation therapy in the conditioning regimen attributes to this risk, and is not frequently used anymore in AA patients, the current cumulative risk of cancer after HSCT in AA patients is not known, but probably lower. Therefore, we conclude that the risk of malignancy after IST should currently not be used as an argument against IST or in favor of HSCT.

In summary, the incidence of malignancies after immunosuppressive treatment in AA patients is increased compared with the general population. Our competing risks analysis excludes HSCT as a confounding factor. Furthermore, we provide definitive evidence that the cancer risk also pertains to solid malignancies. Overall, our findings emphasize the importance of long-term surveillance of AA patients after IST.

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