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Aplastic anemia - a population-based study of epidemiology, treatment, and prognostic factors

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i föreläsningssal Arvid Carlsson, Medicinaregatan 3, torsdagen den 8 oktober 2020, klockan 09.00

av **Krista Vaht**

Fakultetsopponent: Professor Eva Hellström Lindberg, Karolinska Institutet, Sverige

Avhandlingen baseras på följande delarbeten

I. Vaht K, Göransson M, Carlson K, Isaksson C, Lenhoff S, Sandstedt A, Uggla B, Winiarski J, Ljungman P, Brune M, Andersson P-O. Incidence and outcome of acquired aplastic anemia: real-world data from patients diagnosed in Sweden from 2000-2011. Haematologica. 2017;102(10):1683-1690.

II. Vaht K, Göransson M, Carlson K, Isaksson C, Lenhoff S, Sandstedt A, Uggla B, Winiarski J, Ljungman P, Brune M, Andersson P-O. Low response rate to ATG-based immunosuppressive therapy in very severe aplastic anaemia - A Swedish nationwide cohort study. European J Haematology. 2018;100(6):613-620.

III. Vaht K, Göransson M, Carlson K, Isaksson C, Lenhoff S, Sandstedt A, Uggla B, Winiarski J, Ljungman P, Andersson P-O, Brune M. High Graft-versus-Host Disease-Free, Relapse/Rejection-Free Survival and Similar Outcome of Related and Unrelated Allogeneic Stem Cell Transplantation for Aplastic Anemia: A Nationwide Swedish Cohort Study. Biology of Blood and Marrow Transplantation. 2019;25(10):1970-1974.

IV. Vaht K, Brenner J, Bram Ednersson S, Ljungman P, Brune M and Andersson P-O. Bone marrow expression of CD68/CD163 macrophages, IL-17 and FOXP3 cells in aplastic anemia and their relation to prognosis. Manuscript

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Abstract

Background and aims. Aplastic anemia (AA) is a rare but life-threatening disease. The introduction of immunosuppressive treatment (IST) and hematopoietic stem cell transplantation (HSCT) has considerably improved the outcome of patients with AA. However, modern-day population-based data are limited. This thesis aimed to retrospectively analyze the incidence, treatment modalities, survival, and immune markers in the bone marrow of patients diagnosed with AA in Sweden from 2000–2011.

Patients and methods. Patients were included via the National Patient Registry and diagnosed according to the Camitta criteria. All data were collected from medical charts. In paper IV, immunohistochemistry was used to obtain data on regulatory T cells and macrophages in the bone marrow.

Results and conclusions. We identified 257 confirmed cases, with an overall incidence of 2.35 cases per million inhabitants per year. The 5-year overall survival (OS) was >90% in patients aged up to 39 years but 38.1% in patients aged ≥60 years. Multivariate analysis showed that age ≥40 years, very severe AA, and no specific therapy were independent risk factors for inferior survival. First-line IST treated patients (n=158) showed a 47% response rate with no difference regarding the age groups or anti-thymocyte globulin (ATG) formulation. The response was significantly associated with the severity grade at the time of treatment initiation, and very severe AA patients exhibited a response rate of 22%. Sixty-eight patients underwent HSCT with a 5-year OS of 86.8%. The graft-versus-host-disease-free, relapse/rejection-free survival at 5 years was 69.1%. Patients aged ≥40 years had higher transplant-related mortality that translated into a lower 5-year OS. In paper IV, we found lower numbers of FOXP3-positive regulatory T cells in AA patients without predictive value for IST response and that patients with a higher number of CD163-positive macrophages had a better 5-year OS, but this benefit was only observed in the non-severe AA group. In conclusion, younger patients have very good long-term survival regardless of the choice of therapy, whereas the outcome for patients ≥60 years remains poor. Very severe AA patients respond poorly to ATG, which indicates the need for a different treatment approach.

Keywords: aplastic anemia, real-world data, ATG, HSCT, regulatory T cells

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