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Allogeneic hematopoietic stem cell transplantation as immunotherapy

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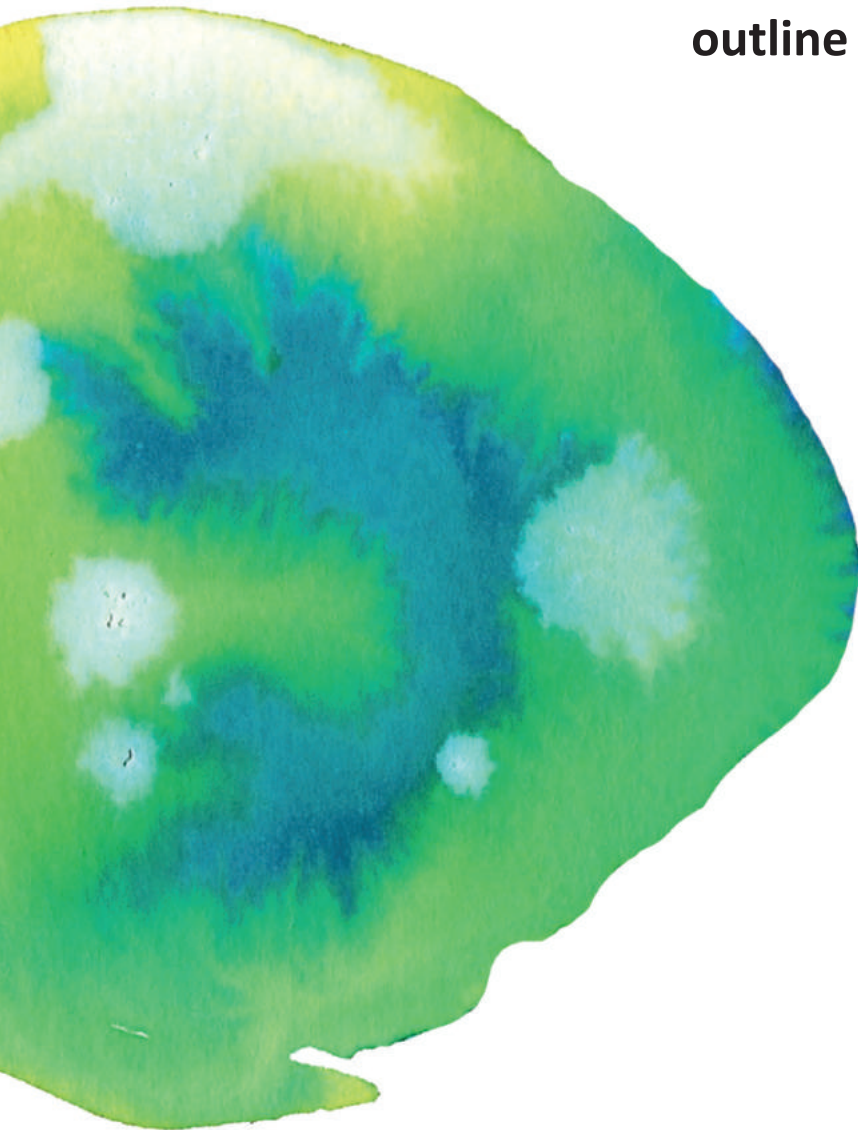
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CHAPTER 1

General introduction and outline of the thesis



M.A. Gillissen

General introduction

Acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS) are myeloid malignancies with a poor prognosis. Allogeneic hematopoietic stem cell transplantation (HSCT) is often applied as consolidation therapy, to induce a graft versus leukemia (GvL) immune response. However, this is a high-risk therapy with major complications, excluding many people for this treatment. The aim of this thesis was to study GvL immune-biology, because a better understanding of GvL immune responses will lay the foundation to develop less harmful, more effective therapies. Historically, the focus has been on the role of T cells and NK cells in GvL immune responses. We studied the role of B cells in GvL immune responses in patients with AML and MDS who were treated successfully with an allogeneic HSCT.

AML and high-risk MDS

Acute myeloid leukemia (AML) is a malignant transformation of myeloid precursors in the bone marrow. The disease is characterized by an uncontrolled expansion of leukemic blasts that quickly accumulate and interfere with the normal function of bone marrow.¹⁻⁴ AML accounts for 30% of all leukemia in adults and is a high-risk malignancy with long-term, disease-free survival obtained in 20-30% of the patients.^{1,3-5} The prognosis of AML depends on cytogenetic and molecular alterations of malignant hematopoietic progenitor cells. Risk-stratification is based on the World Health Organisation (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues that takes into account published data on the prognostic significance of cytogenetic and molecular alterations.^{2,6,7} In Table 1, AML classification into four prognostic groups are shown; favorable (overall survival of almost 70%), intermediate-I, intermediate-II and adverse (overall survival of less than 20%), with their respective 3-year disease free and overall survival rates. Although AML occurs at all ages, it mainly affects the elderly; the average age of patients at disease onset was 68 years in a large Dutch cohort.^{1,8} Treatment outcomes for patients younger than 60 years of age have improved over the last decades to five-year survival rates of 40 – 50%, but this can be mainly ascribed to significantly improved supportive care.^{1-4,6,7} Only 33% of older patients with AML receive any form of chemotherapy, with the remaining patients unfit for treatment.^{1,4,9} Due to this low percentage of older patients receiving chemotherapy, the higher risk of therapy-related complications and the higher incidence of poor-risk disease, the survival rates of the elderly have hardly improved over the last decades with a median five-year survival of only 10%.^{1,2,8,10}

Table 1. AML classification into four genetic groups according to the 2008 revised World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues^{2,9}

Genetic group	Subsets	CR	DFS (3 yrs)	OS (3 yrs)
Favorable	t(8;21)(q22;q22);			
	<i>RUNX1-RUNX1T1</i>			
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22);	Age<60: 96%	Age<60: 55%	Age<60: 66%
	<i>CBFB-MYH11</i>	Age>60: 83%	Age>60: 24%	Age>60: 33%
	Mutated <i>NPM1</i>			
	without <i>FLT3-ITD</i> *			
	Mutated <i>CEBPA</i> *			
Intermediate-I	Mutated <i>NPM1</i>			
	and <i>FLT3-ITD</i> *			
	Wild-type <i>NPM1</i>	Age<60: 76%	Age<60: 23%	Age<60: 28%
	and <i>FLT3-ITD</i> *	Age>60: 61%	Age>60: 10%	Age>60: 11%
	Wild-type <i>NPM1</i>			
	without <i>FLT3-ITD</i> *			
Intermediate-II	t(9;11)(p22;q23); <i>MLL3-MLL</i>	Age<60: 79%	Age<60: 34%	Age<60: 45%
	Cytogenetic abnormalities not classified as favorable or adverse	Age>60: 63%	Age>60: 11%	Age>60: 16%
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2);			
	<i>RPN1-EVI1</i>			
	t(6;9)(p23;q34);	Age<60: 50%	Age<60: 10%	Age<60: 12%
	<i>DEK-NUP214</i>	Age>60: 39%	Age>60: 6%	Age>60: 3%
	t(v;11)(v;q23);			
	<i>MLL</i> rearranged			
	-5 or del(5q); -7; abn(17p); complex karyo- type**			

CR: complete remission; DFS: disease free survival; OS: overall survival; * normal karyotype; ** three or more other chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions.

Myelodysplastic syndrome (MDS) is a myeloid neoplasm with stem-cell-derived clonal myelopoiesis, altered proliferation and differentiation.^{2,10} This heterogeneous group of diseases is characterized by cytopenia, dysplasia in one or more of the myeloid lineages, ineffective hematopoiesis and an increased risk to develop AML. Fifteen percent of MDS cases can be related to prior cancer treatment consisting of radio- and chemotherapy.^{11,12} Minimal criteria

to diagnose MDS are the presence of 10% or more dysplastic cells in bone marrow or blood within a specific myeloid lineage, and exclusion of AML. The distinction between MDS and AML is defined by the amount of malignant blasts present in the bone marrow; in MDS this proportion is lower than 20%.^{2,9,10,13,14} MDS is categorized using the WHO Classification.² With the revised International Prognostic Scoring System (IPSS-R) very low, low, intermediate, high and very high risk groups can be defined based on cytogenetic aberrations, percentage of myeloblasts in bone marrow, hemoglobin, absolute neutrophil count (ANC) and thrombocyte levels (Tables 2 and 3).¹⁴ The average age at diagnosis of MDS exceeds 70 years, and therefore intensive therapy is not applicable for most patients.^{10,14} Overall survival is 4,5 years.^{3,11}

Table 2. The revised International Prognostic Scoring System (IPSS-R) for MDS^{2,9}

Points:	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
Bone marrow blasts (%)	≤ 2	-	2- 5	-	5-10	> 10	-
Hemoglobin	> 10	-	8-10	< 8	-	-	-
Platelets	≥ 100	50-100	< 50	-	-	-	-
ANC	≥ 0.8	< 0.8	-	-	-	-	-

Cytogenetics: *very good*: -Y, del(11q); *good*: del(5q), del(12p), del(20q), double including del(5q); *intermediate*: del(7q), +8, +19, i(17q), any other single or double independent clones; *poor*: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities; *very poor*: complex: >3 abnormalities

Table 3. MDS risk stratification based on scoring in table 2.

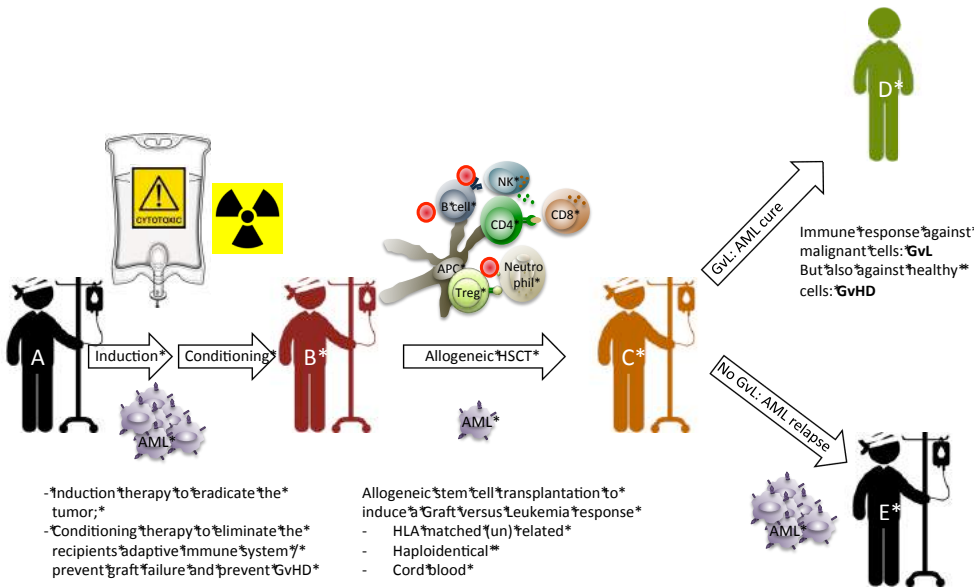
	Risk score	Patients (%)	Median survival (yrs)
Very low	≤ 1,5	19	8,8
Low	> 1,5-3	38	5,3
Intermediate	3-4,5	20	3,0
High	4,5-6	13	1,6
Very high	> 6	10	0,8

In this thesis the focus has been on AML and high risk MDS (MDS-RAEB I and MDS-RAEB II), classified according to the 2008 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. In 2016 this classification was revised.⁹

Allogeneic hematopoietic stem cell transplantation

Treatment of AML and high risk MDS typically involves two cycles of intensive chemotherapy, to maximally reduce tumor load, followed by allogeneic HSCT to eradicate residual disease and maintain complete remission. In the 70's and 80's it became clear that the curative effect of allogeneic HSCT does not depend on the replacement of diseased bone marrow, but on the immune disparity between donor and patient to allow graft versus leukemia (GvL) immune responses.^{15,16} Allogeneic HSCT can in fact be considered as immunotherapy (figure 1) and when this was realized reduced intensity induction conditioning regimens (RIC or RIST (reduced intensity conditioning or - stem cell transplantation) were developed, that solely rely on the induction of anti-leukemia immune responses by the graft. The use of less intense (non-myeloablative) conditioning regimens made more patients eligible to receive an allogeneic HSCT, including the elderly and patients with co-morbidities.^{15,17}

Figure 1. Schematic overview of the treatment of a patient diagnosed with AML



A patient diagnosed with AML is first treated with chemotherapy to maximally reduce tumor load (A). Chemotherapy and radiotherapy induce tissue damage to which the immune system responds and this results in an overall inflamed state of the body (B). The patient then undergoes allogeneic HSCT (C). If donor immune cells recognize and eliminate the remaining leukemic cells (graft versus leukemia (GvL) response) she is cured. This most often happens at the cost of graft versus host disease (GvHD) (D). If no allo-immune response against residual leukemic cells is induced, AML will relapse (E).

Graft versus leukemia and graft versus host immune responses

Thus, allogeneic HSCT is an effective treatment for AML and MDS, when transplanted immune cells from the donor produce strong immunological responses against non-self tumor cells (GvL). Although allogeneic HSCT is curative in significant numbers of patients, transplantation related complications such as graft versus host disease (GvHD; a donor-immune response against non-malignant recipient cells) and opportunistic infections account for 15-30% mortality.^{3,17} GvHD and GvL immune responses involve a complex not yet completely understood cascade of interactions between donor and host innate and adaptive immune systems, reviewed by Jenq and Van den Brink in 2010.¹⁵

Initiating events include recipient conditioning with chemotherapy and radiation that cause damage to host tissues. This leads to release of inflammatory cytokines and danger associated molecular pattern molecules (DAMPs) as well as translocation of microbial products from the intestine, which altogether leads to the activation of innate immune cells.^{15,18,19} The second phase involves the activation and proliferation of antigen presenting cells (APCs) like dendritic cells, macrophages and B cells. Dendritic cells for example take up antigens and upon interaction with T cells mature to become professional APCs that migrate to secondary lymphoid tissues where they activate the adaptive immune system by presenting peptides from damaged cells to T cells in a major histocompatibility complex (MHC) restricted manner: CD8 cytotoxic lymphocytes via MHC-I and CD4 T cells via MHC-II. Macrophages need interferon gamma (IFN γ) stimulation, secreted by T helper cells, cytotoxic T cells, natural killer (NK) cells and innate lymphoid cells type 1 (ILC1) to phagocytose antigens and present peptides in an MHC-II restricted way. B cells can also function as APC, via internalization of soluble antigens that are specifically bound to their unique B cell receptor via receptor-mediated endocytosis. APCs subsequently initiate an effector phase by activating T cells, B cells and by further recruitment of innate effector cells.^{15,20} These events cumulate in GvHD while in the same cascade of immunological events residual tumor cells are sampled and provoke GvL responses.^{15,21,22}

Box 1 | Innate immune cells involved in GvL responses

Dendritic cells	Present antigen to lymphocytes leading to activation of these cells
Macrophages	Phagocytic cells that are critical in innate immunity but can also activate the adaptive immune system
NK cells	Cytotoxic lymphocytes. Express a killer inhibitory-receptor (KIR), important in GvL

The observation that lymphocyte depletion of the graft for example by antibodies directed against CD52 (alemtuzumab) did prevent GvHD at the expense of disease relapse (loss of GvL responses) demonstrated the importance of lymphocytes in allo-immune responses.^{18,19,23} T cells are believed to be the main players in GvL responses. T cell responses are for example directed against human telomerase reverse transcriptase (hTERT), mucin 1 (MUC1), survivin, Wilms tumor protein 1 (WT1), melanoma-associated antigen (MAGE), melanoma antigen preferentially expressed in tumors (PRAME) and renal tumor antigen 1 (RAGE-1) (reviewed by Anguille et al, 2012),^{20,24-26} and minor histocompatibility antigens. Minor histocompatibility antigens (mHA) are distinct HLA-binding peptides encoded by polymorphic genes that differ between the donor and recipient and such mismatch has been associated with GvL responses.^{21,22,27-30} Other lymphocyte subsets such as NK cells are also involved. NK cells express killer cell immunoglobulin like receptors (KIRs) that interact with HLA-class I alleles, referred to as KIR ligands, expressed on immune and non-immune system cells. Interactions between KIRs and their ligands licenses NK cells to full responsiveness but prevents killing of KIR-ligand expressing cells. The most well-known KIR ligands are HLA molecules.³¹ Tumor cells that have down-regulated KIR ligands, or that express KIR ligands not matching with donor KIR receptors as is the case in GvL are killed by these licensed NK cells.²³⁻²⁶

Box 2 | Adaptive immune cells involved in GvL response

- T cells
- CD4 (helper) cells** produce cytokines, support B cell antibody class switching and activate and assist cytotoxic T cells.
 - CD8 (cytotoxic) cells** recognize specific antigens in an MHC-I restricted manner and destroy these cells. They also produce IFN γ .
 - Regulatory cells (Treg)** maintain tolerance to self-antigens; suppress or down-regulate induction and proliferation of effector T cells.
- B cells
- Antigen presenting cells (APCs)**, B cell receptor specific antigen presentation.
 - Memory cells**, antigen experienced B cells that can rapidly be re-engaged when the same antigen is encountered.
 - Plasma cells** produce large amounts of monoclonal antibodies directed at one specific antigen.

The role of B lymphocytes in allogeneic HSCT

In the context of GvL responses, bone marrow derived lymphocytes, also known as B-lymphocytes or B cells, have received less attention compared to T cells and NK cells. B cells express antigen receptors that do not function in an HLA or MHC restricted manner. Upon activation, B cells differentiate into antibody producing plasma cells. Antibodies are specific for their target protein; upon binding, they neutralize this target (for example in case of viruses) or opsonize target cells to be recognized and eliminated by effector cells such as NK cells, neutrophils and macrophages.^{27-30,32}

Several groups have demonstrated the presence of chronic myeloid leukemia (CML) and AML-specific antibody responses after allogeneic HSCT, using serological analysis of recombinant cDNA expression libraries (SEREX) and protein micro-arrays.^{20,30,33,34} CML in particular is immunogenic and donor lymphocyte infusions (DLI) to treat relapsed CML have been associated with long-term disease remissions. After DLI, antibodies against CML28, CML66 and related adhesion focal tyrosine kinase (RAFTK) appeared that were associated with favourable CML outcomes.^{23,33,35-37} In AML patients, antibodies against M-Phase Phosphoprotein 11 (MPP11),³⁸ nucleolar and spindle associated protein 1 (NuSAP1), an antigen predominately expressed by CD34+CD90+ hematopoietic stem cells and leukemic cells, against angiogenic cytokines and others were detected after allogeneic HSCT.^{30,39} Finally, paternal HLA has been suggested to serve as an antigen in GvL B cell responses. Leukemia free survival was improved in haplo-identical HSCT recipients who received stem cells from their mother, compared to patients who received haplo-identical stem cell transplants of other family members, and antibodies against paternal antigens were present in these patients.^{23,35}

While these data suggest that B cells and antibodies are associated with GvL responses, the technologies used in these studies did not allow for functional testing of these antibodies. The actual contribution of leukemia-associated antibodies to GvL responses remains therefore unknown.

Outline of the thesis

The overall aim of this thesis was to study the role of B cells and the antibodies they produce in GvL responses after allogeneic HSCT. In this chapter (**Chapter 1**) a general introduction to AML, the immune system and allo-immune responses after allogeneic HSCT is presented. **Chapter 2** describes the case report of a patient who developed AML relapse after he had been treated with rituximab, a B cell depleting agent, for severe graft versus host disease. We demonstrated the presence of AML specific antibody-producing B cells at the time of maximal AML suppression. In **Chapter 3** we showed in a larger group of AML patients that allogeneic HSCT recipients developed tumor-specific antibodies. Some of these antibodies were directed against the U5 snRNP200 protein complex, a component of the spliceosome that is normally expressed intracellular but is expressed on the cell membrane by AML blasts. U5 snRNP200 complex antibodies are cytotoxic; upon interaction with U5 snRNP200 complex expressing AML blasts they kill these cells. To reliably quantify cytotoxic antibody activity we developed the modified FACS calcein AM retention assay: a high throughput flow cytometer based method to quantify cell death induced by cytotoxic antibodies, complement dependent cell death (CDC) or antibody dependent cellular cytotoxicity (ADCC) (**Chapter 4**). In **Chapter 5** we describe one of the other antibodies that we identified by screening the donor B cell repertoire of AML survivors. This antibody, AT1413, targets a specific glycoform of CD43 (CD43s) that is overexpressed by malignant myeloid cells of all WHO 2008 AML and MDS types. Interaction of AT1413 with target cells killed AML blasts in vitro and in vivo. AT1413 therefore has high potential as a therapeutic antibody in AML and high-risk MDS. In **Chapter 6** the role of B cells in GvL responses is reviewed and put in the larger perspective of tumor-immunology and tumor-immunotherapy. **Chapter 7** is the English summary and epilogue to this thesis with a personal note and speculation on future treatment options of AML and high risk MDS. **Chapter 8** summarizes this thesis in Dutch. At the end of the thesis **five appendixes** can be found including a list of authors and affiliations, a portfolio, the author's list of publications and curriculum vitae and finally a word of thanks to everyone who made this thesis possible.

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