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Epidemiology and Biology of Relapse after Stem Cell Transplantation

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Introduction

Relapse after autologous or allogeneic hematopoietic stem cell transplantation has become the most frequent cause of treatment failure. The 3rd International Workshop on Biology, Prevention, and Treatment of Relapse after Stem Cell Transplantation held in Hamburg / Germany in November 2016 under the auspices of EBMT and ASBMT aimed to provide an update about development and achievements which have been obtained since the 1st workshop in 2009 and the 2nd in 2012.

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Here, this review summarized epidemiology of relapse (M.H.), the role of microenvironment (H.S.) and tumor stem cells in the biology of relapse (A.E. / O.H. / J.V.) as well as the role of HLA loss as tumor escape mechanisms (L.V. / C.T.).

Epidemiology of posttransplant relapse: have we made any progress?

More than a million hematopoietic stem cell transplantations (HCTs) have been done since the first successful ones in 1968, with about 50,000 done annually, worldwide.¹ Especially the number of transplantations is growing outside North America and Europe.² Although initially used to treat non-malignant marrow disorders like primary immune deficiencies and aplastic anemia, most of the HCTs in the current era treat malignant disorders, primarily blood cancers. While long acknowledged to be curative, at least in some patients, in situations where conventional chemotherapy is ineffective, application of HCT for malignancy increased only slowly when first introduced in the 1970s. Recent years witnessed increased utilization, primarily due to expanded donor and graft sources, less toxic pretransplant conditioning and better supportive care leading to better outcomes, even in older and sicker patients. There is little doubt that HCT can now be done more safely, with reported rates of transplant-related mortality decreasing from about 50% in the 1970s to as low as 10% in certain patient groups in the current era.^{3,4,5,6,7} According to data from the Center for International Blood and Marrow Transplant Research (CIBMTR), transplant-related events such as graft-versus-host disease, Infection and organ toxicity or second cancers accounted for 30%, 52%, 43%, 63% or 57% of posttransplant deaths in patients receiving autologous, HLA-identical sibling, HLA-mismatched related, unrelated donor or unrelated cord blood HCTs, respectively, for leukemia, multiple myeloma or lymphoma in 2012–13 (Figure 1). Corresponding rates for the proportion of deaths related to relapse were 70%, 48%, 57%, 37% and 43% (Figure 1).

The proportion of deaths due to relapse is disappointing, given that control of malignancy was the indication for all of these HCTs and raises the question of whether we have made any progress in exploiting and enhancing the anti-cancer efficacy of HCT over the past three decades. To address this question, we analyzed data for 308,745 patients reported to the CIBMTR. These patients underwent HCT in 1980–2014 for acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia, lymphoma or multiple myeloma. Patient characteristics are shown in Table 1. We calculated the five-year rates of transplant-related mortality (TRM, defined as death occurring in the absence of relapse or progression), relapse and treatment failure (defined as occurrence of relapse or TRM or 1 - progression-free survival) by decade, for the entire cohort and for subsets defined by patient and disease characteristics. Figure 2 shows the five year rates of these outcomes according to the decade of transplantation, with Figure 2A depicting trends after allotransplantation and 2B after autotransplantation. The risk of TRM decreased over time, while the risk of relapse increased, for both auto- and alloHCTs. Overall treatment failure rates were relatively stable. Of course, the kinds of patients and diseases treated changed substantially over this 35-year period as is evident from Table 1. Additionally, reduced intensity conditioning, which decreases the toxicity of allotransplantation but may increase relapse, was used with frequency only after 2000, which might account for higher relapse risks after recent allografts. To mitigate the confounding effects of these changes in

assessing trends in efficacy and toxicity, we examined outcomes in a group of patients whose eligibility for transplantation was relatively similar over the 25-year study period. For allogeneic transplantation, we chose adults, ages 20–45, transplanted for AML in first complete remission with myeloablative conditioning. For autotransplants, we chose adults, ages 20–45 years, transplanted for chemosensitive non-Hodgkin lymphoma. Figures 2 and 3 show five-years outcomes for these more restricted groups of patients. Again, we see decreasing rates of TRM but increasing rates of relapse, with lesser changes in rates of treatment failure.

What does this all mean? First of all it is a picture, even in the subset analysis, painted with broad strokes. We did not adjust for every factor that might influence either TRM or relapse risk and one can certainly find subgroups with both lower TRM and lower relapse risks than those depicted in these graphs. Additionally, the variables available for analysis across the time periods were insufficient to fully characterize the biology of the diseases transplanted. For example, as cure rates with intensive chemotherapy regimens for childhood ALL increase, the population referred for transplantation undoubtedly has disease that is biologically more aggressive and more difficult to cure, regardless of the therapy. Similarly, our ability to identify molecular abnormalities associated with prognosis means that those with good prognosis mutations (e.g., NPM1 mutations in AML) are less likely to be transplanted and those with poor prognosis mutations (e.g. FLT3 mutations) are more likely to be transplanted. But that was not the purpose of the exercise, which aimed to show, overall, in the broad population of patients undergoing transplantation, the impact of more than three decades of evolution and dedicated basic and clinical research to improve the outcomes of HCT. And there is cause for satisfaction, in that HCT has become a much safer procedure and is now available to in many more patients than was the case in the 1980s. Most of these patients have few effective alternatives. Do these data mean that increasing safety decreased the antitumor efficacy of HCT? Well, it is possible that is the case for some interventions but mostly it is a case of competing risks, defined as events where the occurrence of one precludes the occurrence of the other. Eliminating the incidence of one competing risk will inevitably increase the frequency of the other, even if the *underlying risk* of the other event does not change. All of the patients who now do not die early of GVHD or regimen-related toxicity remain at risk of relapse. On the other hand, the data suggest that, overall, we have not *increased* the anti-tumor efficacy of HCT in a meaningful way. However, given the better safety profile of HCT in general, our increasing understanding of the biology of the diseases we treat and of the mechanisms of posttransplant relapse and availability of new agents, both drugs and cellular therapies, we may now be poised to make the same kind of progress with relapse that we have seen in TRM. In assessing strategies to improve the efficacy of HCT, we must understand that success of a specific strategy will often be disease- and sub-disease specific. Even the long-recognized graft-versus-tumor effects of GVHD differ in different diseases as shown in both historic and recent studies.^{8,9,10,11} Evaluation of maintenance therapies that target specific mutations or tumor types must be studied in a target-specific way, which will require collaboration of many centers. Although the disease-risk index¹² is a useful tool for categorizing the disease-related prognoses of patients across multiple diseases, such grouping may not be ideal to elucidate differential effects of specific agents in diseases with very different biology. And both the

diseases treated and the specific drugs used may influence the impact of “dose-intensity”, which may account for the differences across studies evaluating the use myeloablative versus reduced intensity conditioning regimens. Finally, strategies may have to be different for autologous versus allogeneic HCT, or for regimens that use specific GVHD prevention strategies, e.g. post-transplant cyclophosphamide versus T-cell depletion versus standard calcineurin inhibitor based approaches. The challenges are great but no greater than the challenges of decreasing TRM and increasing donor availability, in which we have made so much progress over the past three decades.

Role of microenvironment

As stated above, relapse has become a frequent cause of failure of stem cell transplantation, and rates of failure have remained stable. Thus, novel approaches are clearly needed. We propose to target leukemia cells and their stromal microenvironment with T cells recognizing cancer-specific mutations. Key support for this powerful and exciting concept comes from (i) a much advanced understanding of leukemia and its cancer microenvironment, (ii) the affordability of defining the complete set of expressed truly cancer-specific mutations for any given patient, and (iii) mutation-specific T cell responses emerging as the unifying principle of the most effective immunotherapy not only in mice but also in humans.¹³

Several past studies have laid the groundwork for the new concept: (i) Niches in the bone marrow microenvironment have been defined that either promote or prevent cancer relapse after allogeneic stem cell transplantation.¹⁴ (ii) The number of minor histocompatibility antigens (mHA) as the primary targets of GVL effects¹⁵ is continuously increasing (now over 50).¹⁶ Some mHAs are preferentially expressed by the hematopoietic system, and T cells may target them as self- or allo-restricted peptide.¹⁷ Allo-MHC restricted T cells can overcome problems of self tolerance to self antigens such as mHA¹⁷ and may have higher affinity TCRs. However, neither more mHA targets nor higher avidity T cells are likely to reduce the danger of provoking GVHD. (iii) Many ongoing efforts focus on generating small molecule inhibitors that can target selectively cancer-specific mutations. So far however, even clinically effective drugs are not truly cancer-specific; for example, imatinib inhibits the normal Abelson kinase not just the BCR-ABL fusion protein.¹⁸ Therefore, no current approach targets cancer cells or their stromal microenvironment¹⁹ in a truly cancer-specific way.

By contrast, T cell receptors can recognize with an astounding and exquisite specificity single amino acid substitutions caused by a single nucleotide substitution leaving normal cells completely untouched because they express only the non-mutant peptide.^{20,21} There are usually 12 different MHC molecules in a patient to present somatic cancer-specific mutations that are recognizable by CD4⁺ or CD8⁺ T cells. Thus there is a large number of possible mutation-specific targets even though the absolute number of somatic mutations (10–20) in leukemias such as AML, ALL, and CLL is low compared to that observed in adult solid tumors (see below).^{22,23,24} Although different cancer patients may have mutations in the same genes, the sequence encoding a mutant peptides is rarely shared between patients. Therefore a truly individualized approach is required. The power of MHC

class II-restricted CD4⁺ T cells in GVL and GVHD has been increasingly appreciated²⁵, encouraging us to focus on targeting cancer mutation-specific MHC-Class II restricted epitopes. The bone marrow microenvironment seems to be ideal for this approach since it constitutively expresses MHC Class II on stromal cells.²⁶ Considering the crucial role of the microenvironment for leukemic cell survival and escape¹⁴, it is obvious that targeting cancer stroma could be used to eradicate residual cancer cells. Destroying the stromal bone marrow microenvironment in which the leukemia cells reside would be restricted to the immediate vicinity of the cancer cells. Reasons for this specificity is that sufficient amounts of mutant antigen are needed for sensitizing the stromal cells for destruction. Such amounts occur only in the stromal cells directly surrounding the cancer cells. Thus, experimental evidence indicates^{27,28,29} that non-malignant stroma cells pick up and cross-present cancer-specific target molecules released from neighboring cancer cells. These molecules include neoantigens encoded by nsSNV or other cancer-specific mutations.^{20,21} Thus, by eradicating the stromal niches in which cancer cells hide, T cells can eradicate cancer cells and prevent relapse.^{27,28,29,30}

The cancer microenvironment consists of non-malignant cells and extracellular matrix in which cancer cells are embedded (for review see³¹). A synonym for microenvironment is “stroma” which literally means “bed” in ancient Greek. However, cancer stroma is far more than just a physical structure holding the cancer cells. Instead, cancer stroma is essential not only for cancer cells to grow and escape but also for their eradication.³² All cancer cells depend on being surrounded by nonmalignant stromal cells. Thus, cancer cells attract the stromal cells and instruct them with very specific signals to provide factors and conditions that the cancer cells need to survive, proliferate and invade. This regulatory circuit is often being referred to as a paracrine stimulatory loop.^{33,34,35,36,37,38}

Cancer stroma has three major cellular components, (i) neutrophils and macrophages derived from bone marrow-derived, circulating blood leukocytes^{27,36}, (ii) fibroblasts derived from sessile (local) not circulating precursors³⁸, and (iii) endothelial cells, also derived from sessile precursors.³⁷ All of the three cell types neutrophils^{33,34,35,39,40} macrophages^{41,42}, endothelial cells⁴³ as well as fibroblasts³⁸ (for review see⁴⁴), play key roles in the stroma of cancers. Several lines of evidence suggest that fibroblasts differ in function dependent on their anatomic site from which they originate.^{44,45} This means cancer cells may disseminate to many sites but not be able to induce the fibroblast stroma conducive to survival and formation of metastasis. This may well be the basis for Paget’s 1889 seed and soil hypothesis (for review see³⁸).

The details of the mechanisms whereby stromal destruction eradicates cancer cells are not yet fully understood. However, it is clear from chimera experiments that the BM- as well as the non-BM-derived compartments must (i) both be targeted by the T cells, (ii) express the receptors for TNF as well as IFN- γ ²⁹ and (iii) express the relevant MHC class I and/or II molecules.^{27,29,46,47} Surprisingly, cancer cell destruction can be very effective even when the cancer-specific antigen is exclusively being cross-presented on the stromal cell and not directly recognizable on the cancer cell.⁴⁸ This is important since cancer cells can lose or lack the MHC Class I or MHC Class II molecules (see below). Thus, indirect presentation leads to highly specific eradication of cancer cells.^{46,48} The mechanisms involved may be

related to a remarkable experimental observation: recipient CD8⁺ T cells recognizing alloantigen cross-presented on neighboring stromal cells eliminated allogeneic MHC Class I negative bone marrow stem cells while leaving the syngeneic, also MHC Class I negative bone marrow stem cells completely unharmed.⁴⁹ Single neoepitopes⁵⁰ may require the collaboration of CD4⁺ as well as CD8⁺ T cells at the effector phase^{46,48} for effective neoantigen-specific stromal destruction. In any case, T cell receptors exquisitely specific for mutant neoantigen can be expressed on T cells that are then adoptively transferred to eradicate advanced long established cancers.⁵⁰ These T cells will destroy the niches in which residual cancer cells hide and achieve curative treatment, provided that the targeted mutant neoantigen is sufficiently cross-presented by the adjacent stromal cells. In principle, donors of the allogeneic stem cell transplants and/of the patients could also be vaccinated against mutant-antigens in an effort to prevent cancer relapse. These highly patient-individualized approaches are currently being pursued by vaccinating melanoma patients using RNA based vectors⁵¹ or long peptides⁵² encoding the mutant neoepitopes. Even if these active vaccinations should prove therapeutically ineffective, they could serve to generate T cells and isolate mutation-specific TCRs. These TCRs could then be used in mutation-specific TCR gene therapy.²¹ So-far this approach has only been tested in mice even though it had remarkable therapeutic effects. Stem cell transplantation offers excellent opportunities to pioneer such studies in patients, and these truly novel approaches may well make a significant impact reducing cancer relapse.

The role of tumor stem cells in the biology of relapse

Identification of the cells responsible for long-term tumor propagation is critical to determine which cells must be targeted to ensure disease eradication and prevent relapse. It has been established that some cancers, such as acute myeloid leukemia, follow a hierarchical stem cell model, whereby the tumor is driven by a subpopulation of rare cells with intrinsically defined stem cell properties.^{53,54} In contrast, the stem cell frequency in tumors such as melanoma is substantially higher.⁵⁵ This points towards a stochastic model of tumor propagation, in which a high proportion of tumor cells have the capacity to drive tumor growth.

In acute lymphoblastic leukemia (ALL), the bulk of the evidence suggests that the disease follows a stochastic model. We have previously shown that blasts with the capability to reconstitute the leukemia are found in populations with mature and immature immunophenotypes.⁵⁶ Limiting dilution assays also showed high leukemia-initiating cell (LIC) frequencies in ALL (1:40 to 1:2900 cells).⁵⁷ More recently, we have used clonal tracking to demonstrate that xenografted ALL is driven by high numbers of functionally homogeneous founder cells which maintain the leukemia over serial transplants.⁵⁸ Taken together, these data support a model where a majority of blasts can propagate the disease. This is not entirely surprising given the capacity of normal mature lymphoid cells to clonally expand. In acute myeloid leukemia (AML), the story is different and there is indeed strong evidence for a stem hierarchy with a small population of specialized leukemic stem cells that maintain and propagate the disease.⁵⁹ However, there is also significant variability in respect to phenotype and frequency of the cells that can propagate the leukemia.^{60,61}

The ability for self-renewal is intertwined with intrinsic and extrinsic factors which influence the propagating capacity of LIC.^{60,61} Analysis of copy number alterations has demonstrated that ALL samples consist of a pool of genetically distinct subclones, commonly related by Darwinian evolutionary trees.^{62,63} These subclones may differ in their leukemia repopulating capacity, leading to changes in the composition of the propagating pool.^{64,65} When subjected to pressures such as therapy, this process of clonal evolution can lead to the emergence of resistant clones which drive relapse.^{66,67,68} A complete model for the evolution of relapse must unify the elements discussed above. A typical leukemia is likely to consist of several genetically distinct subclones, with varying numbers of LIC suggesting that often a high proportion of the individual cells comprising these subclones will be capable of propagating the leukemia. This will provide an abundance of potential units for clonal selection and evolution. The evolutionary process provides a means for blasts to gain advantageous mutations in response to selective pressures, which combined with selection of fitter pre-existing clones may lead to the emergence of therapy resistant clones and relapse.⁶⁹

In addition to intrinsic genetic differences, the role of extrinsic factors such as the microenvironment must be considered. Leukemic blasts are known to modulate the bone marrow environment⁷⁰ which can lead to drug resistance in response to therapy.⁷¹ A recent study has demonstrated rare dormant, treatment resistant stem cells. Notably in ALL, resistance is dependent on interactions with the endosteal niche; release from this environment induced proliferation and sensitised the cells to drug treatment.⁷² This work demonstrates the influence of the microenvironment on the behaviour of leukemic blasts in a manner which appears to be stochastic.

It is therefore important to consider the role of the microenvironment in protecting cells from chemotherapy. Although this alone does not explain the emergence of drug resistant relapse, it will facilitate development of resistant phenotypes in cells which survive chemotherapy, which may be enhanced by epigenetic reprogramming.⁷³ It is highly likely that these processes of niche remodelling and epigenetic plasticity are relevant in allowing cells to survive graft vs leukemia effects and immune-targeted therapies.⁷⁴ Escape mutants to CAR T-cells or monoclonal antibodies such as blinatumomab have been commonly reported^{75,76,77} and although some may have a genetic basis, it is well established that tumor microenvironments can influence the function of immune effector cells.⁷⁸

Future therapies must utilise underlying mechanistic understanding to rationally design therapeutic combinations which target both all leukemic blasts with self-renewal potential and specific pathways involved in the emergence of (intrinsically and extrinsically) treatment-resistant subclones. This will also require a thorough characterisation of interactions between leukemic cells and their niche, with the aim of disrupting pathways which facilitate the survival and selection of LIC.

Role of HLA loss

Mutation, downregulation or complete genomic loss of Human Leukocyte Antigen (HLA) molecules is commonly observed in newly-diagnosed solid tumors, suggesting that these

cancers become clinically evident only after having gained a means to evade T cell-mediated immune surveillance.^{79,80,81} Conversely, hematological malignancies rarely display alterations in HLA molecules at clinical presentation, with the exception of some rare subtypes.^{82,83} This observation suggests that either hematological tumors are more sensitive to the activity of Natural Killer cells, endowed with the ability to recognize and eliminate cells that have lost HLA Class I expression, or develop too rapidly and aggressively to be significantly edited by the patient immune system.

Nevertheless, patients suffering from hematological cancers are exposed to potent immune pressure when they undergo allogeneic hematopoietic stem cell transplantation (HSCT). Allogeneic HSCT is in fact universally recognized as a highly effective and broad-spectrum form of adoptive immunotherapy, in which donor-derived immune cells recognize not only tumor-specific antigens, but even more potently minor histocompatibility antigens or, in case of partially HLA-incompatible HSCT, the patient-specific HLA molecules.^{84,85} In particular, in the context of haploidentical family donor HSCT, donor T cells are preferentially unleashed against the fully mismatched HLA haplotype, and their potent primary alloreactivity, if not controlled, can rapidly lead to fatal graft-versus-host disease.⁸⁶

In this highly peculiar immunogenetic context, we first described that after HSCT residual leukemic cells can undergo genomic loss of the mismatched HLA haplotype to evade the control operated by alloreactive donor T cells and outgrow into clinical relapse.⁸⁷ This event, termed “HLA loss” henceforth, is the consequence of acquired uniparental disomy (also called copy-neutral loss of heterozygosity, cnLOH) of a large genomic region of chromosome 6p, often encompassing all HLA class I and class II loci. Of notice, by this mechanism not only the leukemic cells lose the main targets of donor T cell alloreactivity and render itself “invisible” to circulating T cells, but also conserve a physiological copy number of HLA class I genes, thereby limiting the activation of NK cell-mediated responses.^{88,89} (see figure 4)

Of interest, in all cases analyzed to date the HLA loss leukemic clone was not evident before HSCT, suggesting that it was either generated after transplant or present as a minimal fraction of the leukemic bulk in the absence of immune pressure, and providing a remarkable proof-of-concept on the ability of leukemic cells to evolve in a selective environment.

After the initial report, we and others extended the observation of HLA loss relapses to different HSCT contexts and diseases.^{90,91,92,93} The highest incidence has been reported in T cell-replete haploidentical HSCTs for myeloid malignancies, in which HLA loss relapses can account for up to one third of the total relapses, and have been shown to be significantly linked to the dose of donor T cells infused into the patient and to the occurrence of chronic GvHD after HSCT.^{94,95} Notably, HLA loss relapses have been recently reported to occur with similar frequency also after haploidentical HSCTs employing post-transplant cyclophosphamide (PT-Cy) as GvHD prophylaxis.^{96,97,98} This finding suggests that even though PT-Cy can dramatically decrease the risk of severe GvHD after haploidentical HSCT, it does not eliminate T cell alloreactivity against the partially HLA-mismatched leukemia.

The considerable incidence of HLA loss relapses documented in T cell-replete haploidentical transplants, together with the absence of a clear association between NK cell alloreactivity and protection from these relapse variants⁹⁴, support the notion that whereas in T cell-depleted haploidentical transplants NK cell alloreactivity represents the main driver of the Graft-versus-Leukemia (GvL) effect, its role in the most recent platforms of haploidentical HSCT is blunted by competition with T cells⁸⁷ or by the concomitant drugs⁹⁹ and alloreactive T cells appear to be the main GvL mediators in this setting.

Cases of HLA loss have been reported also after partially HLA-mismatched unrelated donor HSCT.^{100,101} However, these studies (and others that failed to detect HLA loss variants in similar settings^{94,102}) were all conducted in very small and heterogeneous cohorts. Therefore, it is to date impossible to accurately estimate the actual frequency and associated risk factors for HLA loss in unrelated donor HSCT: we might however speculate that the incidence of HLA loss relapses might be lower than in haploidentical HSCT, due to the fact that in unrelated donor HSCT donor-recipient HLA mismatches are commonly fewer than in the haploidentical setting and, if present, can involve both patient HLA haplotypes, balancing the selective pressure mediated by donor alloreactive T cells and blocking escape routes to leukemic cells. However, larger multicenter studies are warranted to confirm this hypothesis, including also the study of relapses after umbilical cord blood transplantation, to date totally unexplored.

It is important to note that the documentation of HLA loss at relapse is not merely a biological curiosity, but has relevant and direct clinical implications: by losing the main targets of donor T cell alloreactivity, HLA loss variants become in fact less susceptible to respond to donor lymphocyte infusions (DLIs).⁸⁷ For patients with HLA loss relapses it is therefore advised to consider alternative salvage strategies, including re-transplantation from a different donor or cellular therapies based on unconventional target recognition modalities such as for instance chimeric antigen receptor-modified T cells.^{88,103} Assessment of eventual HLA loss before administering therapeutic DLIs at relapse is therefore highly recommended after haploidentical HSCT, in which the phenomenon is remarkably frequent in all reported series, and is at least worth considering for relapses after unrelated donor HSCTs.¹⁰⁴ The recent development of “HLA-KMR”, a reliable and easy-to-implement quantitative PCR-based molecular assay for the detection of HLA loss relapses,¹⁰⁵ will thus not only be instrumental to conduct larger retrospective and prospective studies to analyze the phenomenon in different HSCT settings, but even more importantly will facilitate rapid clinical decision-making and patient-tailored therapeutic interventions.

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Figure 1.
Causes of death among patients transplanted for malignancy in 2012–2013 (Data from the Center for International Blood and Marrow Transplant Research).

Figure 2A-B.

Five-year outcomes after allogeneic hematopoietic stem cell transplantations for hematologic malignancy by decade (Data from the Center for International Blood and Marrow Transplant Research). **(A)** Five-year outcomes (in percents) after autologous hematopoietic stem cell transplantations for hematologic malignancy by decade (Data from the Center for International Blood and Marrow Transplant Research). **(B)**

Figure 3A-B.

Five-year outcomes (in percents) after allogeneic hematopoietic stem cell transplantations for acute myeloid leukemia in first complete remission using myeloablative conditioning in patients aged 20–45 years, by decade (Data from the Center for International Blood and Marrow Transplant Research). **(A)** Five-year outcomes (in percents) after autologous hematopoietic stem cell transplantations for chemosensitive non-Hodgkin lymphoma in patients aged 20–45 years, by decade (Data from the Center for International Blood and Marrow Transplant Research). **(B)**

Figure 4.

Loss of mismatched HLA in leukemic cells after haploidentical HSCT. Schematic model of the causes and consequences of genomic loss of the patient-specific HLA haplotype at relapse after transplantation. Leukemic cells, heterozygous at diagnosis for the shared (in blue) and the mismatched patient-specific (in red) haplotype, are exposed to an intense immunological pressure after transplantation, mostly mediated by donor T cells expressing alloreactive T cell receptors (in green) and targeted against the mismatched HLA haplotype. This selective environment favors the emergence of mutant variants that lack the patient-specific HLA haplotype, and are therefore no longer recognized by donor T lymphocytes.

Table 1.

Characteristics of 308,745 patients receiving their first allogeneic or autologous hematopoietic stem cell transplant for a hematologic malignancy in 1980-2014 and reported to the CIBMTR.

	Year of transplantation			
	1980-89	1990-99	2000-2009	2010-2014
Total N	21,672	89,756	121,892	75,425
Median age				
Allogeneic	27 years	32 years	40 years	51 years
Autologous	33 years	48 years	57 years	58 years
Disease				
Allogeneic				
Acute myeloid leukemia	33%	30%	42%	49%
Myelodysplastic syndromes	2%	5%	10%	15%
Acute lymphoblastic leukemia	29%	22%	22%	21%
Chronic myeloid leukemia	30%	32%	13%	4%
Lymphoma	4%	6%	11%	10%
Multiple myeloma	1%	3%	2%	1%
Autologous				
Acute myeloid leukemia	30%	14%	6%	1%
Acute lymphoblastic leukemia	11%	3%	<1%	<1%
Chronic myeloid leukemia	4%	2%	<1%	<1%
Lymphoma	49%	59%	41%	35%
Multiple myeloma	5%	22%	51%	63%
Myeloablative Conditioning (allogeneic only)	100%	99%	77%	65%