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Therapy Resistance Mechanisms in Hematological Malignancies

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Abbreviations:

AI, artificial intelligence

ALL, acute lymphoblastic leukemia

AML, acute myeloid leukemia

AraC, cytarabine

AraC-TP, Ara-C-triphosphate

BTK, Bruton´s tyrosine kinase

CAR, chimeric antigen receptors

CLL, chronic lymphocytic leukemia

CML, chronic myeloid leukemia

CYP, cytochrome P450

CHIP, clonal hematopoiesis of indeterminate potential

DDR, DNA damage response

DNA, deoxyribonucleic acid

GST, glutathione-*S*-transferase

HPC, hematopoietic progenitor cell

HSC, hematopoietic stem cell

LSC, leukemic stem cell

MM, multiple myeloma

MRD, minimal residual disease

NHEJ, non-homologous end joining

NK, natural killer

PARP, poly-ADB-ribose polymerase

P-gp, P-glycoprotein

SCT, stem cell transplantation

TKI, tyrosine kinase inhibitor

UGT, uridine diphospho-glucuronosyltransferase

VAF, variant allele frequency

Abstract

Hematologic malignancies are model diseases for understanding neoplastic transformation and serve as prototypes for developing effective therapies. Indeed, the concept of systemic cancer therapy originated in hematologic malignancies and has guided the development of chemotherapy, cellular therapies, immunotherapy, and modern precision oncology. Despite significant advances in the treatment of leukemias, lymphomas and multiple myelomas, treatment resistance associated with molecular and clinical relapse remains very common. Therapy of relapsed and refractory disease remains extremely difficult, and failure of disease control at this stage remains the leading cause of mortality in patients with hematologic malignancies. In recent years, many efforts have been made to identify the genetic and epigenetic mechanisms that drive the development of hematologic malignancies to the stage of full-blown disease requiring clinical intervention. In contrast, the mechanisms responsible for treatment resistance in hematologic malignancies remain poorly understood. For example, the molecular characteristics of therapy-resistant persisting cells in minimal residual disease (MRD) remain rather elusive. In this mini-review we want to discuss that cellular heterogeneity and plasticity, together with adaptive genetic and epigenetic processes, lead to reduced sensitivity to various treatment regimens such as chemotherapy and pathway inhibitors such as tyrosine kinase inhibitors. However, resistance mechanisms may be conserved across biologically distinct cancer entities. Recent technological advances have made it possible to explore the underlying mechanisms of therapy resistance with unprecedented resolution and depth. These include novel multi-omics technologies with single cell resolution combined with advanced biocomputational approaches, along with artificial intelligence (AI), and sophisticated disease models for functional validation.

Introduction

Hematological neoplasms remain life-threatening, malignant systemic diseases. Following on from the successful establishment of combination chemotherapy in the 1980s and 1990s, the development of molecular targeted therapies at the beginning of the millennium, and with the current development in the field of immunotherapeutics, such as CAR-T cells, the cure rates for some hematological neoplasms have increased from zero to 50 to 70 % during the last 50 years. Even for multiple myeloma (MM), still incurable in most patients, survival has improved due to several new therapeutic strategies and drug classes. However, therapy resistance now constitutes the major barrier for further improvements towards cure. It is evident that therapy resistance often encompasses not only resistance towards one drug or modality but rather forms a general phenomenon that can render various therapies ineffective. The predominant focus within the field on cellular transformation is shifting towards understanding resistance mechanisms, minimal residual disease and the specifics of relapsed and refractory disease (Figure 1).

Management of therapy resistance remains a major challenge across the whole range of hematological malignancies. Therefore, new approaches to overcome resistance either towards a specific drug or combination treatments following an initially successful therapy are urgently required. Insights into the underlying resistance mechanisms offer the best chance to develop novel strategies with the aim to improve clinical management towards cure for relapsed and refractory patients.

Mechanisms of resistance

Resistance to clinical drugs remains one of the greatest challenges facing chemotherapy and precision oncology today. Figure 2 summarizes important mechanisms of resistance in hematological malignancies as described below.

Two main types of clinical resistance can be distinguished: Patients who do not respond to first line treatment exhibit primary (or intrinsic) resistance, also known as refractory disease. Secondary (or acquired) resistance occurs in patients that respond to treatment at the beginning but develop resistance later on [1]. A plethora of complex biological adaptations can mediate treatment resistance, which can largely be subdivided into cell autonomously controlled molecular mechanisms and cellular strategies involving stem cell identity and interactions with the tumor microenvironment including the immune system. Both groups are overlapping, and therapy resistance mechanisms can often be highly complex involving cellular and molecular features [2].

Drug specific resistance mutations. Next generation sequencing has revolutionized the understanding of genetic cancer drivers and identified numerous mutations leading to cancer initiation, development, maintenance, and progression. Among these are mutations that result in constitutively activated tyrosine-kinases which had driven the development of a large number of tyrosine kinase inhibitors, a number of which are now approved or in clinical evaluation. A classic example is imatinib, which blocks the BCR-ABL kinase driving chronic myeloid leukemia (CML) [3, 4]. Secondary resistance occurs by acquiring mutations that prevent imatinib binding (E255K and M351T) [5], but second (dasatinib, nilotinib) and even third (asciminib, ponatinib) generation inhibitors have been developed to overcome this resistance [6]. Moreover, third generation inhibitors are effective in both wildtype and T315I mutant BCR-ABL [7]. Similar principles have been observed in MM by mutations in CRBN, the intracellular target of lenalidomide and pomalidomide, as well as in chronic lymphocytic leukemia (CLL) or acute lymphoblastic leukemia (ALL) by mutations in Bruton´s tyrosine kinase (BTK), the target of ibritinib, resulting in drug resistance to this major class of drugs [8, 9].

Downstream reactivation of the blocked pathway. This mechanism maintains the activity of the targeted pathway downstream of the block. Examples include the paradoxical activation of the MAPK pathway in, e. g. melanoma and myeloma cells treated with BRAF-inhibitors by acquired concomitant RAS mutation on the one hand [10] and the mutation of PLCG2 following ibrutinib therapy in CLL on the other hand [11]. Identification of those mechanisms has led to the development of combination treatments, e. g. using BRAF- in combination with MEK- inhibitors, which already have entered clinical routine [12].

Activation of compensatory signaling pathway. Alternative pathways can be activated to circumvent the treatment mediated block. Examples include the compensatory up-regulation of multiple receptor kinases (EGFR, IGF1R) in breast cancer treated with HER2-inhibitors or activation of the EGFR receptor in BRAF-inhibitor treated

melanoma cells [13, 14]. Also, compensatory signaling mechanisms can emerge upon tyrosine kinase inhibitor (TKI) treatment in CML [15].

Amplification of the target. A genetic response to pathway inhibitors is genetic amplifications of the target itself which can be observed in some melanoma patients (BRAF-amplification) and also occur in acute myeloid leukemia (AML) patients treated with FLT3-inhibitors. In the latter, STAT1 activation, or NRAS and IDH2 mutations can mediate resistance to FLT3-inhibitors [16, 17].

Drug efflux pumps. Upregulation of the expression of drug efflux pumps such as the multidrug efflux pump P-glycoprotein (P-gp), the product of the ABCB1 (multi-drug resistance 1; MDR1) gene has been described for dozens of tumor types including leukemias and are thought to be at least in part responsible for primary and secondary resistance to chemotherapy. Certain stem cells express these efflux pumps at high level and it is thought that this may contribute to the natural resistance of cancer stem cells to various treatment regimes. However, drugs blocking these transporters have been unsuccessful or had to be stopped due to severe side effects. Thus, the role of efflux pumps in clinical settings remains uncertain [18].

Metabolic inactivation of therapeutic drugs. Drug activation *in vivo* involves complex mechanisms in which substances interact with different proteins. These interactions can modify, partially degrade, or complex the drug with other molecules or proteins, ultimately leading to its activation [2]. Many anticancer drugs must undergo metabolic activation in order to acquire clinical efficacy. One example of this is observed in the treatment of AML with cytarabine (AraC), a nucleoside drug that is activated after multiple phosphorylation events that convert it to AraC-triphosphate (AraC-TP). Down-regulation or mutation of enzymes in this pathway or overexpression of the AraC-TP-inactivating enzyme SAMHD1 [19] can reduce the activation of AraC leading to AraC drug resistance. Other important examples of drug inactivation include the cytochrome P450 (CYP) system, glutathione-*S*-transferase (GST) superfamily, and uridine diphospho-glucuronosyltransferase (UGT) superfamily [20]. CYP1-3 classes are particularly important for inactivation of chemotherapeutics. For example, the epigenetic up-regulation of CYP3A5 leads to primary and secondary resistance to TKIs and Paclitaxel in pancreatic cancer and likely many other cancer entities [21].

DNA damage repair. The repair of damaged DNA is a critical component of anticancer drug resistance. In response to DNA damaging chemotherapy drugs, DNA damage response (DDR) mechanisms can reverse the drug-induced damage [22]. For example, platinum-containing chemotherapy drugs such as Cisplatin cause harmful DNA crosslinks, which can lead to apoptosis. However, resistance to platinum-based drugs often arises due to nucleotide excision repair and homologous recombination, the primary DNA repair mechanisms involved in reversing platinum damage. Thus, the efficacy of DNA-damaging cytotoxic drugs depends on the failure of the cancer cell's DDR mechanisms. Inhibition of repair pathways used in conjunction with DNA damaging chemotherapy could sensitize cancer cells and therefore increase efficacy of the therapy [22]. Key to the repair of DNA strand breaks are the poly (ADP-ribose)

polymerases (PARP1 and PARP2), DNA damage sensors and signal transducers that operate by adding poly (ADP-ribose) chains (PARylation) on target proteins [23]. BRCA1/2 mutant cells with loss of function of BRCA1/2 show synthetic lethality with PARP-inhibition due to the pharmacologic inhibition of DNA strand break repair by non-homologous end joining (NHEJ) mediated by PARP1/2 in a cell which cannot repair via the alternative route of homologous recombination repair [24, 25]. The concept has entered clinical practice for breast and ovarian cancers, but in this setting, various resistance mechanisms have been identified including the genetic re-activation of a functional BRCA gene [23]. In summary, the DDR system is clearly involved in therapy resistance against chemotherapies and further exploration is needed to develop more strategies to overcome it.

Cancer Stem Cells. Next generation sequencing combined with genetic and functional analyses have shaped much of our understanding of cancer. These assays also revealed astonishing high degree of clonal and cellular heterogeneity within tumors. This heterogeneity is thought to be a major driver of primary/secondary resistance [26]. The discovery of clonal hematopoiesis of indeterminate potential (CHIP) in the elderly healthy population has provided additional evidence that the cell of leukemia origin are normal multipotent cells with HSCs being the most likely candidate cell of origin for many leukemias. Subsequent mutations in the clone carrying the initiating mutations (such as DNMT3A, TET2, ASXL1 or p53) typically not occur at the stem cell level, but further downstream at the level of progenitors leading to the generation of leukemic stem cells (LSCs) and progression into leukemia. LSCs have the clonal capacity to re-initiate the leukemia as demonstrated by transplantation into immunocompromised mice and are responsible for tumor initiation, maintenance, progression, and therapy resistance [27, 28]. While LSCs can phenocopy altered stem/progenitors, they typically resemble myeloid progenitors which maintain long-term self-renewal activity [29, 30] and mediate drug resistance by mechanisms including dormancy, enhanced DNA repair, drug efflux, metabolic features, pro-survival programs and mitophagy [31]. Recent data suggest that chemotherapy resistance of LSCs can be mediated by upregulation of BCL-2 [32]. Moreover, treatment of AML with the BCL-2 inhibitor venetoclax in combination with azacitidine may specifically target therapy resistant LSCs by blocking oxidative phosphorylation [33-37]. However, individual LSCs have not yet been characterized in molecular detail due to the fact that they are rare and cumbersome to isolate prospectively. Moreover, there is significant intra- and inter-patient heterogeneity among LSCs as well as reversible plasticity, which further complicates their analysis [29]. The addition of single cell technologies to the already available technical repertoire now facilitates the interrogation of the molecular programs operational in therapy resistant LSCs in patients. A better understanding of the molecular and cellular basis of LSCs in patients will have important implications for the design of therapeutic strategies, with particular importance for patients who undergo relapse.

Dormancy and metabolism. The state of dormancy has been proposed as an important mechanism mediating therapy resistance in leukemias and solid tumors [38]. Cellular

dormancy can be defined as a long-lasting reversible quiescent state in which the cell demonstrates low metabolic activity [39]. Indeed, biosynthetic processes, such as transcription, splicing and translation are reduced to an absolute minimum. In contrast, survival programs and gene networks maintaining cellular identity (stemness) are activated [40]. One factor that promotes the dormancy state in stem cells is repression of the MYC transcription factor. While complete repression of MYC results in apoptosis in most somatic cells, it induces dormancy or an embryonic diapause state in cells harboring stem cell features [41]. Recently, the dormancy/diapause related senescence state has been identified as a loss of MYC-mediated resistance mechanism in AML [42]. Dormant cells are not only highly resistant to anti-proliferative drugs including chemotherapy, but also to inhibitors that block signaling pathways. Dormancy/embryonic diapause is an evolutionary conserved cellular program that allows the cell or the organism to survive unfavorable environmental conditions, such as temperature extremes, drought or reduced food availability [35]. This program is thought to be highly relevant for the clinical observation of tumor dormancy and is ultimately linked to stem cells features. Tumor dormancy has been suggested to be responsible for late relapses in malignancies such as AML [42, 43], breast and prostate cancers as well as other tumor entities [38]. While cancer cells are therapy resistant during dormancy, their re-awakening renders them vulnerable to chemotherapy [44]. Thus, a two-step approach of activation following by elimination could be an effective treatment strategy. Nevertheless, the identification and molecular characterization of dormant tumor stem cells isolated from patients remains poorly understood [31].

Microenvironment and niches. Adult hematopoietic stem cells (HSCs) and progenitors (HPCs) reside in the bone marrow within highly orchestrated architectures known as niches. Niche compartments include a complex network of mesenchymal stromal cells including Leptin receptor, Nestin or CXCR4 expressing perivascular cells, osteolineage cells, endothelial cells, sympathetic nerves, non-myelinating Schwann cells and megakaryocytes [45]. LSCs are able to reprogram their niches to promote further malignant growth while restricting normal hematopoiesis [46]. LSCs can also express the fatty-acid transporter CD36 and co-opt the adipose tissue to create a microenvironment that supports leukemic growth and resistance to chemotherapy [47]. While there is no doubt that niches in hematological malignancies promote malignant growth and are involved in mediating therapy resistance, the underlying molecular mechanisms remain elusive. Some niche-mediated factors critical for leukemia growth are also clinically explored and include CXCR4, VLA4 or CD47 inhibitors [48]. Of interest, MM has been identified as one of the model diseases for close interaction with the bone marrow microenvironment, utilizing auxiliary cell secreted cytokines as growth and survival factors for MM cells as well as cell-cell interactions resulting in cell-adhesion mediated drug resistance (reviewed in [49]). However, the protective niche for relapse-initiating MM cells and the mechanistic interplay of its individual components remain to be defined.

Immune escape. Immune escape of malignant hematopoietic cells in patients with or without allogeneic stem cell transplantation (SCT) is a main cause of relapse.

Mechanisms of immune evasion after allo-SCT often involves abrogation of leukemia cell recognition due to loss of mismatched HLA genes mediating leukemia relapse [50]. In the absence of allo-SCT, the downregulation of HLA class II molecules has been identified as a mechanism of immune evasion in chronic myeloid leukemia (CML), Hodgkin and aggressive B-cell lymphomas, limiting the host antitumor immune response [51]. MM is also associated with both cellular and humoral immune deficiencies, indicating that the evolution of the disease from a precursor state is associated with an immunosuppressive milieu that fosters immune escape and tumor growth [52]. Specific repression of NKG2D ligands on AML stem cells has recently been identified as a mechanism to mediate evasion from natural killer (NK) cells linking stemness features to NK cell immune escape [53]. Other mechanisms of immune evasion include immunosuppression by immune-checkpoint ligand expression (PD-L1, CD155), production of anti-inflammatory factors (IL-10, TGF-beta) or tumor suppressive molecules (IDO, CD73), repression of pro-inflammatory cytokines (IL-15, G-CSF), or acquisition of novel driver mutations (FLT3-ITD, KRAS, PTEN) [54, 55].

Minimal residual disease

Minimal residual disease, the detection of residual cancer (stem) cells during therapy, serves as an important prognostic factor for the outcome of patients and is therefore an important clinical parameter to stratify the risk of patients suffering from relapse. In particular, hematological diseases are stratified by various parameters including morphologic, cytogenetic as well as molecular data into prognostic subgroups that guide treatment decisions. The depth of the models used to predict patient´s prognoses suggests an excellent understanding of mechanisms affecting disease outcome at the time of diagnosis or in first remission. Multiple constantly refined scores exist that can be used to predict individual patient´s outcome. Detection of MRD has emerged as a crucial prognostic parameter for multiple hematological malignancies (e. g. ALL, AML, MM). If MRD data are available, these now guide important treatment decisions, such as allogeneic stem cell transplantation [56]. However, upon relapse, which occurs in about 50-90 % of all patients, most prognosis stratifying tools and scoring schemes fall short. Indeed, relapsed or refractory disease itself often presents the worst prognostic factor for overall survival. In addition, a shorter period of the relapse free interval signals a worse prognosis in many diseases, including MM, for example. The mechanisms responsible for therapy resistance and survival of leukemic cells found in MRD are very poorly understood. Therefore, sophisticated detection of the remaining disease burden after initial therapy is emerging as an important predictor of outcome in multiple cancers. Molecular monitoring of MRD is well established in ALL and CML where MRD levels guide therapy decisions. Similarly, the importance of MRD detection, for example by measuring the variant allele frequency (VAF) of mutations such as NPM1c, is increasingly recognized in AML and MM. While molecular methods to detect and monitor MRD are steadily improving, isolation of malignant (stem) cells within MRD remains challenging due to their very low cellular frequency in patients. As an example, in AML, single cell multi-omics technologies will identify, isolate and

deeply characterize the molecular landscape of therapy resistant leukemic stem cells in patients with MRD.

Curent and future efforts to overcome resistance mechanisms in hematological malignancies

Combination chemotherapy. Single drugs can induce remissions in leukemia and multiple myeloma. However, soon after the first implementation of single drug chemotherapy in ALL, it emerged that almost every patient suffered from relapse within the first year. Repetitive treatment using the same substance was no longer effective. Systematic investigations as part of multicenter studies, promoted widely in Germany through a Federal Ministry of Education and Research initiative in the early 1970s, enabled complex combined chemotherapy protocols for AML and ALL to be developed in the 1980s and 1990s. This meant that approximately 70 % of patients attained complete remission after the induction regime, followed by consolidation therapy. Since then, about 15-60 % of AML patients are cured by intensive chemotherapy depending on biological AML characteristics and patient age. Still, many patients suffer relapses and ultimately succumb to therapy resistant disease. Similarly, in MM, systematic development of drugs and therapy regimens have resulted in significant progress as well. Triple or even quadruple combination therapies are now standard of care and do prolong patient survival. Nonetheless, MM ultimately remains a fatal disease for almost all affected patients.

Stem cell transplantation. The concept of stem cell transplantation was developed based on the premise that a myeloablative conditioning regimen, followed by autologous or allogeneic transplantation, would result in an improvement in long-term treatment results. Autologous transplantation based on high dose melphalan remains an important treatment modality in multiple myeloma. Allogeneic SCT has come to form an integral component of risk-stratified first-line treatment in AML since the 1990s [57]. Indeed, it became clear that the main therapeutic benefit of allogeneic transplantation is related to the so-called graft versus leukemia effect, where the immune clearance of residual leukemia cells by donor-derived lymphocytes can result in remission. Despite the benefit of allogeneic SCT disease relapse remains a common problem [58]. Still, allogeneic SCT comprises the first immunotherapy concept that was developed into clinical practice.

Targeted therapy. The introduction of a TKI based therapy at the turn of the millennium ushered in a new era of targeted therapies for hematological neoplasms. Historic long-term survival rates were 60 % in chronic phase CML. Since introduction of the TKI imatinib, more than 90 % of patients experience survival times of more than 10 years [59]. This success in a myeloproliferative disease, initiated by a single genetic defect, was then quickly applied to TKI usage in other malignancies, although the results have been less impressive in many diseases. Still, this treatment principle now represents an important part of the overall therapy strategy for many hematological diseases. Examples include JAK2 inhibitors for myeloproliferative diseases, c-KIT inhibitors for

AML as well as for systemic mastocytosis and BRAF-inhibitors in some MM cases. In addition, BCL2 or IDH1/2 inhibitors targeting metabolic pathways in myeloid diseases [60] and finally proteasome inhibitors targeting the Achilles' heel of MM [61] supplement conventional therapeutic approaches. BCL2 inhibition by venetoclax has emerged as a new treatment paradigm in several hematological malignancies. Venetoclax is highly effective in combination therapy in AML whereas monotherapy in AML lacks efficacy [62, 63].

Immunotherapy. Since the establishment of the treatment of lymphatic neoplasms with a monoclonal anti-CD20 antibody, the principle of immune-driven treatments of lymphatic (anti-CD38) and myelogenous (anti-CD33) diseases has evolved as an integral component of the overall therapy concept of malignant hematological diseases. The development of bi-specific antibodies and the first direct immunologically effective treatments using genetic modification of T-cells to express chimeric antigen receptors (CAR) currently represents one of the most innovative areas targeting relapsed hematological neoplasms [64]. They may become available also for first-line treatment of high-risk diseases.

Future aspects of therapy resistance in hematological malignancies

Current unmet clinical needs highlight the impact of disease resistance. Insight into hematological disease mechanisms has led to the development of novel therapies that have substantially improved disease outcomes. Today, the majority of hematological cancers respond to first line therapy with at least a 10 to 100-fold reduction in the number of malignant cells. However, the development of therapy resistance has accompanied every new development in the treatment of patients. Therapy resistance with relapsed or refractory disease accounts for the vast majority of deaths in patients suffering from hematological malignancies. This statement holds true even for the most aggressive treatments such as allogeneic SCT. Indeed, even more dose intensive and aggressive therapies still fail to eradicate the disease as illustrated by high-dose chemotherapy and autologous stem cell transplantation in MM. Therapy resistant disease is uniformly associated with poor outcome. However, resistant disease may even be regarded as a separate entity with distinct pathogenetic mechanisms and phenotypes that might resemble other therapy resistant hematological malignancies even more than the original *de novo* disease. Therefore, systematic and innovative depiction and analyses of cell-autonomous and extrinsic mechanisms of therapy resistance will guide future therapeutic strategies to overcome therapy resistance in hematological malignancies.

Conflict of interests

Dr. Carsten Müller-Tidow declares that Clinical trials and research in the Department are supported by several pharmaceutical companies. The other authors declare no conflict of interest.

Author contributions

Wolf-K. Hofmann, Andreas Trumpp, and Carsten Müller-Tidow wrote the article. Wolf-K. Hofmann revised and edited this article. The work reported in the review has been performed as specified in the text.

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Figure 1: Schematic description of a typical disease course in hematological malignancies.

Figure 2: Major mechanisms of resistance in hematological malignancies.