Multiple Myeloma Therapy

Subjects: Hematology

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Multiple myeloma (MM) is a complex hematologic malignancy characterized by the uncontrolled proliferation of clonal plasma cells in the bone marrow that secrete large amounts of immunoglobulins and other non-functional proteins. Despite decades of progress and several landmark therapeutic advancements, MM remains incurable in most cases. Standard of care frontline therapies have limited durable efficacy, with the majority of patients eventually relapsing, either early or later. Induced drug resistance via up-modulations of signaling cascades that circumvent the effect of drugs and the emergence of genetically heterogeneous sub-clones are the major causes of the relapsed-refractory state of MM. Cytopenias from cumulative treatment toxicity and disease refractoriness limit therapeutic options, hence creating an urgent need for innovative approaches effective against highly heterogeneous myeloma cell populations.

multiple myeloma immunotherapy targeted therapy

1. Immunotherapy

1.1. Immune System Dysreguation

A hallmark of the underlying biology of MM is the immune system dysfunction, which is caused by various mechanisms and is believed to play a central role in the pathogenesis of the disease by promoting clonal cell proliferation via immune escape and contributing to drug resistance [1][2]. Loss of tumor antigenicity via impaired expression or alterations of tumor antigens on the surface of MM cells and upregulation of inhibitory surface ligands can lead to tumor escape from immune surveillance, along with defects in antigen processing/presentation [3][4][5][6][7][8][9][10]. This is supported by the robust T-cell response to MM antigens in bone marrow samples of patients with MGUS but absence of this phenomenon in the bone marrow of patients with active MM, despite similar clonal PCs populations [11][12].

The dysregulation further involves the tumor microenvironment, including alterations in the T and NK compartments, with upregulation of inhibitory molecules/ligands, resulting in an immunosuppressive milieu [13][14][15][16][17][18]. The increased recruitment of immunosuppressive cells such as Tregs, regulatory B cells (Bregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), along with the simultaneous reduction in cytotoxic T lymphocyte (CTLs) and defective function of antigen-presenting DCs, leads to decreased humoral and cytotoxic immunity [14][18][19][20][21]. Several novel agents that have been developed over the past decade are subsumed under the umbrella of immunotherapy and target different aspects of the immune

system to eradicate MM cells. These agents include monoclonal antibodies, immune checkpoint inhibitors, bispecific antibodies, genetically engineered immune cells, and peptide vaccines.

1.2. Naked Monocloal Antibodies

Naked monoclonal antibodies (mAb) target antigens primarily expressed on the surface of PCs and lead to cell death via several different mechanisms. Currently, there are multiple antigens studied as potential targets, with the most important being CD38 and signaling-lymphocyte-activating molecule family-7 (SLAMF7), against which mAb have been developed are broadly used in clinical practice.

1.3. Immune Checkpoint Inhibitors

Immune checkpoints are inhibitory receptors on the surface of T cells that mediate immune tolerance to self-antigens, by suppressing the T cell compartment when activated during the antigen presenting process [22][23]. There is evidence that the cytotoxic tumor lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1) immune checkpoints are highly expressed on the surface of T, B, and NK cells in the bone marrow of patients with MM [24][25]. The binding of these receptors to their ligands on antigen presenting cells (APC) and/or tumor cells leads to suppression of cytotoxic T cells and upregulation of Tregs, thus inhibiting the immune response, favoring cancer cell growth via immune escape [23][24][26]. Experiments have shown that PD-L1, the major ligand of the PD-1 receptor, can be upregulated on malignant PCs [26]. MM cells with high PD-L1 expression appear to be more proliferative and resistant to therapy, indicating increased aggressiveness [27]. T cell immunoreceptor with Ig and ITIM domains (TIGIT) and lymphocyte activation gene-3 (LAG-3 or CD223) are other immune checkpoints on the surface of T cells involved in T cell regulation by activating Tregs and inhibiting cytotoxic T cells [28][29][30][31]. Increased expression of LAG3 on T cells in the bone marrows of MM patients is associated with sustained T cell stimulation leading to T cell exhaustion, which can potentially contribute to immune escape [32].

Immune checkpoint inhibitors (ICI) are a distinct category of “naked” mAb targeting molecules that constitute immune checkpoints. The ICI mainly evaluated in MM are the anti-PD-L1 mAb, which block the binding of PD-L1 to its PD-1 receptor. PD-1/PD-L1 blockade alone was not efficacious in phase 1 studies [32][33]; however, combination approaches with different drug classes such as IMiD and anti-CD38 mAb appeared promising. In preclinical studies, IMiD reduced the expression of PD-1 receptors on T cell surfaces and also down-regulated PD-L1 on MM cells, supporting a potential synergetic effect with PD-L1 inhibitors [34]. In vivo studies have also shown that long exposure to PD-1 blockade enhances the anti-CD38 ADCC, suggesting a potential clinical benefit to combining anti-PD-L1 ICI with anti-CD-38 mAb [35].

Clinically, several studies have evaluated PD-1 blockade using pembrolizumab or nivolumab with IMiD such as lenalidomide and pomalidomide; however, they failed to demonstrate improvement in disease response. Interestingly, a combination of pembrolizumab with lenalidomide was associated with high rates of toxicity and increased risk of death; thus, the FDA put a hold on studies investigating combinations of anti-PD-L1 ICI with IMiD [36][37][38]. Anti-PD-L1 inhibitors have also been used in combination with daratumumab without safety warnings but

no clinical benefit so far [39][40][41][42]. Nivolumab is currently being tested in combination with carfilzomib and pelareorep in a phase 1 trial (NCT03605719). More recent phase 1 and 2 trials are examining the efficacy and safety of anti-LAG 3 (BMS-986207) and anti-TIGIT (BMS-986207 or COM902) ICI alone or combined with other agents (NCT04354246, NCT04150965). To date, the use of ICI alone or in combination with traditional anti-myeloma agents has not proven efficacious in the clinical setting and is currently not recommended.

1.4. Antibody Drug Conjugates

A novel type of therapy that has recently been investigated in the clinical setting is the antibody drug conjugates (ADC). ADC are mAb against a specific tumor target on the surface of malignant cells that carry a small cytotoxic agent (payload), such as microtubule inhibitors and agents damaging DNA, utilizing a cleavable or non-cleavable linker [43][44]. When it reaches its target, the ADC is internalized with eventual release of the payload into the cytoplasm of malignant PCs, leading to cell death [44] (**Figure 1**). Cleavable linkers are degradated by enzymes in the cytoplasm of the malignant cells, whereas non-cleavable linkers require processing and degradation of the mAb complex into the lysosomes in order to release the toxic payload [44]. The target of ADC should ideally be a molecule highly expressed on the surface of malignant PCs with very low or no expression on other cell types, including hematopoeitic cells, to avoid systemic toxicity [45]. ADC can also exert their effects via ADCC, ADCP, or CDC [46][47].

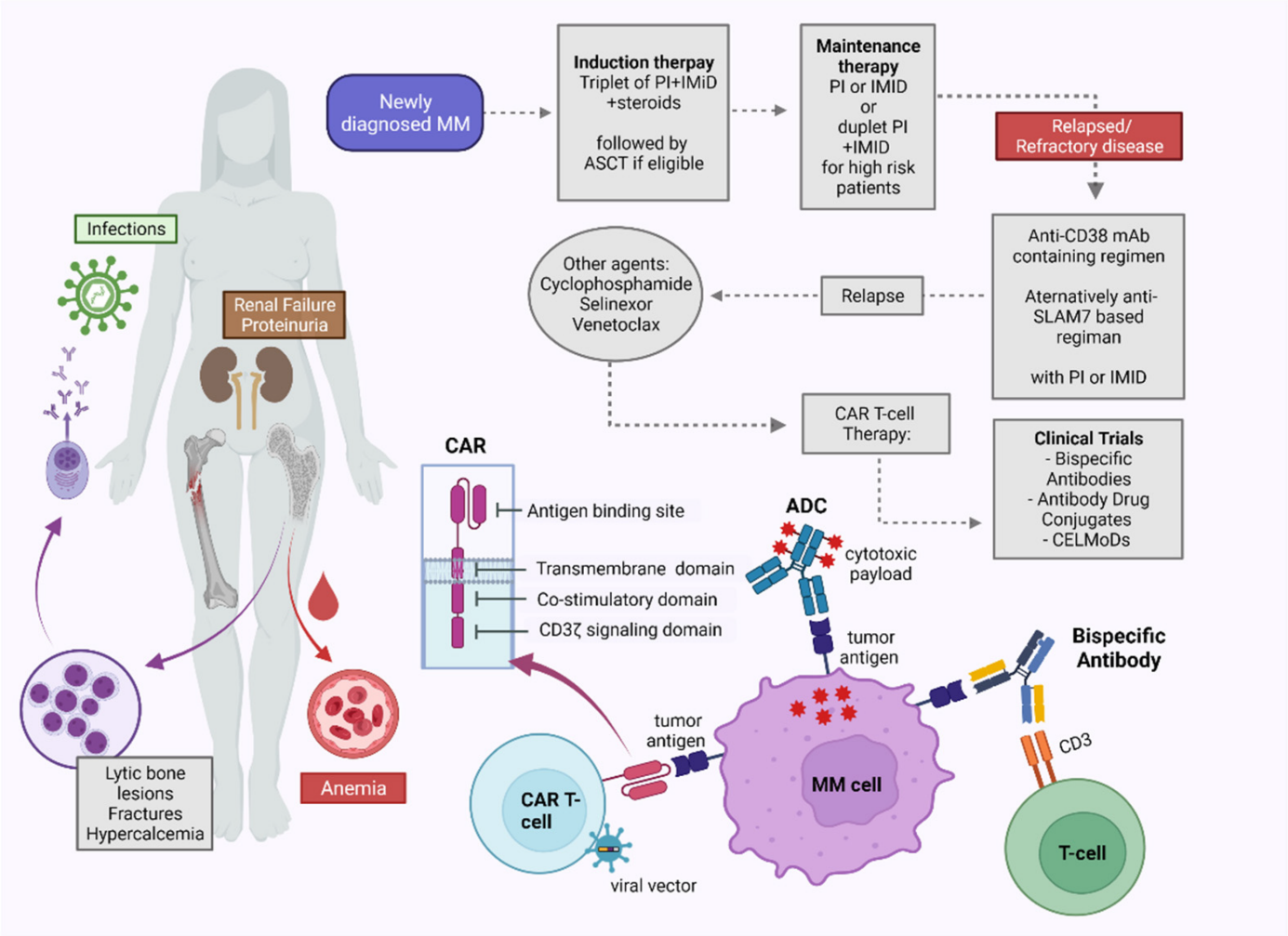

Figure 1. The basic principles of the immunotherapies in MM and their place in the current treatment landscape. CAR T cells are T cells genetically modified with the use of a viral vector to express a chimeric antigen receptor on their surface, which targets specific tumor antigens of malignant plasma cells. Similarly, bispecific antibodies are monoclonal antibodies targeting both an antigen on the malignant MM cells and simultaneously an antigen on the surface of physiologic T cells, creating an immunologic bridge. ADC are monoclonal antibodies against antigenic epitopes on the surface on MM cells, carrying a cytotoxic payload. The binding of the above agents to their antigenic targets on malignant MM cells leads to activation of the immune system, with subsequent destruction of the MM cells.

1.5. Bispecific Antibodies

Bispecific antibodies (bsAbs) are mAb designed to bind to a target on the surface of the malignant myeloma cells and effector cells (T or NK cells), creating an immunologic bridge leading to the destruction of the tumor cell by the activated effector cell [48] (**Figure 1**). There are several bsAbs currently being tested in the preclinical and clinical settings. The most popular antigenic targets on PCs include BCMA, CD38, GPRC5D, and FcRH5 [49]. GPRC5D is a G-protein–coupled receptor with unclear function that is highly expressed on the surface of myeloma cells [50]. FcRH5 belongs to the immunoglobulin superfamily and is located only on the surface of B cells with increasing

expression on myeloma cells [51][52]. At present, all bsAbs in clinical trials target the CD3 on the surface of T cells [49]. However, in a preclinical level, bispecific NK-cell engagers are also under investigation with good anti-myeloma activity [53][54][55].

1.6. Chimeric Antigen Receptor (CAR) T Cell Therapy

Chimeric antigen receptors (CAR) are synthetic transmembrane receptors that are designed to selectively recognize specific antigens on the surface of target cells [56][57]. The extracellular antigen recognition domain typically consists of a single-chain variable fragment (scFv), whereas the intracellular activation domain is typically derived from the CD3ζ chain that subsequently induces T cell activation upon antigen binding [58][59][60] (**Figure 1**). First-generation CAR lacked a costimulatory domain, resulting in only moderate responses [61]. However, the next-generation CAR included co-stimulatory signaling endodomains, such as CD28, CD137 (4-1BB), or inducible T cell co-stimulator (ICOS), in an attempt to mimic the co-stimulation occurring during physiological T cell activation via TCR recognition by APC, with subsequent improvement in T cell responses [62].

The CAR T cell production starts with collection of T cells from patients and continues with the transfer of the gene encoding the CAR construct into the genome of these T cells using a viral vector [63][64]. The CAR gene is subsequently transcribed and expressed as a surface receptor [65][66]. CAR T cell manufacturing occurs ex vivo and takes 4 weeks on average [65][66]. CAR T cell therapy is typically given as a single infusion after the administration of lymphodepleting chemotherapy, which facilitates the proliferation and activity of CAR T cells [67][68].

The choice of target antigen is critical, as it needs to be uniformly expressed on malignant cells with minimal expression on other hematopoietic cells and tissues [65]. BCMA was the first antigen to be targeted in CAR T cell therapy clinical trials [69]. Idecabtagene vicleucel (Ide-cel) was the first CAR T product officially approved for heavily pretreated MM patients, followed by ciltacabtagene autoleucel (cilta-cel), both of which target BCMA on the surface of myeloma cells [70][71]. Ide-cel is composed of a mouse scFv (11D5-3) targeting domain, a 4-1BB (CD137) co-stimulatory domain, and a CD3ζ T-cell activation domain, and uses a lentivirus vector for CAR introduction into the genome of T cells [72][73]. On the other hand, cilta-cel is composed of two llama-derived variable heavy-chain-only (non-scFv) antigen recognition domains targeting two distinct regions of BCMA, a 4-1BB (CD137) co-stimulatory domain, and a CD3ζ T cell activation domain, and uses a lentivirus vector similar to ide-cel [74][75].

Despite the associated high responses, not all patients have durable responses after CAR T cell therapy [76], which is related to several tumor- and CAR-T-cell-construct-related factors [76]. Given that most CAR T cell products target BCMA, there is evidence suggesting that low baseline BCMA expression levels on tumor cells negatively impacts the efficacy of CAR T cells [77]. Additionally, myeloma cells can shed BCMA, leading to lower surface concentration and circulation of soluble BCMA (sBCMA). sBCMA binds to CAR T cells, blocking their interactions with BCMA on the surface of malignant cells, resulting in the decreased efficacy of CAR T cells, as shown in preclinical studies [78][79]. One mechanism that could explain antigenic loss is acquired biallelic BCMA deletion, resulting in decreased BCMA expression [80][81]. High tumor load also appears to negatively affect the efficacy of CAR T cell therapy, perhaps due to CAR T cell exhaustion [70][82]. High expression of immune checkpoints on the

surface on myeloma and CAR T cells can also attenuate CAR T cell activity [60][83][84]. CAR T cells typically induce malignant cell death via the release of toxic granules containing perforin and serine proteases, and the induction of apoptosis via receptor cross-linking. It has been described that, in cases of treatment resistance, tumor cells were found to overexpress several antiapoptotic molecules including serine protease inhibitors or other proteins interfering with crosslinking [85][86].

The quality and composition of T cells in the leukapheresis product can also influence the outcomes of CAR T cell therapy. A high frequency of less-differentiated early memory T cells [87][88][89] and a high CD4/CD8 T cell ratio in the apheresis collection [68][89], which is typically seen in patients early in their disease course [90], leads to higher CAR T cell proliferation, expansion, and persistence and subsequently higher response rates [91][92]. On the contrary, multiple prior therapies in heavily pretreated patients are believed to negatively affect the fitness and constitution of the T-cell compartment.

There are several approaches to overcome these challenges, including dual-targeted CAR T cells harboring two different CAR or one CAR with two different antigen binding domains [93]. Several preclinical studies are currently investigating simultaneous targeting of BCMA and SLAMF7, GPRC5D, or CD38, molecules uniformly expressed on MM cells [85][93][94][95]. Another idea is to manufacture CAR T cells that can secrete checkpoint inhibitory antibodies such as anti-PD1 or anti-PD-L1 or CAR T cells in which genes that express immune checkpoints are knocked down [96][97][98]. Optimizing the structure of CAR by adding a costimulatory domains is also important as it can lead to improved persistence and activity with decreased exhaustion. [82][99][100]. In an effort to collect a more balanced T cell product, which would theoretically enhance CAR T cell function, allogeneic CAR T cells generated from the T cells of healthy donors have also been manufactured and assessed in the clinical context, with promising outcomes and an acceptable side effect profile [101].

1.7. Peptite Vaccines

An attractive approach for controlling tumors is developing synthetic peptide vaccines derived from widely expressed tumor-associated antigens (TAAs), which have the ability to bind multiple MHC class I and class II alleles, thus activating T-cell-mediated tumor destruction. This method is considered safe, and theoretically can be highly potent, specific, and long lasting. [102]. One approach is to target MUC1 (mucin 1, cell surface associated), a mucin-like glycoprotein highly expressed in a variety of epithelial and hematologic tumors including MM [103][104][105]. MUC1 is made of a large soluble extracellular alpha subunit containing the tandem repeats array (TRA) and a smaller beta subunit containing the transmembrane and cytoplasmic domains. The MUC1 signal peptide (SP) domain of the MUC1 binds multiple MHC class I and class II alleles, generating a robust T cell immunity; therefore, it was felt to serve as suitable vaccine candidate. Based on this rationale, a 21mer peptide vaccine encoding the complete signal domain of MUC1 was constructed and named as the ImMucin (VXL100) vaccine. [103][104][105]. In a phase 1/2 study, 15 MM patients were enrolled and vaccinated with ImMucin; however, only 9 patients completed the vaccination course (a total of six doses) [102]. ImMucin vaccination resulted in a significant increase in the percentage of both γ-interferon-producing CD4+ and CD8+ T cells in all patients. Additionally, a 9.4-fold increase in peripheral blood mononuclear cells and a 6.8-fold increase in anti-ImMucin antibodies was noted. Disease

improvement or stability persisted for 17.5–41.3 months post-vaccination. These findings suggested a potential therapeutic benefit of ImMucin in MUC1-positive tumors in MM patients.

Similarly, PVX-410 is a human leukocyte antigen (HLA)-A2-restricted multipeptide vaccine for patients with SMM [106][107]. The vaccine is composed of a unique combination of four immunogenic peptides ($XBP1_{US184–192}$, $XBP1_{SP367–375}$, $CD138_{260–268}$, and $CS1_{239–247}$) derived from specific tumor target antigens (XBP1, CD138, and CS1, respectively) highly expressed on MM cells. These peptides were found to activate the immune system in an HLA-A2-specific manner, inducing antigen-specific CTLs against HLA-A2-positive MM cells. [107]. In a phase 1/2a study, 22 patients with SMM and the presence of HLA-A2 were divided into three groups, PVX-410 (low and target dose) or lenalidomide with PVX-410 [108]. In all cohorts, the PVX-410 vaccine induced a highly effective immune response against MM cells, with expansion of the CD3+ CD8+ CTL compartment against the XBP1, CD138, and CS1 antigenic epitopes. The response was further enhanced during treatment with lenalidomide. In the target-dose cohort, 1 out of 9 patients progressed (median TTP 36 weeks), as well as 1 out of 12 in the combination cohort (median TTP no reached).

A relatively recent phase 1 trial demonstrated the role of the PD-L1 peptide (IO103) vaccine in MM patients [109]. As previously mentioned, upregulation of PD-1/PD-L1 [25][110][111] is associated with poor prognosis in patients with MM [112]. Stimulation with the IO103 peptide stimulated PD-L1-specific T cytotoxic cells against PD-L1-expressing MM cells. In this research, 10 patients with MM who were 6 months post AHCT were enrolled [109]. Patients received vaccination with IO103 up to 15 times within one year. All patients showed a peptide-specific immune response in peripheral blood mononuclear cells and in skin-infiltrating lymphocytes. Three out of ten patients had improvement of response (over 100 days post-transplant) [109].

Quian and colleagues assessed the role of Dickkopf-1 (DKK1), a protein that is highly expressed in MM cells but not in normal tissues, as a potential vaccine candidate. Their in vitro experiments showed that cytotoxic T lymphocytes were able to recognize DKK1 peptides naturally presented by MM cells in the context of HLA-A*0201 molecules. This led to the immune-mediated destruction of MM cells, hence suggesting that DKK1 could be a potentially important antigen for immunotherapy in MM [113]. Further experiments from the same group in mouse murine myeloma models showed that vaccination with DKK1-DNA not only prevented mice from developing MM, but was also therapeutic against active MM. DKK1 vaccination elicited strong DKK1- and tumor-specific CD4+ and CD8+ immune responses, providing extra evidence for targeting DKK1 in MM patients [114]. Despite these encouraging outcomes, vaccination against MM has not been adopted in the clinical setting. There is currently an ongoing pilot phase 1 study exploring the application of the DKK1 vaccine in patients with MGUS and stable or smoldering myeloma (NCT03591614).

2. Targeted Therapies and Small Molecules

2.1. Exportin Inhibitors

The nuclear pore complexes (NPC) are large cylindrical channels, composed of several copies of >30 different proteins called nucleoporins [115]. The main function of the NPC is to fuse the inner and outer nuclear membranes, enabling traffic of vital macromolecules between the nucleus and the cytoplasm, a process which is mediated by specific protein carriers, importins and exportins. [116]. Exportin-1 (XPO1) is one of the most well-characterized nuclear exporters, involved in shuttling of multiple cargo proteins such as tumor suppressor proteins, cell cycle regulators, immune response regulators, and oncogenes, as well as mRNAs, out of the nucleus and into the cytoplasm, enhancing the synthesis of oncoproteins [117][118]. Overexpression of XPO1 leads to increased transfer of tumor suppressor and regulatory proteins into the cytoplasm, which further promotes cell proliferation and halts apoptosis, overall favoring carcinogenesis. Increased XPO1 levels have been observed in a variety of malignancies including CD138+ PCs from patients with active MM and are associated with poor survival outcomes, making XPO1 an attractive molecular target for novel therapies [119]. Selective inhibitors of nuclear export (SINE) are orally bioavailable small-molecule drugs that inhibit XPO1 by attaching to the binding site of the cargo, thus disrupting the nuclear–cytoplasmic trafficking. As a result, tumor suppressor proteins and regulators eventually accumulate in the nucleus, activating the apoptotic process and subsequently causing cell death [120][121].

Selinexor is an XPO1 inhibitor that has reduced the viability of MM cells in preclinical experiments, alone or in synergism with other anti-myeloma agents. [106] In detail, selinexor causes retention of tumor suppressor proteins in the nucleus such as p53, p27, and FOXO and decreases the levels of cell cycle promoters and antiapoptotic proteins, leading to cell cycle arrest, with subsequent caspase activation and cell death [122][123][124] (**Figure 2**). It has also been shown to block NF-kB, which regulates osteoclast differentiation [125]. It is currently approved in combination with bortezomib/dexamethasone or dexamethasone alone in the relapsed/refractory setting, with ongoing trials investigating different combinations with other novel agents [126].

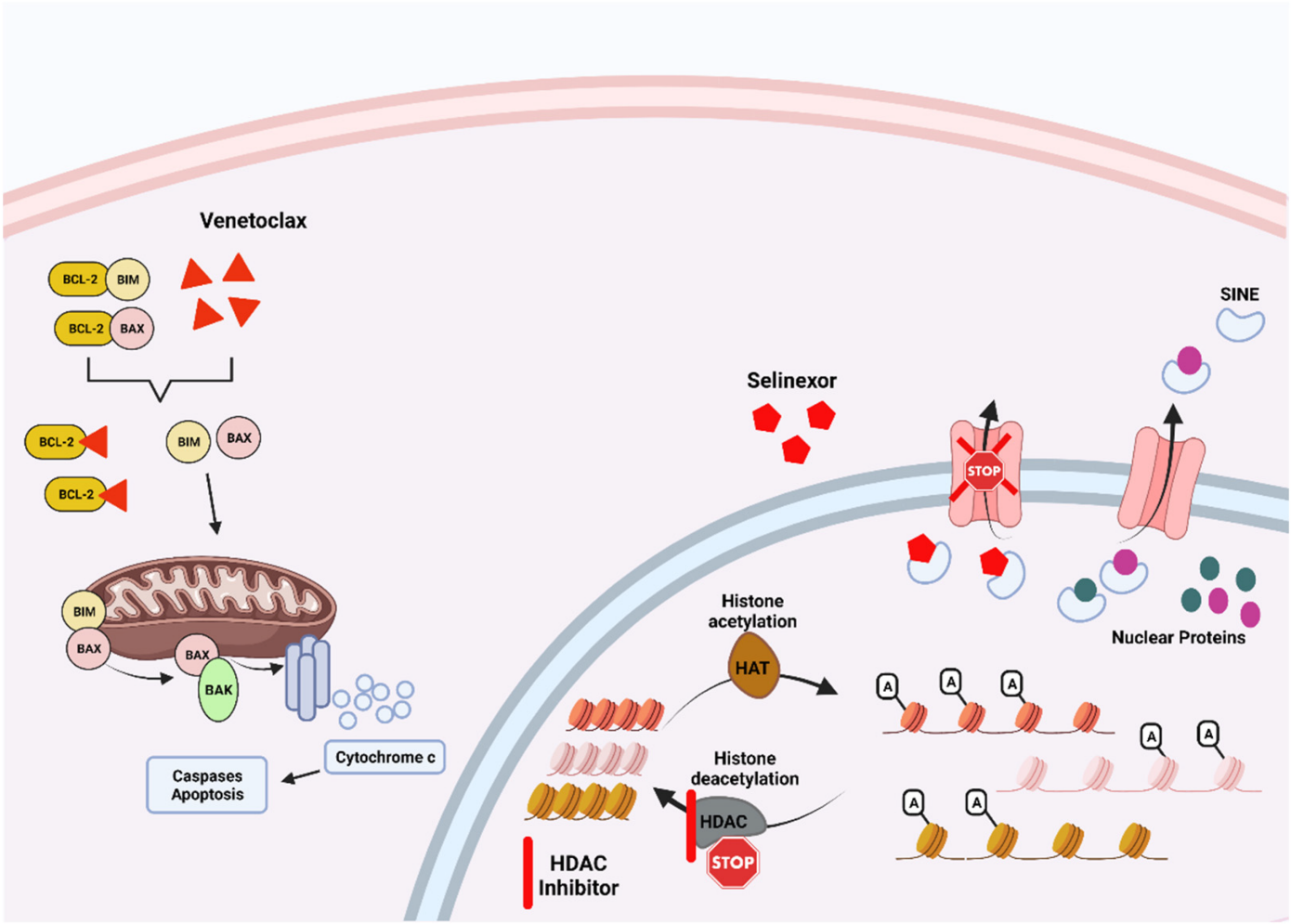

Figure 2. Underlying mechanism of action of selected targeted therapies used for MM in the clinical setting. Venetoclax works by primarily binding to the BCL-2 anti-apoptotic protein, allowing the activation of BAK and subsequently caspases leading to MM apoptosis. Selinexor blocks the transport of vital proteins and other molecules from the nucleus to the cytoplasm of the MM cells, leading to cell death. Histone deacetylation inhibitors act at an epigenetic level, blocking the deacetylation of the DNA in the nucleus of the malignant cell.

2.2. Histone Deacetylase Inhibitors

Histone deacetylase (HDAC) inhibitors act at the epigenetic level, by removing acetyl groups from mainly the histones, proteins forming the nucleosome, which play a critical role in chromatin organization [127] (**Figure 2**). In MM, overexpression of HDAC, especially HDAC-1, has been associated with a poor prognosis and with resistance to PI [128][129]. Panobinostat and vorinostat are pan-HDAC inhibitors leading to blockade of disposal of several proapoptotic proteins through the unfolded protein response, disrupting protein homeostasis and resulting in cell death via apoptosis [130].

Panobinostat was initially approved by the FDA; however, due to lack of confirmatory post-approval clinical studies, required as part of the accelerated approval process, it was withdrawn from the market. Other experimental HDAC inhibitors, such as quisinostat, CUDC-907, and AR-42, have also been studied in the pre- and clinical settings.

2.3. BCL2 Inhibitors

The B cell lymphoma-2 (Bcl-2) protein family consists of pro- and anti-apoptotic proteins which regulate the intrinsic pathway of apoptosis. Bcl-2 is an anti-apoptotic protein of the Bcl-2 family containing four homogeneous domains called BH1, BH2, BH3, and BH4, whereas pro-apoptotic proteins in the same family only contain the BH3 domain and are called BH3-only proteins [131]. The latter subcategory primarily works by binding to anti-apoptotic proteins, activating the BAX/BAK proteins, directly or indirectly, and inducing apoptosis [132][133]. Overexpression of the anti-apoptotic Bcl-2 has primarily been observed in the subgroup of MM patients harboring the translocation of the chromosomes 14 and 17 [134]. High levels of Bcl-2 promote cell survival and tumorigenesis and have been associated with poor outcomes and resistance to traditional anti-myeloma agents; therefore, Bcl-2 represents an attractive target for novel therapies.

Venetoclax is an orally bioavailable BH-3 mimetic that selectively inhibits Bcl-2, disrupting the anti-apoptotic pathway, thus favoring cell death in a TP-53-independent manner. (**Figure 2**) Venetoclax is particularly efficacious in the subset of MM patients with the translocation (11;14). These patients express high levels of Bcl-2, possibly due to increased tumoral dependence upon Bcl-2 [135]. As a result, translocation (11;14) has emerged as the first predictor of susceptibility to Bcl-2 inhibition in MM patients [136]. Venetoclax is not FDA-approved yet; however, the NCCN guidelines recommend its use in RRMM with the translocation (11;14).

2.4. Hypomethylating Agents

While hypomethylating agents have been effective for the treatment of myeloid leukemia, it seems they had limited efficacy in a phase 1b trial of 42 heavily pretreated patients with RRMM. This trial assessed the addition of Azacytidine, a DNA methylation inhibitor, to lenalidomide and dexamethasone with the purpose of overcoming refractoriness to IMiD via interfering with pathways associated with PC differentiation, apoptosis, and immune recognition. The overall response rate was 32%, with 10% achieving very good partial response, and the median PFS was 3.1 months. The levels of the azacytidine-inactivating enzyme cytidine deaminase (CDA) were measured to assess any potential correlation with treatment response, and it was found that low plasma CDA levels were associated with greater clinical benefit [137]. Currently, there is an ongoing phase II trial evaluating azacitidine in combination with daratumumab and dexamethasone in patients with RRMM who have already received daratumumab (NCT04407442).

2.5. Proteolysis-Targeting Chimera

Proteolysis-targeting chimera (PROTAC) is a class of bi-functional degrader molecules that have designed to selectively target and then degrade intractable cellular proteins via activation of the ubiquitin–proteasome system. These molecules typically consist of two ligand-binding domains, one that binds to a E3 ubiquitin ligase and another that binds a protein of interest (POI) [138]. The two domains are connected through a linker. PROTAC ultimately forms a complex between an E3 ligase and POI, which results in ubiquitination and subsequent degradation by the proteasome. The domain of PROTAC binding to an E3 ligase can be either a phthalimide

derivative binding to a cereblon (CRL4 CRBN) E3 ligase (Cereblon PROTAC), or a von Hippel–Lindau (VHL) binding to VHL E3 ligase (VHL PROTAC) [138][139].

An initial PROTAC called dBET1 was constructed using thalidomide (as an E3 ligase binding domain) and JQ1 (as a POI binding domain) [140]. JQ1 is a small molecule binding to Bromodomain-Containing Protein 4 (BRD4). This PROTAC induced cereblon-dependent degradation of BRD4 and subsequent down-regulation of MYC, leading to the cytotoxicity of AML cells [141]. In vitro and in vivo pre-clinical studies in MM models using PROTAC targeting BRD4 and other BET proteins reduced the viability of MM cell lines in a time- and concentration-dependent manner and demonstrated suppressed MYC and Akt/mTOR signaling [142]. PROTAC was able to overcome resistance to PI and IMiD, and their activity was maintained in MM cells with wild-type or deleted TP53. Further studies demonstrated that BET-targeted PRTOAC was able to inhibit cell proliferation of multiple human-derived MM cell lines and fresh myeloma samples and suggested potential synergy with systemic agents including selinexor [143]. Another, newer experimental PROTAC targeting the proteasome substrate receptor hRpn13, which was found to be upregulated in MM, was tested in in vitro studies [144]. Optimization of PROTAC design for potential clinical development is eagerly awaited.

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