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Nucleoside and Non-Nucleoside DNA Methyltransferase 1 Inhibitors in Epigenetic and Combination Therapies in Cancer: A Scoping Review

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Abstract

DNA methylation is an epigenetic mechanism of gene silencing crucial to the regulation of gene expression in normal physiological events such as differentiation and X-inactivation. However, aberrant silencing of regulatory genes can contribute to oncogenic transformation, further perpetuated due to the heritability of these changes down the cell line. Though aberrant DNA methylation is implicated across cancer types, epigenetic therapy with DNA methyltransferase 1 (DNMT1) depleting drugs is only approved in the treatment of hematological cancers. This limitation is due to the drugs' high toxicity, a byproduct of their mechanism as nucleoside analogs. Identifying less toxic nucleoside analogs or developing non-nucleoside analogs is necessary to expand the application of epigenetic therapy. This review examines the existing nucleoside and non-nucleoside DNMT1-inhibitors at various stages of preclinical and clinical development, and overviews prospective applications of epigenetic therapy in solid tumors as monotherapy and combined therapy. The list of drugs reported in this review is non-comprehensive as it excludes primary research on drugs last tested prior to the FDA approval of azacitidine and drugs not tested or inviable in human cells. This is to limit the survey to studies that intend to improve upon the pharmacological profile of the approved drugs. Of particular importance are the recently developed DNMT1-inhibitor (DNMT1-i) GSK analogs and the advancements in protein modeling that have elucidated their mechanism to the greatest precision yet. Not yet discussed in length in secondary literature, these findings provide a clearer model for the development of more specific DNMT-is. Furthermore, evidence showing enhanced efficacy of DNMT1 inhibitors when combined with DNA damaging agents identifies epigenetic combination therapy as a pertinent focus of future research.

Keywords: cancer; epigenetic therapy; DNMT inhibitors; hypomethylation; non-nucleoside; nucleoside; GSK-3685032; GSK-3484862

Introduction

The silencing of tumor suppressor genes such as p16 by DNA methylation is one of the main epigenetic drivers of cancer seen across cancer types. Unlike inherited or acquired genetic mutations, epigenetic modifications do not permanently change the cell's DNA, presenting an opportunity to potentially reverse the heritability of their oncogenic capacity and restore tumor suppressor expression.

DNA methylation is a mechanism of gene regulation that, under normal circumstances, is vital for the proper development and survival of an organism, such as through the silencing of fetal genes after gestation, X chromosome inactivation, or silencing of non-tissue-specific genes in differentiated cells [1, 2]. De novo methylation most commonly occurs during embryonic development through the addition of methyl groups to CpG islands in a gene's promoter by the enzymes DNA methyltransferase (DNMT) 3A and DNMT3B. The enzyme DNMT1 binds methyl groups to newly replicated DNA strands based on the template strand, thereby maintaining silencing patterns in daughter cells over one's lifespan. Though global hypomethylation has been observed as a biomarker across cancer types, the oncogenic potential of DNA methylation is most frequently seen in the silencing of the tumor suppressor gene p16, appearing across human cancers in primary and metastatic tumors [1, 3]. Thus, DNMT1 is a promising target of cancer therapy as its inhibition allows the body to create new cells that lack the oncogenic modification while leaving the epigenome of existing cells intact, slowing tumor growth and encouraging tumor reduction.

Existing techniques target DNMT1 to inhibit its ability to replicate CpG methylation in daughter cells. DNMT1-inhibitors (DNMT1-is) have found efficacy against hematological cancers, but have not been successfully used against solid tumors. This is due to the drug's mechanism as nucleoside analogs, which are associated with cytotoxicity at high doses and extended treatment periods, limiting their usability. However, the advent of non-nucleoside DNMT1-is may abate some of these limitations,

potentially expanding the use of demethylating therapy. Additionally, employing epigenetic therapy in combination with traditional cancer therapies could enhance the efficacy of both treatments and revitalize anti-tumor action in treatment-resistant patients. This review overviews the efficacy and mechanisms of the DNMT1-is currently in development in order to direct further research and highlight the potential of epigenetic therapy. The discussion of the newly-developed GSK analogs serves to introduce to secondary literature the first class of DNMT1-is specifically synthesized with the DNMT1 crystallography model and the promise this methodology may hold in epigenetic therapy.

Methods

This review utilized a literature search over review articles, primary research, and clinical trials to identify the breadth of clinically-viable DNMT1-inhibitors and their current stage of development. Holistic analysis of this information informed assessment of the prospects of these drugs to direct focus for future research.

Initial literature search to ascertain the scientific current landscape was conducted on Google Scholar using search term "DNMT1 methyltransferase inhibitors cancer", excluding articles with drug- or cancer type-specific focus, and including only systematic reviews published in 2016 or later to obtain the most current data obtained after the 2015 publication of the DNMT1 crystal model. The three articles that met these criteria were used as reference to investigate primary research on the drugs mentioned therein [44-46].

Inclusion criteria for primary research included (1) experimental data in human cancer cell lines in vitro or xenografted in animal models, or in human subjects, (2) peer-reviewed journals, and (3) papers written in English. Exclusion criteria included (1) papers on drugs whose most recent primary data predated the FDA approval of azacitidine in 2004 in order to include only findings that intend to improve upon or pose an alternative to this traditional therapy. (2) Case studies, (3) observational data, and (4) bio-inactive, clinically inviable, and untested drugs were also excluded.

These searches were conducted on Google Scholar, National Library of Medicine, and ClinicalTrials.gov using search terms "[drug name] + cancer", "+mechanism", "+ solid tumor", "+ combination therapy". Studies in non-DNMT1-targeted epigenetic therapy and non-monotherapy were excluded except where specifically stated.

All eligible primary research per drug was manually evaluated to identify notable findings, including corroborated data across trials and significant differences from nucleoside-drug features. Data was also reported in order of priority from clinical trials, then human cell lines in mouse models, and lastly in vitro human cell lines. Tables 1 and 2 in the Appendix summarize these features according to this method of evaluation.

Results

Nucleoside DNMT1 Inhibitors

The only DNMT1-i currently approved for clinical use are the drugs 5-aza-2'-deoxycytidine (decitabine) and 5-aza-cytidine (azacitidine) for the treatment of myelodysplastic syndromes and acute myeloid leukemia. These drugs have been shown to be effective in hematological cancers as monotherapy, but have seen little success in the treatment of solid tumors. These limitations have prompted the development of several other DNMT1-inhibiting agents, many of which utilize the same 5-azacytosine (5-aza) base as decitabine and azacitidine (Appendix Table 1). The 5-aza derivatives are nucleoside analogs that can be incorporated into DNA in place of cytosine, the usual locus of methylation, and form irreversible covalent bonds with DNMT1 during DNA replication, rendering it inactive and promoting its proteasomal degradation [4]. The cytotoxicity associated with this class of DNMT1-inhibitors has been evidenced to be a result of its specific mode of action and metabolism rather than being a consequence of hypomethylation itself. Primarily, the incorporation of the nucleoside-DNMT1 complex into the DNA confers genomic instability through vulnerability to double-stranded breaks, point mutations, and gene rearrangements [5]. Off-target effects are also associated with the drugs, such as the disruption of thymidylate metabolism, which is involved in the production and maintenance of nucleosides [6]. However, global hypomethylation itself is also implicated in genomic instability, as demethylation of centromeric regions makes chromosomes more vulnerable to breaks [7]. Such genetic damage can induce cell cycle arrest and apoptosis, driving the drug's efficacy in tumor reduction. However, this effect is nonspecific to cancerous cells and harms healthy tissue, much like many first-line cancer therapies.

Several 5-aza analogs were specifically tailored to avoid some of these known mechanisms of toxicity. Many drugs like zebularine and guadecitabine, modified to be more resistant to degradation than decitabine, succeeded in being better-tolerated in in vitro and in vivo studies. However, this came at the expense of potency or caused excessive adverse effects during clinical trials. NTX-301, guadecitabine, and NUC013/041 also aimed to improve upon decitabine and azacitidine's short half-lives and poor oral bioavailability [8-10]. Ameliorating these factors could potentially decrease the cost and complexity of administration normally involved in treatment with DNMT1-inhibitors, as the currently-approved drugs require frequent redosing and in-clinic intravenous administration [11]. Additionally, development of low-toxicity, longer-acting DNMT1-inhibitors could expand the application of demethylating treatment beyond hematological cancers, as although hypermethylation is implicated across cancer types throughout the body, solid tumors are responsive only at longer administration periods, at which the drugs' cytotoxicity often outweighs their therapeutic capacity [4].

Non-Nucleoside DNMT1 Inhibitors

Though the development of nucleoside analogs initially dominated research on demethylating agents, recent efforts have turned to exploring non-nucleoside DNMT1-inhibitors in hopes that action through an alternative mechanism will avoid the toxicity inherent to the mechanism & metabolism of their nucleoside predecessors (Appendix Table 2).

Antisense oligonucleotide (ASOs) DNMT1 inhibitors presented a promising alternative, theorized to target DNMT1 with high specificity and minimal off-target effects upstream of the DNMT1 pathway. ASOs are engineered to specifically complement the mRNA sequence of their target protein, resulting in base pairing of the strands which prevents translation into protein, either by obstruction or degradation of the mRNA [12]. By simply decreasing the amount of DNMT1 present to replicate DNA methylation in daughter cells, this mechanism avoids the risks associated with incorporation of a disruptive moiety into the DNA. The ASO MG98 showed initial success in in vitro models, downregulating DNMT1 mRNA and protein dose-dependently, showing re-expression of silenced p16 gene products in human breast cancer cells, and reducing tumor volume in colon cancer cells [13,14]. However, results in Phase I and II clinical trials were mixed, with only some patients showing decreased global methylation, inconsistent DNMT1 downregulation that was not dose-dependent, and a lack of antitumor effect in both myeloid leukemias and solid tumors [15-18]. Though it was initially suggested that the observed variability may be due to differing receptivity by tumor type, the lack of significant DNMT1 downregulation seen across cancer types instead suggests that MG98 could be ineffective as a DNMT1-inhibitor. This may be explained by a compensatory mechanism causing gene upregulation or alternative splicing to maintain DNMT1 activity in the presence of the ASO [19]. Though currently unexplored, the existence of such a compensatory mechanism would complicate the potential for ASOs as a demethylating agent in cancer treatment.

Identifying a molecule that directly inhibits DNMT1 is thought to offer the simplest mechanism with the lowest likelihood of off-target interference. Of the numerous naturally-occurring substances observed to inhibit DNMT1, very few are actually viable as a drug. However, studying these molecules is useful in elucidating their chemical structure and mechanisms of action to guide development of more specific agents. This examination reveals two common mechanisms of direct DNMTIi: SAM antagonism and DNA binding. These inhibitors compete or interfere with the respective binding sites on DNMT1, where SAM (S-adenosylmethionine) is used as the methyl donor for methylation at the bound DNA locus. It should be noted, however, that these categories are not restrictive and many DNMT1-i are observed to use mechanisms whose details are not fully known [20, 21]

The newly discovered quinoline-based molecule SGI-1027 and its more potent analog MC3343 bind DNMT1 with greater potency and specificity than azacitidine and decitabine and showed antitumor effect in a variety of cancer cell lines in vitro [22]. Enzyme kinetics analysis by Gros et. al. found evidence of a mechanism wherein MC3343 binds competitively to the DNA binding site of DNMT1. Interestingly, the inhibitor also binds co-operatively with DNA and can only bind DNMT1 in the presence of DNA [21]. These characteristics may explain the molecule's high binding specificity, but do not necessarily rule out the potential for off-target interference. In vivo testing is needed to examine MC3343's effects on organismal health, but knowledge of the molecule's structure and kinetics can facilitate the process of understanding and improving its action as a drug.

Advances in protein modeling techniques have enabled the development of inhibitors designed specifically to bind to an enzyme's active site. The compound RG108 is one such inhibitor, developed using a homology model of the DNMT1 active site. Still only in its preclinical stages, the molecule showed antitumor effect, global hypomethylation, and reexpression of silenced genes in prostate cancer cell lines in vitro [23]. Though RG108 appears to be significantly less potent than the leading nucleoside drugs, it shows remarkably low cytotoxicity even at high doses. This low toxicity was suggested to be due in part to RG108's unique binding pattern, in which the drug appeared to preferentially demethylate euchromatic regions and leave centromeric regions largely untouched, as centromeres are important in maintaining chromosomal stability [24]. Further research is needed, however, to support this hypothesis. RG108 is also notable in its nonspecificity to DNMT1, as studies observed the inhibition of DNMT3a and 3b in treated cells [23]. This may be due to the structural similarity of the three enzymes' catalytic domains, as subtler differences are difficult to discern using homology modeling. RG108's nonspecificity complicates its potential as a cancer drug, as the effects of DNMT3a and 3b inhibition on the body are poorly understood and introduce greater likelihood of off-target interference. The three DNMT enzymes are known to operate synergistically, and changes in one DNMT's expression can up- or down-regulate the other's expression. One study found that DNMT1 and DNMT3b depletion in combination actually induced invasiveness in non-cancerous breast cells in vitro [25]. Contrarily, a study of RG108 in an endometrial cancer cell line associated with DNMT3b overexpression produced significant antitumor effect correlated with hMLH1 (human MutL homolog, mismatch repair gene) reexpression and DNMT3b inhibition [26]. However, this study neglects to consider multiple variables, as it relies on a pre-established correlation between hHMLH1 methylation and DNMT3b overexpression to conclude that hHMLH1 reexpression is induced by DNMT3b inhibition, without assessing DNMT1 or DNMT3a expression. Thus, it is impossible to decipher which enzyme(s)'s inhibition were responsible for the

antitumor effect observed, and whether DNMT3b inhibition aided or hindered this effect. The existing evidence on RG108 is inconclusive. Although the drug's low toxicity appears promising, further in vitro and in vivo testing is needed to characterize its full range of effects.

The publication of the crystallography model of DNMT1, which provides a more detailed impression than homology modeling, has since enabled the synthesis of compounds with specificity only for the desired DNMT [47, 48]. These compounds are the GSK analogs, a family of dicyanopyridine compounds that reversibly bind DNMT1 with high specificity, rapidly initiating hypomethylation and causing a more robust and less toxic antitumor effect than decitabine and azacitidine in vitro and in vivo acute myeloid leukemia mouse models [27]. Horton et. al. conducted a detailed examination of the molecular mechanisms of several GSK analogs, in which it was illustrated that the planar GSK molecules intercalate exclusively between CpG base pairs of hemimethylated DNMT1-bound DNA strands. Upon intercalation, the inhibitor interacts with the active site loop to impede DNA's entry, preventing methylation [28]. Additionally, the inhibitor marks the DNMT1 enzyme for degradation, reducing DNMT1 levels in the cell [29]. Though the GSK compounds are less toxic than the nucleoside analogs, there is some variation between analogs. One study found GSK-3685032, the inhibitor found to be successful in mouse models in the previously referenced Pappalardi et. al. study, to show both greater cytotoxicity and less potency against DNMT1 than its enantiomer, GSK-3484862. DNMT1 knockout experiments indicated that the observed toxicity was not due to the drug itself or hypomethylation, but rather some process downstream of GSK-DNMT1-DNA complex formation [27, 29]. Similarities observed between nucleoside analogs and GSK in DNMT1 knockout studies and the shared DNMT1 degradation step in their mechanisms raise the question of whether the two drugs induce the same source of toxicity [29]. Though seemingly discouraging, this possibility could direct research towards modulating a common target to abate nucleoside- and non-nucleoside-induced toxicity. The extensive knowledge provided by the crystallography model and its pursuant research is a critical resource for future advancements in DNMT1-i efficacy.

Discussion

Expanding the Scope of Demethylating Treatment

As hypermethylation induces a great variety of cancers, widening the application of demethylating treatment beyond hematological cancers is a pertinent endeavor, especially since traditional therapies – surgery, chemotherapy, and radiotherapy – may be unsuitable or ineffective for some patients.

Prospects for Solid Tumors

As monotherapies for solid tumors, azacitidine and decitabine have undergone preclinical and clinical testing for several years in efforts to find receptive tumor types and dosage regimens with little success. However, recent studies using new formulations of the traditional drugs and new DNMT1-i yield some hopeful results.

New formulations of azacitidine and decitabine offer less intensive and potentially more targeted methods of administration, factors that may increase their suitability for solid tumors. A Phase 1 study of oral azacitidine (CC-486) in patients with relapsed or refractory solid tumors showed responses in three of the eight patients studied with nasopharyngeal cancer, a stride ahead of older trials that found no response at non-toxic doses in most patients [30, 31]. Another Phase 1 clinical trial on a unique formulation of inhalable azacitidine on advanced non-small cell lung cancer patients showed tolerability, significant decrease in bronchial epithelial methylation, and negligible plasma levels of azacitidine, indicating that the drug could be contained in the lung tissue and out of systemic circulation. One of eight patients exhibited an objective treatment response, but clinical testing with a larger sample size is needed [32]. Additionally, studies using subcutaneous azacitidine and decitabine in hematological and skin cancers indicate enhanced efficacy at lower doses, though it is uncertain whether this method of administration allows for a more targeted response [33-35]. These studies present perhaps the most promising results among solid tumor epigenetic monotherapies, supporting the value of developing different formulations of DNMT1-i to optimize their efficacy.

Though many of the newer DNMT1-i in development have seen success in in vitro against solid tumor cell lines, this evidence is rarely predictive of the drugs' efficacy and tolerability in humans. As of yet, only a few non-nucleoside analogs have reached clinical trials, including MG98 and TdCyd. However, results in the MG98 trials were inconsistent in efficacy despite being well-tolerated. TdCyd testing, unfortunately, had to be halted due to the frequent incidence of adverse effects and one treatment-related death [15-18, 36]. Another 5-aza analog, FdCyd, recently completed Phase II trials against breast, urothelial, and head and neck tumors. Though the treatment was found to be tolerable, only a small minority of patients showed partial response and the study was ultimately terminated early due to insufficient response. 64% of evaluable patients showed p16 reexpression, but this was not associated with clinical response. Still, it was noted that urothelial cancers appeared particularly receptive in the early stages of treatment compared to the other tumor types, suggesting further specific evaluation [37].

Assessing the evidence across clinical trials, there appears to be a persisting difficulty treating solid tumors using systemically-administered DNMT1-depleting monotherapies, with the drugs showing either excessive toxicity or insufficient response. Though it is possible that some of the lower-toxicity DNMT1-i could mitigate this effect if they pass preclinical stages, the nature of DNMT1

itself may be its primary obstacle in fighting solid tumors. DNMT1 can make changes to the epigenome only during DNA replication in the S phase, and compared to the highly proliferative cells of hematological cancers, solid tumors tend to have fewer S phase cells. This would imply that a longer duration of DNMT1-depleting treatment would be needed to see a response – as data supports – and a greater proportion of the drug would be metabolized without exerting its effects on its intended target, while proliferative cells accumulate the resultant damage. However, this suggests that cancers with known high S-phase fractions, such as breast and endometrial cancer, may be more receptive targets [38].

Combined Therapies

Despite the numerous limitations involved with DNMT1-i as monotherapy, studies on combined therapies present a plethora of opportunities to target cancer in a multi-faceted way.

A common issue with long-term treatment is acquired resistance, in which a once-effective therapy can no longer be used. Numerous in vitro, in vivo, and clinical studies support the resensitization of drug-resistant cancer cells, including solid tumors, by decitabine and azacitidine to drugs such as doxorubicin, vemurafenib, and enzalutamide. Moreover, one clinical study in melanoma patients found that combination treatment with subcutaneous decitabine and vemurafenib in skin cancer produced responses at a fraction of the clinical decitabine dose used in monotherapy [33, 39]. This is thought to occur through the reexpression of silenced tumor-suppressor genes once responsive to anticancer drugs, supported by the incidence of dysregulated methylation seen in drug-resistant cells. Similarly, DNMT1-i have also been known to synergize with immunotherapy [39, 40]. This is suggested to be due both to the aforementioned mechanism, and through the reexpression of suppressed ERVs (endogenous retroviral sequences) and other proteins recognized by T cells to induce an innate immune response [40, 41]. Furthermore, studies using decitabine and DNMTi-RG108 found increased radiosensitivity and enhanced growth inhibition in treated breast, colon, and esophageal cancer cells. These cells showed a greater apoptosis rate, G2/M phase arrest, and an increased proportion of cells in G1. Though the specific mechanism is unknown, analysis suggested a complex multi-gene pathway reactivated by demethylation [39, 41].

Conclusion

Though progress in hypomethylating treatment has long been impeded by the toxicity of the approved nucleoside drugs, the advances in protein modeling and construction of the GSK-analogs opens the field to more intensive study and fine-tuning of the existing drugs.

Further investigation into the sources of toxicity in the nucleoside drugs and GSK is needed, focusing on known shared mechanism steps including DNMT1 degradation, in order to determine potential for abatement or reversibility. Particular attention should be given to understanding the mechanism of RG108 due to its preferential binding and lower toxicity to see if its effects are reproducible with greater anticancer action.

Additionally, current clinical trials suggest a difficult path for epigenetics in monotherapy but indicate a highly lucrative application in combination therapy for more robust and targeted treatment across tumor types. Focusing research, particularly clinical trials, on cancers with known high S-phase fraction may find more responsive targets for demethylating therapy. This highlights the importance of continuing research specifically in demethylating agents in combined therapy, particularly with the newly discovered DNMT1-is.

List of Abbreviations

5-aza: 5-azacytosine
AML: acute myeloid leukemia
ASO: antisense oligonucleotide
DN: deoxyribonucleoside
DNA: deoxyribonucleic acid
DNMT1: DNA methyltransferase 1
DNMT1-i: DNA methyltransferase 1 inhibitor
ERV: endogenous retroviral sequence
MDS: myelodysplastic syndrome
RN: ribonucleoside
SAM: S-adenosylmethionine

Conflicts of Interest

The author declares that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

This study did not require ethics approval and/or participant consent as it involved only review of existing literature.

Authors' Contributions

NM: designed study, collected and analyzed references, drafted the manuscript, and gave final approval of the version to be published

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