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Mini-review

Partnering with PARP inhibitors in acute myeloid leukemia with FLT3-ITD

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ABSTRACT

Internal tandem duplications within the juxtamembrane domain of *fms*-like tyrosine kinase 3 (FLT3-ITD) occur in acute myeloid leukemia (AML) cells of 20–25% of patients and are associated with poor treatment outcomes. FLT3 inhibitors have been developed, but have had limited clinical efficacy due to development of resistance, highlighting the need for better understanding of the function of FLT3-ITD and how to target it more effectively using novel combination strategies. Poly (ADP-ribose) polymerase (PARP) inhibitors have shown efficacy in cancers with impaired homologous recombination (HR) due to BRCA mutations, but PARP inhibitor efficacy has not been fully explored in BRCA-proficient cancers, including AML. Recent research has connected inhibition of FLT3-ITD signaling to downregulation of numerous DNA repair proteins, including those involved in HR, and the novel combination with PARP inhibitors induces synthetic lethality in AML. Additionally, PARP inhibitor therapy may also target the highly error-prone alternative non-homologous end-joining (ALT NHEJ) DNA repair pathway in which PARP participates, thereby decreasing genomic instability and development of therapy resistance. Therefore, PARP inhibitors may be attractive therapeutic agents in combination with FLT3 inhibitors in FLT3-ITD AML.

1. Introduction

Acute myeloid leukemia (AML) is a markedly heterogeneous malignancy characterized by accumulation of abnormal myeloid precursors in the bone marrow and blood [1]. AML is the most common form of acute leukemia in adults and results in the most leukemia-related deaths annually.

Current standard AML treatment, consisting of cytotoxic chemotherapy with or without hematopoietic stem cell transplantation, is curative in 35–40% of patients under the age of 60 years [1]. However, the majority of AML patients are older, and older patients cannot tolerate or do not respond to cytotoxic chemotherapy, and are frequently treated with less intensive approaches [1]. Current treatment strategies result in an overall survival of only 5–10 months in older patients, and cure only 5–15% [1]. It is therefore clear that new strategies for treatment of AML are necessary to improve patient outcomes.

The heterogeneity of AML has become increasingly well-defined with the advent of new and better molecular techniques, and genetic changes in AML have been linked to prognosis [1,2]. Additionally, novel therapeutic agents targeting mutations in AML cells are in development including IDH1/2 inhibitors, BCL2 inhibitors, DNA methyltransferase (DNMT) inhibitors, and tyrosine kinase inhibitors targeting mutations in *fms*-like tyrosine kinase 3 (FLT3) [3]. Notably, two FLT3 inhibitors, midostaurin [4] and gilteritinib [5], were recently approved by the United States Food and Drug Administration (FDA).

2. FLT3 mutations

Mutations in the gene encoding FLT3 are among the most common molecular changes found in AML, affecting AML cells of approximately 30% of patients [6]. FLT3 is a receptor tyrosine kinase that functions in regulation of proliferation and differentiation of normal hematopoietic stem cells and is expressed on AML cells [2,6]. FLT3 mutations include internal tandem duplications (ITD) in the juxtamembrane domain and point mutations in the activating loop of the tyrosine kinase domain (TKD) [6]. FLT3-ITD is present in 20–25% of AML, while TKD mutations are present in approximately 5% [2].

While both FLT3-ITD and FLT3-TKD mutations cause constitutive activation of FLT3 signaling [6], pathways differ, leading to differences in clinical presentation and prognosis. Constitutive signaling induced by FLT3-ITD is aberrant, activating signal transducer and activator of transcription (STAT) 5 and its downstream targets, in addition to

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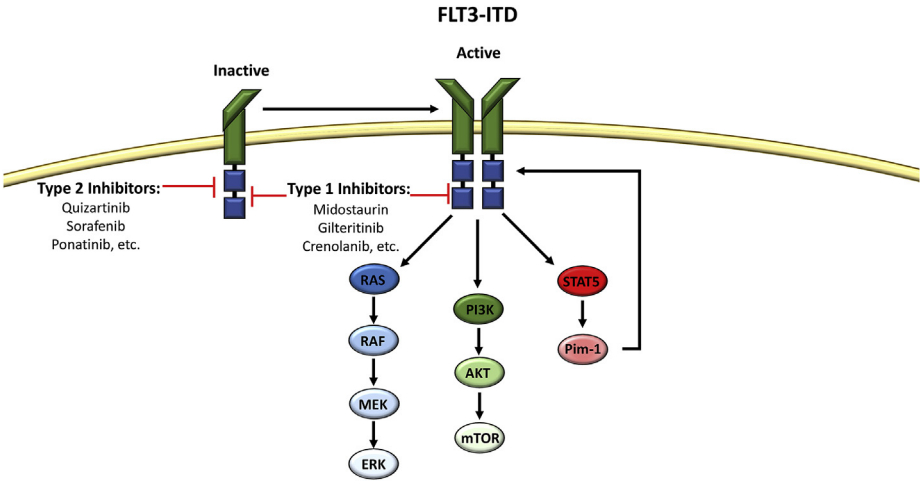

Fig. 1. FLT3 inhibitors reduce signaling downstream of the FLT3-ITD receptor. Type 1 inhibitors such as midostaurin, gilteritinib and crenolanib bind the ATP-binding pocket when the receptor is in the active conformations. Type 2 inhibitors such as quizartinib, sorafenib, and ponatinib bind a site adjacent to the ATP-binding pocket that is only exposed when the receptor is inactive.

phosphoinositide 3 kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) and RAS/mitogen-activated protein kinase (MEK)/extracellular-signal-regulated kinase (ERK) signaling [1,6] (Fig. 1). In contrast, FLT3-TKD mutations signal more similarly to the wild-type FLT3 receptor, activating PI3K/Akt/mTOR and RAS/MEK/ERK, but not STAT5 [7].

AML with FLT3-ITD presents with high white blood cell counts and the prevalence of FLT3-ITD is highest in AML with a normal karyotype [2,6]. Additionally, though there is some variability based on concurrent nucleophosmin 1 (NPM1) mutations and on allelic ratio, FLT3-ITD is generally associated with high relapse rate after treatment response, rapid onset of relapse and short overall survival [2,6]. In contrast, AML with FLT3-TKD mutation does not have a distinctive presentation and has an intermediate, rather than an unfavorable, prognosis [2].

The high frequency of FLT3-ITD as well as the poor outcomes of AML patients with FLT3-ITD have made this receptor a particularly attractive candidate for rational drug design of molecularly targeted treatments [1,6]. However, current targeted FLT3 inhibitors have yet to demonstrate the anticipated therapeutic effectiveness and as a result, new efforts are being directed toward validating novel combinations with these inhibitors to increase their success [3,8].

3. FLT3 inhibitors

Current FLT3 inhibitors are classified as first- and second-generation, as well as types I and II. First-generation FLT3 inhibitors, such as midostaurin, are tyrosine kinase inhibitors (TKIs) that were identified or developed for other purposes but were then also found to inhibit FLT3. They have broad receptor tyrosine kinase specificity which may be beneficial for inhibiting additional signaling pathways in AML cells [8]. In contrast, second-generation FLT3 inhibitors, such as quizartinib and gilteritinib, have greater selectivity for the FLT3 receptor and are more potent FLT3 inhibitors [8]. Type I FLT3 inhibitors, including midostaurin and gilteritinib, bind the receptor in its active conformation, while type II inhibitors, including quizartinib, bind in its inactive conformation [8] (Fig. 1). While Type I inhibitors are effective in inhibiting both FLT3-ITD and FLT3-TKD mutations, FLT3-TKD mutations at D835, the most common site, favor the active conformation, and type II inhibitors are therefore not effective [8] (Table 1).

The development of FLT3 inhibitors was initially undertaken with the expectation of success similar to the groundbreaking results seen with imatinib mesylate in the treatment of chronic myelogenous leukemia (CML). In CML, the BCR-ABL fusion gene encodes a constitutively active receptor tyrosine kinase [9]. Treatment with single-agent BCR-ABL-targeted TKIs such as imatinib mesylate is highly effective in inducing remissions and long-term disease control in CML [9]. However, this level of efficacy has not been seen with FLT3 inhibitors in AML with FLT3 mutations.

Although the rationale for FLT3 inhibitor drug design is supported by the success of BCR-ABL inhibitors in CML, FLT3 inhibitors have encountered numerous challenges in clinical trials. A major shortcoming of first-generation inhibitors has been dose-limiting toxicities associated with their inherent off-target effects [8]. Second-generation inhibitors are more specific to the FLT3 receptor and thus have fewer off-target effects and dose-limiting toxicities. However, although second-generation FLT3 inhibitors produce better initial response rates, their specificity makes them more susceptible to induction of resistance mechanisms. For example, the second-generation type II inhibitor, quizartinib, induced responses in more than half (53%) of patients with FLT3-ITD, but responses lacked durability, lasting only months [10], and loss of response to quizartinib was found to be associated with development of new activating TKD mutations which caused resistance to type II inhibitors [8,11]. Additionally, though the second-generation type I inhibitor gilteritinib has shown efficacy in the relapsed/refractory setting which led to its FDA approval in November 2018, there is still eventual disease progression [5].

The limited single-agent success of FLT3 inhibitors has prompted research into combining them with other agents. Combination of the first-generation type I inhibitor midostaurin with cytarabine with daunorubicin chemotherapy improved outcomes [4], leading to its FDA approval in combination with first-line chemotherapy for AML with FLT3 mutations in April 2017. Additionally, targeted combination approaches based on the biology of FLT3 mutations have the potential for enhanced benefit without enhanced toxicities. Novel combinations with FLT3 inhibitors are being explored for the treatment of AML with FLT3 mutations (Table 1) [8].

4. PARP inhibitors and their mechanisms of action

Poly (ADP-ribose) polymerase (PARP) 1 is a nuclear protein that works by poly-ADP-ribosylating (PAR) itself and other proteins to catalyze the repair of DNA single-strand breaks (SSBs) and double-strand breaks (DSBs), and particularly alternative non-homologous end-joining (ALT NHEJ) [12–16]. PARP inhibitors cause accumulation of SSBs and DSBs by blocking PARP1 activity and subsequently base excision repair (BER) [17]. Formation of DSBs in this manner triggers the homologous recombination (HR) repair pathway [18], but cancer cells with mutated or missing HR proteins, particularly BRCA1 and 2, cannot repair these lesions and thus die by the mechanism known as synthetic lethality (Fig. 2).

PARP inhibitors have shown efficacy in BRCA1-and 2-deficient breast and ovarian cancers because they have impaired HR [19]. Clinical trials using PARP inhibitors have led to the FDA approval of

Table 1
FLT3 inhibitors in clinical trials for AML.

		Combinations Under Investigation			
Name	Other Targets	Chemotherapy	Targeted	Other Agents	FDA Approval
First Generation Inhibitors					
Type I:					
Midostaurin (PKC412)	AKT, Fgr, Flk-1, KIT, PDGFRβ, PKA, PKC, Src, Syk, VEGFR1, VEGFR2	Cladribine, Cytarabine, Daunorubicin, Idarubicin, Etoposide, Fludarabine, Mitoxantrone	DNMTi: Azacitidine, Decitabine mTORi: Everolimus (RAD001) Pim Kinase Inhibitor: LGH447 Proteosome Inhibitor: Bortezomib	Itraconazole	AML (2017): 1st line in FLT3 mutated AML combined with standard chemotherapy
Sunitinib (SU11248)	KIT, PDGFRβ, RET, VEGFR2	Cytarabine, Daunorubicin, Idarubicin	None	None	Gastrointestinal Stromal Tumors (2006): Resistant and/or progressive disease Renal Cell Carcinoma (2006/2007): Advanced disease Pancreatic Neuroendocrine Tumors (2011): Advanced stage/metastatic disease Renal Cell Carcinoma (2017): Adjuvant treatment of high risk, recurrent disease
Type II:					
Ponatinib (AP24534)	ABL, FGFR1, KIT, LYN, PDGFRα, RET, SRC, TEK, VEGFR2	Cytarabine, Idarubicin	DNMTi: Azacitidine	None	ALL (2012): Philadelphia chromosome-positive, resistant to other inhibitors CML (2012): Resistant disease
Sorafenib (DB00398)	KIT, PDGFRβ, RAF, RET, VEGFR1, VEGFR2, VEGFR3	Busulfan, Cladribine, Clofarabine, Cytarabine, Daunorubicin, Fludarabine, Idarubicin, Mitoxantrone	CDKi: Palbociclib DNMTi: Azacitidine, Decitabine FLT3i: Crenolanib HDACi: Vorinostat Proteosome Inhibitor: Bortezomib Protein Translation Inhibitor: Omacetaxine Mepesuccinate SINE: Selinexor	Plerixafor, Filgrastim	Kidney Cancer (2005): Advanced renal cell carcinoma Liver Cancer (2007): Unresectable hepatocellular carcinoma Thyroid Cancer (2013): Progressive, relapsed/refractory, or metastatic disease
Second Generation Inhibitors					
Type I:					
Crenolanib (CP-868-596)	PDGFRβ	Cytarabine, Daunorubicin, Etoposide, Fludarabine, Idarubicin, Mitoxantrone	DNMTi: Azacitidine FLT3i: Sorafenib	None	No
Gilteritinib (ASP2215)	ALK, AXL, LTK	Cytarabine, Daunorubicin, Idarubicin	BCL2 Inhibitor: Venetoclax DNMTi: Azacitidine PD-L1 Antibody: Atezolizumab	None	AML (2018): Relapsed or refractory AML with FLT3 mutations
Type II:					
Quizartinib (AC220)	KIT, PDGFRβ, RET	Cytarabine, Daunorubicin, Idarubicin	BCL2 Inhibitor: Venetoclax DNMTi: Azacitidine, Decitabine MDM2 Inhibitor: Milademetan	None	No

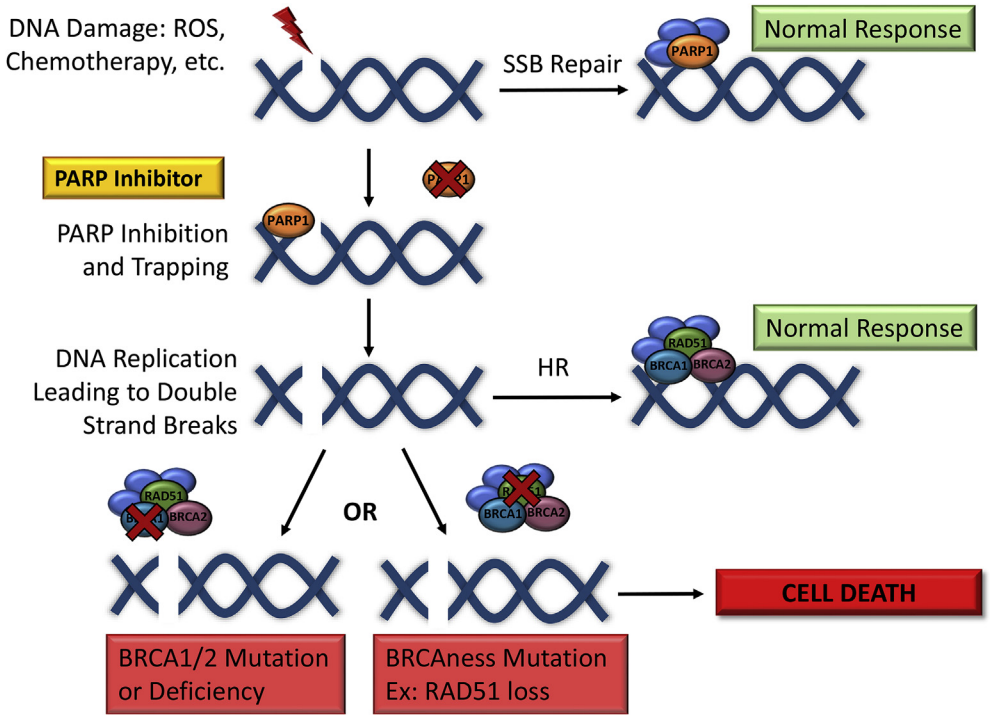

Fig. 2. Synthetic lethality in HR-deficient cells with the use of PARP inhibitors. Normal cells that experience damage can repair the damage using PARP-catalyzed single-strand break (SSB) repair. When PARP inhibitors are used, SSB repair is inhibited and PARP1 may be trapped to break sites, leading to the accumulation of SSBs which will then develop into double-strand breaks (DSBs) during DNA replication. Healthy, unmutated cells can use homologous recombination (HR) to repair the break. In cancer cells with BRCA1/2 deficiencies or deficiencies in other key HR proteins such as RAD51 (shown), HR can no longer occur and the DSBs are cytotoxic.

olaparib, rucaparib, and talazoparib in BRCA-deficient cancers [20–23]. Recently, deficiencies in numerous other proteins involved in HR have been found to lead to a comparable impairment of DSB repair, and this loss of function is termed BRCAness for its similarity to the BRCA-deficient phenotype [19]. Because of this functional similarity, attempts are underway to expand the efficacy of PARP inhibitors to cancers with BRCAness [24]. Recent work has also focused on more potent PARP inhibitors, such as talazoparib, which have been shown to cause enhanced cytotoxicity by virtue of trapping PARP in chromatin [25].

Studies in both AML and CML have shown that PARP inhibitors olaparib and talazoparib may have therapeutic potential [26]. Notably, PARP inhibitors are now being explored in FLT3-ITD AML with the idea of first inhibiting DSB repair that is upregulated through aberrant FLT3 signaling [27,28]. Research has connected inhibition of FLT3-ITD signaling with downregulation of HR similar to BRCAness, suggesting that novel combination strategies, including FLT3 inhibitors with PARP inhibitors, may induce synthetic lethality to more effectively treat FLT3-ITD AML [27,28]. PARP inhibitor therapy may also target the upregulated error-prone DSB repair pathway, ALT NHEJ, in which PARP1 participates, thus decreasing genomic instability and the development of resistance to therapy [29,30]. PARP inhibitors may also be combined with epigenetic drugs for synergistic cytotoxicity in AML [31].

5. Creating and exploiting an HR defect allowing sensitization to PARP inhibitors in AML

FLT3-ITD has been linked, via STAT5 activation, to upregulation of RAD51, a key HR protein that facilitates DNA strand invasion during HR [27]. The FLT3 inhibitor PKC412 (midostaurin) was shown to downregulate RAD51 mRNA and protein expression and to maintain phosphorylated H2AX levels, markers of DSBs, in MV4-11 cells with FLT3-ITD, and FLT3-ITD AML patient samples, consistent with inhibition of the HR repair pathway [27]. Moreover, short interfering RNA (siRNA) silencing of FLT3 resulted in loss of RAD51 exclusively in cells with FLT3-ITD [27].

More recently, the FLT3 inhibitor AC220 (quizartinib) was found toinhibit key DNA repair proteins including BRCA1 and 2, RAD51, and ligase IV (LIG4) and subsequently reduces the associated DSB repair pathways, HR and non-homologous end-joining (NHEJ), in FLT3-ITD AML cells [28]. Additionally, combining AC220 with the PARP inhibitors olaparib and talazoparib reduced numbers of leukemia stem/progenitor cells with FLT3-ITD in cell culture and also impaired leukemia progression in xenograft mouse models [28]. It was therefore concluded that the DSB repair deficiencies induced by the FLT3 inhibitor in FLT3-ITD AML cells mimicked deficiencies present in PARP inhibitor-sensitive cell lines, and thus the combination of AC220 and PARP inhibitors was synthetically lethal and, as a result, may benefit patients with these mutations [28].

PARP inhibitors have also been evaluated in AML cells with rearrangements of genes encoding transcription factors, including AML1-ETO, KMT2A-AF9 and PML-RARα, which have been linked to altered HR activity. AML1-ETO and PML-RARα rearrangements were associated with reduced expression of key HR genes including *Rad51*, *ATM*, *BRCA1*, and *BRCA2*, as well as a functional inability to recruit RAD51 to DSBs [32]. Due to this BRCAness effect, AML cell lines with these rearrangements also show increased sensitivity to PARP inhibitors, indicating that PARP inhibitor treatment may be effective in these AML subsets [32,33]. Conversely, cells with the KMT2A [formerly mixed-lineage leukemia (MLL)] fusion protein KMT2A-AF9 demonstrated increased HR activity, leading to PARP inhibitor resistance. KMT2A-AF9 was shown to consistently induce the transcription factor HOXA9, which was then discovered to be an upstream regulator of RAD51 and to functionally increase HR when overexpressed [32]. This led to the conclusion that induction of this factor is responsible for PARP inhibitor resistance in these cells [32]. Moreover, HOXA9 knockout resulted in downregulated HR, creating sensitivity to PARP inhibitors, and chemical inhibition of the HOXA9 downstream effector GSK in combination with PARP inhibitor treatment reduced growth of cells with KMT2A fusions both *in vitro* and *in vivo*, similar to single-agent PARP inhibitor treatment of cells with AML-ETO or PML-RARα rearrangements [32]. Additionally, epigenetic profiling has demonstrated that 15–20% of AML present as 'BRCAlow' due to deficiencies in either BRCA1 or BRCA2 making these cells potentially susceptible to PARP inhibition as well [34].

These findings have significant implications for the use of PARP inhibitors in AML, including AML with FLT3-ITD, and indicate the need

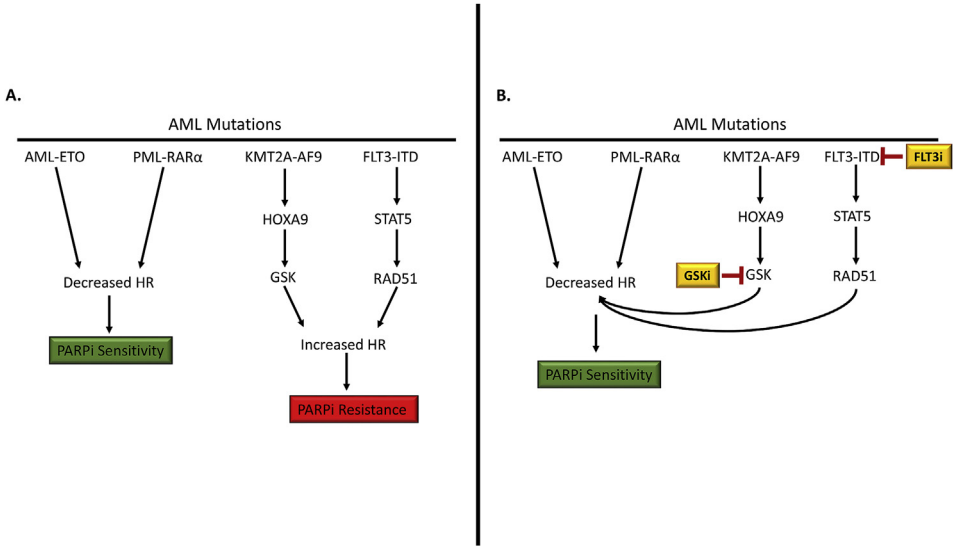

Fig. 3. PARP inhibitor-based synthetic lethality in AML. AML with AML-ETO or PML-RARα rearrangements is inherently sensitive to PARP inhibitors due to reduced homologous recombination (HR), while other rearrangements such as KMT2A-AF9 and mutations such as FLT3-ITD upregulate HR factors, resulting in resistance to PARP inhibitors (A). Use of other targeted inhibitors in these resistant forms of AML can induce a state of HR deficiency, resulting in PARP inhibitor sensitivity (B).

to further define mechanisms of sensitivity and resistance in diverse AML subtypes (Fig. 3). Elucidation of relevant pathways is key to determining whether PARP inhibition is a valid option in AML and how it may be used effectively to target specific AML subtypes.

6. Combining PARP inhibitors with other agents to enhance PARP trapping in AML

Our group has recently published a novel therapy paradigm combining DNMT inhibitors with PARP inhibitors to enhance cytotoxicity in AML cells (Fig. 4). Our paradigm is based on evidence, published by our group and others, for interaction of DNMT1, 3a, and 3b, with PARP1 in DNA damage repair complexes [31,35–37]. DNMT inhibitors reduce DNA methylation and DNMT function in leukemia cells at low doses [38]. Abnormal DNA methylation changes gene expression in cancer cells, and these changes may be reversed with the use of DNMT inhibitors [39,40]. Critical to this idea is that DNMT inhibitors reduce DNA methylation by becoming incorporated into replicating DNA as an altered base and covalently binding DNMTs to their integration sites. This leads to the inhibition of DNMTs' catalytic function, triggering their degradation and nuclear depletion in soluble fractions [41]. In contrast, in insoluble chromatin fractions, DNMT1 actually increases [42]. In our recent report, we outline how DNMT inhibitor-induced binding of DNMTs into DNA also correlates with increased tight binding of PARP1 into chromatin, involving interactions between the two proteins [35,36] that we demonstrated [31] and/or PARP1 and DNMT1 binding at DNA damage sites [37]. In our published study, we have shown that decitabine or azacitidine with talazoparib at low nanomolar concentrations, compared to single drugs, leads to increased tight binding of DNMT1 and PARP1 in chromatin, retention of these proteins directly at sites of SSBs and DSBs for up to 6 h post micro-irradiation, and increased DSB frequency [31]. These dynamics produce synergistic cytotoxicity in cancer cells and *in vivo* tumor responses [31]. Notably, studies in primary AML patient samples showed that while AML patient cells with FLT3-ITD and DNMT mutations were among those that responded to the PARPi/DNMTi therapy, not all samples with these mutations were sensitive to this combination [31]. Therefore, factors yet unidentified dictate sensitivity to this combination therapy. We have used our data outlined above to derive a novel therapy strategy, now in a Phase 1 clinical trial for AML (clinicaltrials.gov; NCT02878785) to enhance the effectiveness of the DNMT inhibitor decitabine by combining it with the PARP inhibitor talazoparib.

Our group has also investigated combinations of PARP inhibitors with histone deacetylase (HDAC) inhibitors, similarly demonstrating enhanced anti-cancer effect in leukemia cell lines and AML patient samples [43]. We demonstrated that treatment with HDAC inhibitors resulted in reduced NHEJ through acetylation of the repair proteins Ku70, Ku80, and PARP. This PARP acetylation was associated with increased binding and subsequent trapping to DSBs with the use of PARP inhibitors and a resultant increase in cell death [43]. Additionally, it has been shown that the triple combination of HDAC, PARP, and DNMT inhibitors produced enhanced synergy in leukemia cells, furthering the use of PARP inhibitors in this disease [44].

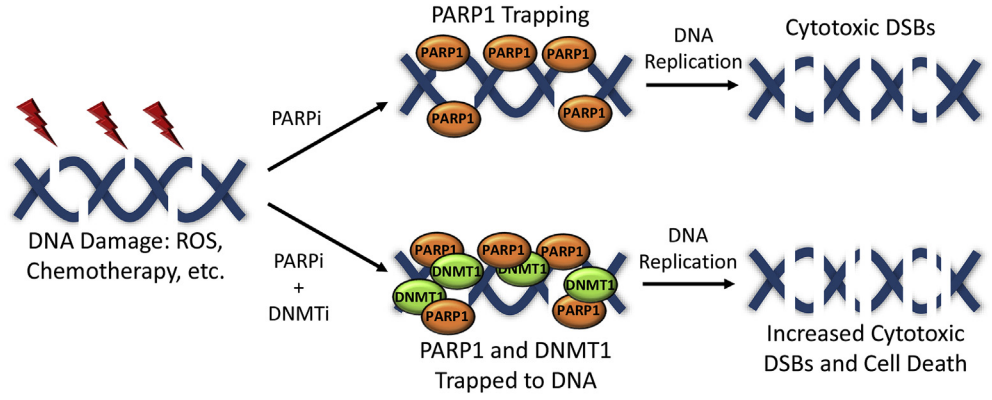

Fig. 4. DNMT inhibitors enhance the cytotoxic effects of PARP inhibitors. PARP inhibitors alone trap PARP1 to single-strand breaks, resulting in the formation of double-strand breaks. When DNMT and PARP inhibitors are combined, large DNMT-PARP1 complexes are trapped to DNA break sites. These bulky adducts result in enhanced formation of cytotoxic double-strand breaks, leading to increased cell death.

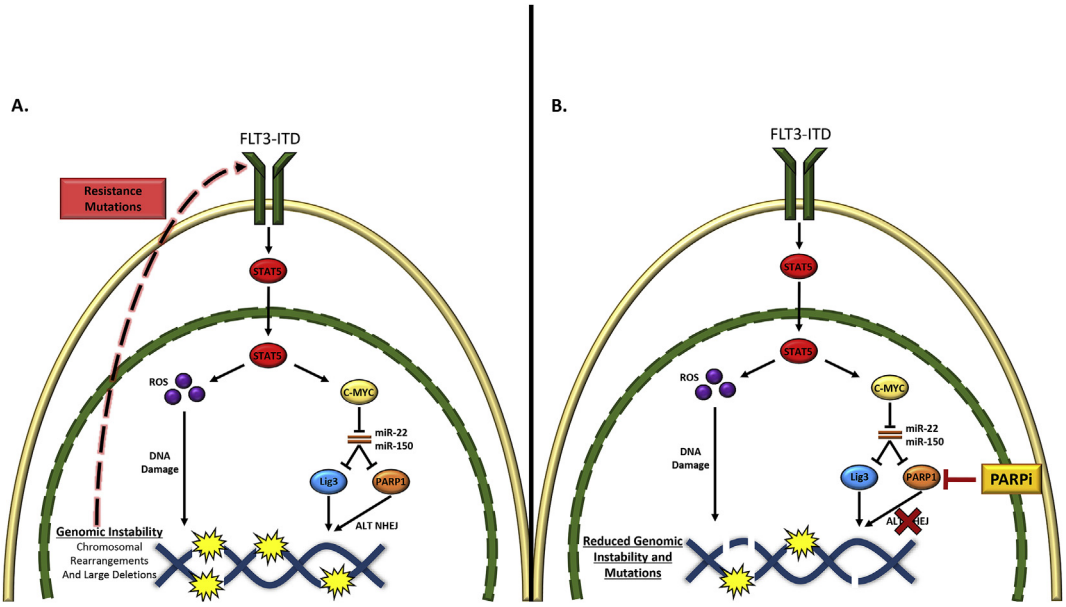

Fig. 5. FLT3-ITD signaling leads to genomic instability that can be reduced with the use of PARP inhibitors. FLT3-ITD signaling leads to downstream upregulation of ligase III (Lig3) and PARP1, key factors in the highly error-prone ALT NHEJ repair pathway. In combination with upregulated reactive oxygen species (ROS), this leads to large genetic aberrations including chromosomal rearrangements and deletions. In turn, these changes make these cells more prone to developing genetic alterations that may cause disease progression and drug resistance (A). The use of PARP inhibitors in these cells can reduce ALT NHEJ and thereby decrease genomic instability, disease progression and drug resistance (B).

7. Using PARP inhibitors to decrease genomic instability

In a recent retrospective study performed at the University of Maryland Greenebaum Comprehensive Cancer Center, we found that, at relapse, a high proportion of patients initially diagnosed with cytogenetically normal FLT3-ITD AML had cytogenetic changes which included rare structural chromosomal translocations [45]. This finding indicates that genomic instability may be significant in leading to relapse and as such, reducing these changes may be therapeutically relevant for treating FLT3-ITD AML [45]. Additionally, FLT3-ITD signaling has been shown to increase generation of reactive oxygen species (ROS), DSBs, and components of highly error-prone DNA repair, including ligase IIIα (LIG3) and PARP1, leading to genomic instability [29,46]. Both LIG3 and PARP1 are key proteins in ALT NHEJ, with PARP1 taking part in the rate-limiting step of displacing Ku-complexes for initiation of ALT NHEJ [30,47]. Significantly, research suggests that LIG3 aids in ALT NHEJ-induced chromosomal translocations [48] but conversely, LIG4 and XRCC4 present in classical Ku-dependent NHEJ prevent ALT NHEJ-induced changes [30,49]. These data indicate that repair in FLT3-ITD AML is highly aberrant and explain the frequency of large DNA deletions seen in this cancer (Fig. 5A) [29,50].

Our laboratory also showed that FLT3-ITD signaling to c-MYC downregulates microRNA (miR)-150 and miR-22 and that their loss leads to increased transcription of the ALT NHEJ factors LIG3 and PARP1, while subsequent inhibition of c-MYC or overexpression of the miRs reversed these effects (Fig. 5A) [29]. Thus we concluded that c-MYC contributes to genomic instability and upregulated ALT NHEJ in FLT3-ITD AML, further defining this process and suggesting that ALT NHEJ may be targeted in this cancer [29]. Additionally, the predominance of PARP1 in the process of ALT NHEJ led to studies showing that PARP1 inhibition strongly reduced chromosomal translocations, indicating that PARP1 is a primary contributor to these changes during ALT NHEJ [30]. Together these data indicate that treatment with clinically relevant PARP1 inhibitors could significantly reduce genomic instability in FLT3-ITD-expressing AML by abrogating ALT NHEJ-mediated repair at multiple points (Fig. 5B).

8. Conclusions

Though FLT3 inhibitors have not had optimal success as single agents, better efficacy is expected through their combination with other therapeutic agents. Thus far, FLT3 inhibitors have been combined with chemotherapy and have had clinical benefit, and targeted combinations have the potential not only for enhanced efficacy, but also for favorable tolerability. FLT3-ITD signaling upregulating HR-mediated DSB repair pathways has led to studies using FLT3 inhibitors to induce HR defects that then can induce synthetic lethality with PARP inhibitor therapy [28].

FLT3-ITD signaling also increases the genomic instability that likely contributes to poor prognosis of FLT3-ITD AML by both increasing the generation of ROS and impacting DSB repair pathways. The novel combination of FLT3 and PARP inhibitors will likely reduce genomic instability, and specifically decrease the acquisition of chromosomal deletions and translocations that likely contribute to disease progression and to the development of resistance. Additionally, combined FLT3 and PARP inhibitor treatment may delay or prevent the emergence of resistance to FLT3 inhibitors via diverse mechanisms including acquisition of mutations. Though this combination must still be investigated in a clinical setting, preclinical data are promising.

Conflicts of interest

The authors declare no conflicts of interest.

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