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Perspective on the Pipeline of Drugs Being Developed with Modulation of DNA Damage as a Target

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Abstract

Inhibitors of various elements of the DNA repair pathways have entered clinical development or are in late preclinical stages of drug development. It was initially considered that agents targeting DNA repair would act to overcome tumor resistance to chemotherapy and radiotherapy. More recent data have shown that targeting DNA repair pathways can be effective in selected tumors via a synthetically lethal route, with single agent activity having been shown with poly-ADP ribose polymerase (PARP) inhibitors. An increased understanding of the biology and interaction of the DNA repair pathways also means that rational combination of DNA repair inhibitors may also give great benefit in the clinic. *Clin Cancer Res; 16(18); 4527–31. ©2010 AACR.*

Repair of DNA and, thus, preservation of the genetic code are critical for normal cellular function. To this end, human cells have at least five recognized pathways that protect the genome by signaling specific types of DNA damage and carrying out repair (reviewed in refs. 1–3). In cancer cells, these pathways represent a curious dichotomy; it is well recognized that mutations in the pathways can predispose to cancer and are hallmarks of many of the hereditary cancer syndromes (4–6). However, once an immortalized tumor cell has developed, the DNA repair pathways can be used by this cell to overcome many of our standard anticancer treatments and, hence, are a cause of treatment resistance. Increasing evidence in the literature shows that tumor tissue has high levels of some elements of the DNA repair pathways (7, 8), and is able to use these pathways to repair damage caused by many of our standard anticancer therapies. Therefore, inhibiting DNA repair may "level the playing field" and make the tumor more vulnerable to treatment.

The major DNA repair pathways are direct repair, mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), and double-strand break (DSB) recombinational repair, which includes both nonhomologous end-joining (NHEJ) and homologous recombinational repair (HHR; refs. 1, 2, 9). O^6-alkylguanine-DNA alkyltransferase (MGMT, OGAT, ATase) is the main component of the direct repair pathway, an efficient mechanism of DNA repair in which the altered base is corrected without removal or disruption of the phosphodiester backbone. Overexpression of ATase in mammalian cells confers resistance to DNA-alkylating agents (reviewed in ref. 10), and is a major factor in tumor resistance to these drugs. NER is involved in the repair of UV damage and removal of bulky DNA adducts, such as those caused by cross-linking agents. MMR repairs replication errors and is frequently mutated in cancer cells allowing tolerance of such lesions (11–13). BER is involved in the repair of single-strand breaks, contributing to resistance to ionizing radiation and alkylating agents. Recombinational repair has two pathways: the error-free HRR in dividing cells and error-prone NHEJ active in G1. These two pathways repair much of the damage caused by radiotherapy and chemotherapeutic agents, such as cisplatin and mitomycin C (2).

Some compounds in the clinic or in late preclinical development inhibit direct repair and elements of the base excision and DSB repair pathways. The initial development of inhibitors of DNA repair pathways was designed to overcome chemo- or radio-resistance (14–19). However, the increasing knowledge about the complexity and interactions of the DNA damage response pathways, as well as the entry of a range of compounds into the clinic, have led to a fascinating area of drug development, with opportunities for improving on existing treatments and for the design of rational combinations of novel agents to improve treatment response. Table 1 shows the range and variety of these DNA damage response modulators that have entered the clinic in recent years.

Chemo-potentiation

When considering the pipeline of novel agents that have entered clinical development or are at a late preclinical phase over the last 5 years, it is worth briefly reviewing the earlier trials in which blocking a DNA repair pathway was the primary aim. To date, a common theme has emerged in the majority of trials, which seems to be limiting the effectiveness of this strategy potentiation of normal tissue toxicity. Depletion of MGMT and, hence, disruption of the direct repair pathway by O^6benzylguanine or lomeguatrib was successfully achieved more than 10 years ago. These agents were combined with carmustine and temozolomide, respectively, and although pharmacodynamic assays confirmed depletion

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Table 1. DNA damage response–modulating drugs in clinical development, grouped by repair pathway targeted

Agent	Company	Administration	Single and/or Combination Therapy	Disease indications	Clinical status
Direct repair (MGMT)					
O^6benzylguanine			Combination BCNU	GBM	Phase II complete
Lomeguatrib	KuDos	Oral	Combination with TMZ	Melanoma	Phase II complete
Single-strand break repair (PARP inhibitors, PARPi)					
PF0367338 (AG014699)	Pfizer	IV	Combination ++ single agent	Solid tumors, melanoma	Phase I and II complete and others ongoing
Olaparib (AZD2281)	AztraZeneca (KuDos)	Oral	Combination ++ single agent	BRCA defective, solid tumors various	Phase I and II studies completed and ongoing
Veliparib (ABT888)	Abbott	Oral	Combination ++	Various solid tumors	Phase I and II studies completed and ongoing
Iniparib (SAR240550, BSI 201)	Sanofi Aventis (Bipar)	IV	Combination	Triple negative breast	Phase III complete
MK4827	Merck	Oral	Single agent	Solid, BRCA ovarian	Phase I ongoing
CEP-9722	Cephalon	Oral	Combination with TMZ	Solid tumors	Phase I ongoing
E7016 (GPI 21016)	Eisai (MGI Pharma)	Oral	Combination with TMZ	Solid tumors	Phase I ongoing
LT673	Biomarin	Oral		Solid tumors	Phase I planned
Single-strand break repair (APE1 inhibitors APE1i)					
TRC102	Tracon	Oral	Combination with pemetrexed	Solid tumors	Phase I complete
Methoxyamine		IV	Combination with TMZ	Solid tumors	Phase I suspended
DSB repair (RAD51 inhibitor, RAD51i)					
MP470	Supergen	Oral	Single agent	Lymphoma and/or solid tumors	Phase I ? opened
DSB repair (ATM inhibitor, ATMi)					
KU55933	AstraZeneca (KuDos)	?	?	?	Preclinical
CP466722	Pfizer	?	?	?	Preclinical
DSB repair (DNA PK inhibitor, DNA PKi)					
NU7441	AstraZeneca (KuDos)	?	?	?	Preclinical

NOTE. Data taken from ClinicalTrials.gov (http://clinicaltrials.gov/) compounds that are thought to be in late preclinical development are also included for completeness.

Abbreviations: IV, intravenous; TMZ, temozolomide; GBM, glioblastoma multiforme; BCNU, carmustine or bis-xhloronitrosourea; ? indicates clinical studies not yet initiated.

of the target, this was achieved at the expense of the chemotherapeutic dose (14, 17). Enhanced normal tissue toxicity, in the form of more profound myelosuppression, meant that a significant reduction in chemotherapy dose was required, and phase II studies did not show a benefit in terms of increased tumor response (15, 18). When the first poly-ADP ribose polymerase (PARP) inhibitor in cancer treatment entered the clinic in 2003, it was also evaluated in combination with chemotherapy, with the initial reports being that a PARP-inhibitory dose of drug could be given with full dose temozolomide (19). This finding was not borne out in the subsequent phase II study, in which a 25% reduction in cytotoxic dose was needed for a tolerable regimen (20). Although this small study did suggest a possible clinical benefit of the combination, this has yet to be confirmed in a randomized study.

Enhancement of normal tissue toxicity is emerging as a common theme with some of the other PARP inhibitors when combined with chemotherapy. Studies with ABT888 (veliparib) and AZD2281 (olaparib) with a range of cytotoxic

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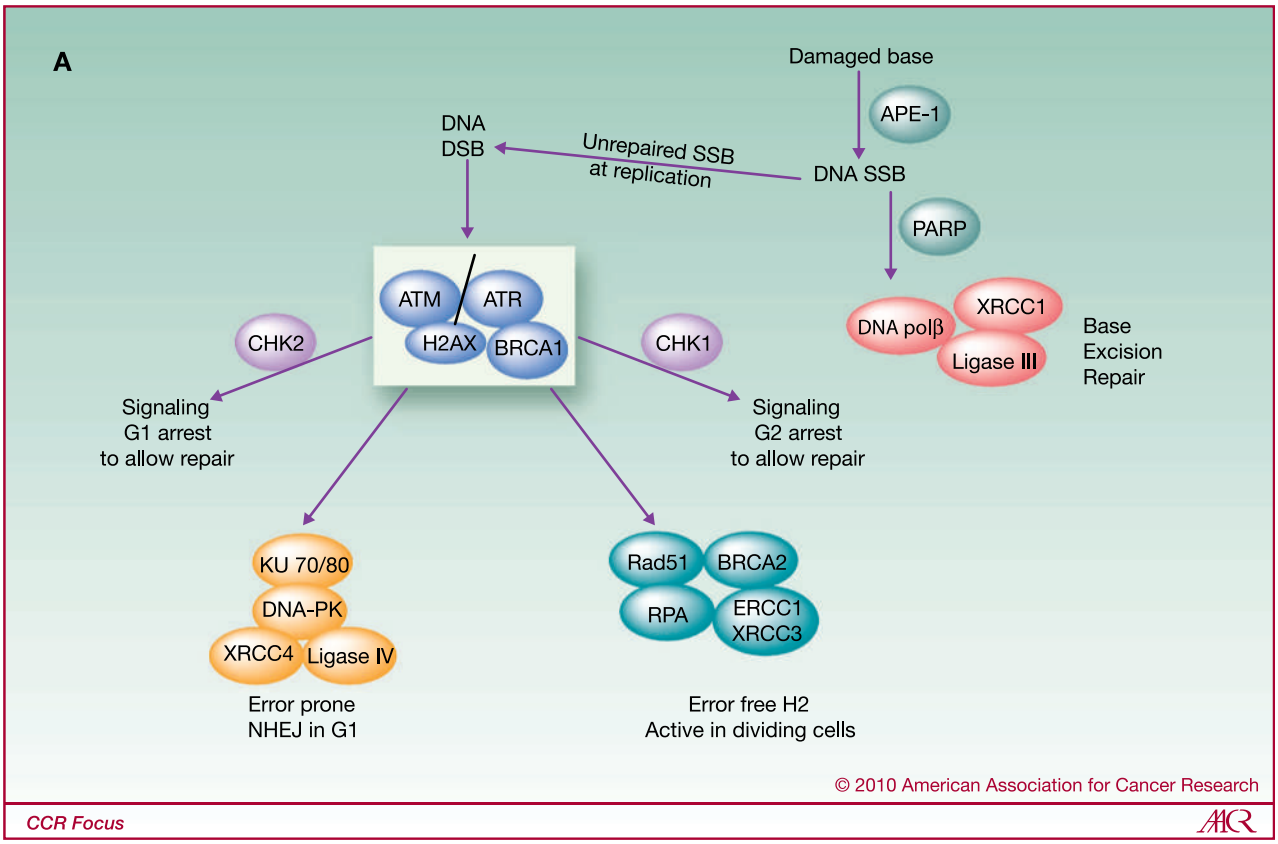

Fig. 1. Simplified schematic of signaling and repair of single- and double-DNA strand breaks to illustrate the interactions between pathways and potential rational inhibitor combinations. A, damaged DNA bases are excised involving APE-1, and single-strand break (SSB) activates PARP, which recruits other components of BER. In a dividing cell, unrepaired SSB will become DSB. The presence of DSBs is signaled via the ATM/ATR pathways. In nondividing cells, G1 arrest is signaled via Chk2, and NHEJ pathways repair the break. In dividing cells, G2 arrest allows error-free repair using HR.

agents have reported the need to reduce chemotherapy dose because of enhanced myelosuppression (21–23). The outlying data in this area are from the combination of BSI-201 with carboplatin and gemcitabine in triple negative breast cancer, in which very encouraging evidence of increased activity was observed with no increase in toxicity (24, 25). It has been speculated that this may be due to the intermittent schedule of dosing of the PARP inhibitor allowing bone marrow recovery. This theory would argue for the increased activity being due to chemo-potentiation, rather than single-agent PARP activity, acting through synthetic lethality on the proposed HRR-deficient triple-negative phenotype, as other studies showing single-agent activity have required continuous and profound PARP inhibition (26–28). Other agents targeting DNA damage response in late preclinical development are entering the clinic [inhibitors of DNA-dependent protein kinase (DNA PK), ataxia telangiectasia mutated (ATM), ATM- and Rad3-related (ATR), and RAD51; refs. 29–33]. These agents have also shown the ability to potentiate the activity of cytotoxic drugs in preclinical models; it remains to be seen whether this can be done without the increased toxicity and subsequent dose reductions that have been required in many of the previous studies. It may be that we are able to use these powerful inhibitors to fuller potential in the area of radiopotentiation. Radiation causes DNA single- and double-strand breaks, and many of the DNA repair inhibitors have been shown to be radio-potentiating (29, 30, 34). The increasing use of highly technical radiotherapy techniques [intensity modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), and tomotherapy] may allow radiation and/or inhibitor combination studies in which tumor response is improved without consequent increase in normal tissue toxicity.

One of the very exciting developments in the field of DNA damage response research in the last few years has been the preclinical (35, 36) and subsequent clinical demonstration (26–28) of the ability to cause synthetic lethality in selected cell types using a DNA repair inhibitor without also using a DNA damaging agent. Although, first shown with the use of PARP inhibitors in patients with familial breast and ovarian cancer carrying the BRCA genes, it has opened up the possibility that this much less toxic strategy may be a benefit in patients with sporadic tumors if a predictive molecular phenotype can be identified. Many research groups are now working to develop functional assays for DSB repair competence, or molecular signatures that will allow enrichment of patient populations within trials. An additional consequence of this pioneering research has been that DNA

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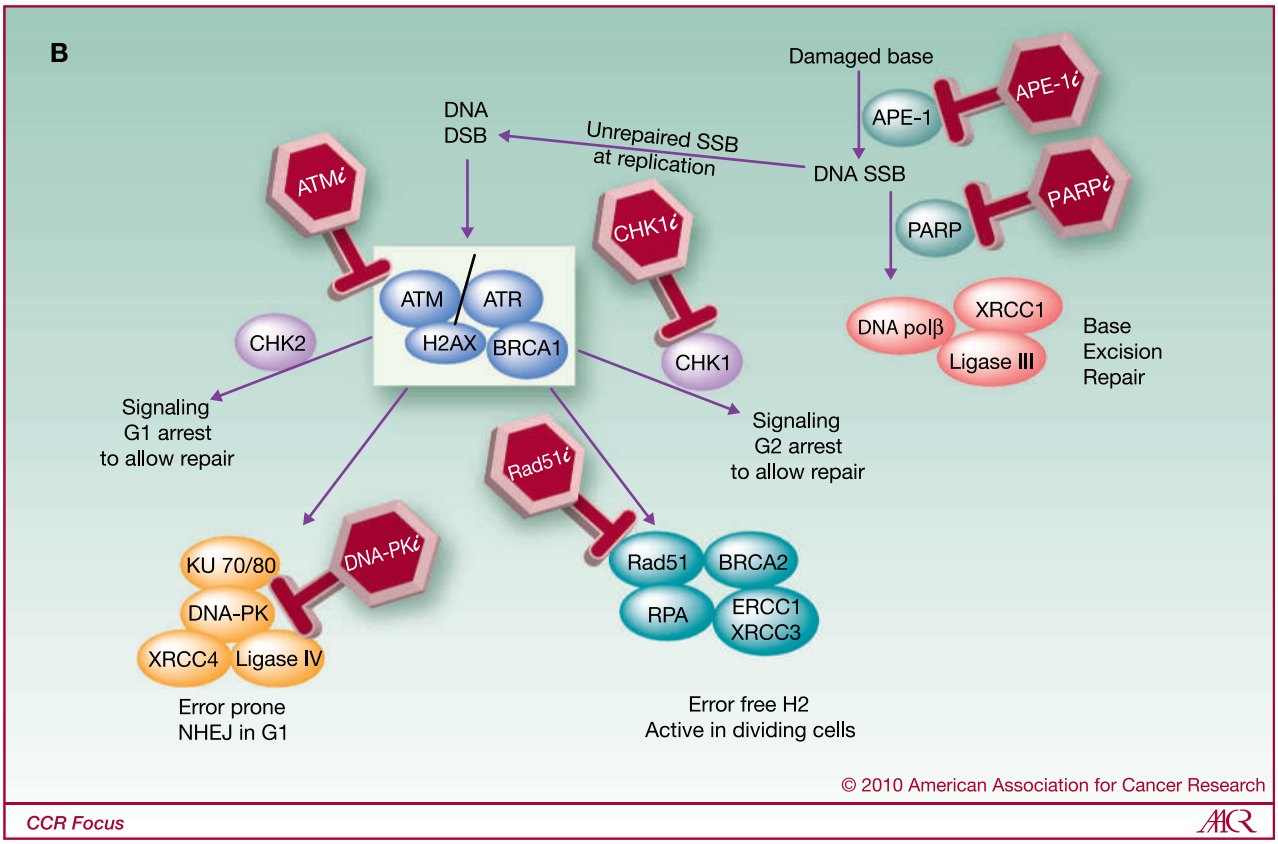

Fig. 1. *Continued*. B, simplified schematic of signaling and repair of single- and double-DNA strand breaks showing the points of action of current inhibitors in the clinic or in late preclinical development. Additionally, it is highlighted that Chk1 inhibitors have entered the clinic, presenting an opportunity to combine these agents with DNA damage response modulators.

repair inhibitors have been recognized as potentially active anticancer agents in their own right. With the expanding knowledge of the DNA damage response pathways and the plethora of drugs entering clinical development targeting different elements of these pathways, it will be possible to design trials in which novel combinations of repair inhibitors, including the checkpoint inhibitors (37–39), may be active, or in which patients are selected on the basis of the oncogenic mutation status of their tumor, for example mutations in ATR, ATM, or the Fanconi proteins may also predict for sensitivity to PARP inhibitors (40, 41). Figure 1A summarizes, in simplified form, the BER and DSB pathways, emphasizing the close interactions and cross talk between the BER and DSB repair pathways and cell-cycle checkpoint signaling. Figure 1B illustrates the current DNA damage response–modulating drugs targeting these pathways and related checkpoint signaling illustrating the fascinating potential for rational combination of these novel agents.

Conclusion

As the DNA repair inhibitors continue to move forward in clinical development, we need to be able to learn from and build on the lessons of history, so that the true potential of these drugs is realized. It is likely that they will ultimately be used in combination regimens; the response rates in the BRCA population are not at the levels seen in chronic myeloid leukemia and gastrointestinal stromal tumor with imatinib. Therefore, much work remains to be done in exploring scheduling to avoid increased toxicities. When a DNA damage–modulating agent is to be used to prevent repair, and so potentiate the activity of the cytotoxic agent, the drugs need to be given concurrently. It may be that pulsed schedules of the modulator would, in this situation, cause the desired tumor-cell kill, but allow normal tissue toxicity to recover. If the modulator is predicted to have single-agent activity in a particular disease setting, then scheduling apart from the cytotoxic with longer duration of coverage might be the optimal route. The interplay between the increasing knowledge of the biology of these pathways and the increasing ability to explore the molecular profile of our patients' tumors using array- and circulating-tumor cell technologies means that this is an exciting, fast moving, and potentially very beneficial area of cancer treatment research.

Disclosure of Potential Conflicts of Interest

R. Plummer, ownership interest and commercial research support for AG014699.

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