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Clinical importance of DNA repair inhibitors in cancer therapy

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The efficacy of cancer chemotherapy and radiotherapy relies on generation of DNA damage. Since intrinsic DNA repair pathways enable cancer cells to survive by repairing these damaged lesions, inactivation of DNA repair coupled with chemotherapy and radiotherapy has a potential to enhance the effect of these therapies. Small molecule compounds that inhibit specific DNA repair proteins have been developed, and early clinical trials are ongoing. While DNA repair inhibitors have been tried mostly as a part of combination therapies with cytotoxic agents, recent reports highlighted a new concept in cancer therapy where DNA repair inhibitors could be used as single agents to selectively kill cancer cells. This concept is based on the findings that cancer cells are frequently defective in particular DNA repair pathway(s) and the presumption that inhibition of the compensatory repair pathway(s) in such cells might be useful to kill them. For example, poly(ADP-ribose) polymerase (PARP) plays a critical role in DNA base-excision repair, and inactivation of this protein increases the number of single-strand breaks (SSBs), leading to double-strand breaks that require to be repaired by homologous recombination (HR) mediated by BRCA1 and BRCA2. Recently, BRCA1- or BRCA2-defective tumour cells were shown to be sensitive to PARP inhibitors alone. This treatment may be tumour-specific because only the BRCA1-/- or BRCA2-/- tumours in the BRCA1+/- or BRCA2+/- patients are completely defective in HR repair. The following short review aims at summarizing the basic mechanisms of DNA repair and the therapeutic options using DNA repair inhibitors in cancer therapy.

Keywords: Cancer therapy, targeted therapy, DNA repair inhibitors, PARP inhibitors, BRCA-defective tumours

The genome DNA is constantly and spontaneously damaged by a variety of DNA-damaging exogenous and endogenous agents. Among the damaged lesions, DNA double strand breaks (DSBs) are considered to be most serious [1]. If these damaged lesions are insufficiently or inaccurately repaired, it would lead to cell death or survival of cells exhibiting genomic instability which is fundamental to several human pathologies including cancer [2]. Several systems to repair DNA damage have, therefore, evolved to maintain the genomic integrity.

Cancer chemotherapy and radiotherapy kill cancer cells by inducing a diverse spectrum of DNA damage, which is normally also recognized by different intrinsic DNA repair pathway(s) (Fig. 1) [3, 4]. Ionizing radiation and radiomimetic drugs such as bleomycin induce DSBs that are predominantly repaired by non-homologous end joining (NHEJ), an error-prone mechanism which directly rejoins DSB ends by ligation and takes place throughout the cell cycle [5]. A part of radiation-induced DSBs is also repaired by homologous recombination (HR), a repair process of greater accuracy and complexity acting during S-G2 phase and requiring a sister chromatid to serve as a template [6]. Alkylating agents including alkylsulphonates and nitrosourea compounds induce DNA base modifications and single strand-breaks (SSBs), which are mainly repaired by the base-excision repair (BER) pathway or nucleotide-excision repair (NER) pathway. BER and NER excise a single damaged DNA base and approximately 24–30 DNA base pairs containing the damaged DNA lesion, respectively [7, 8]. Another alkylator temozolomide alkylates the O^6 position of guanine, which is directly repaired by the alkyltransferase, O^6-methylguanine-DNA methyltransferase (MGMT) [9]. Platinum drugs, such as cisplatin, carboplatin, and oxaliplatin, are DNA crosslinking agents and induce replication-associated DSBs, which are repaired by a combination of NER and HR [10]. Antimetabolites, such as 5-fluorouracil and thiopurines, inhibit nucleotide metabolism and replication fork progression. Topoisomerase inhibitors, such as camptothecins and etoposide, trap topoisomerase I or II which resolves torsional strains imposed on the double helix during DNA replication, and prevent resealing of the DNA breaks [11]. Replication inhibitors such as hydroxyurea induce replication fork stalling and collapse, resulting in indirect DSBs that are repaired by HR [12]. Stalled replication forks are processed by the Fanconi anemia (FA) pathway [13], endonuclease-mediated pathway [14], and RecQ-mediated repair, which involves DNA helicases [15].

While each damaged DNA lesion is repaired predominantly by the lesion-specific DNA repair pathway, there are

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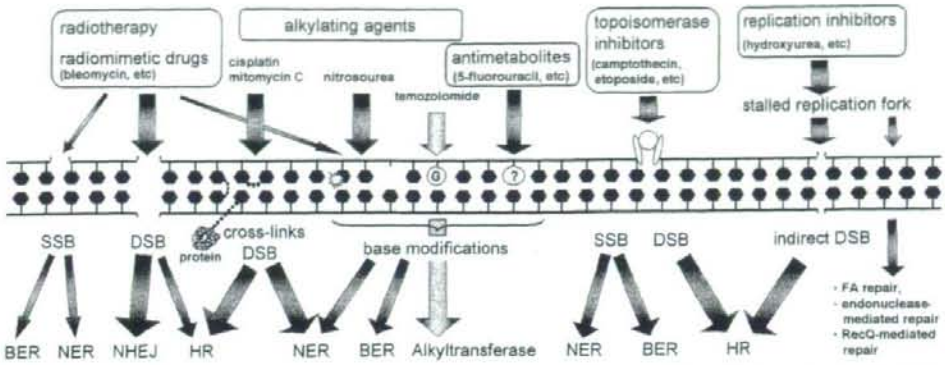

Fig. 1: Overview of the diverse spectrum of DNA damage formed by cancer treatments and the major DNA repair pathway(s) used to process the respective types of damage

also some overlaps and interactions between the pathway(s) acting for the repair of particular legions. For example, SSBs are mostly repaired by BER, but if left unrepaired in the absence of BER, DSBs are formed, which will be repaired compensatorily by HR.

The efficacy of cancer therapy that causes DNA damage may be explained by the ability of the tumour cells to overcome the intrinsic DNA repair pathways that normally repair the damaged lesions. Selective inhibition of such repair pathways in combination with the DNA-damaging therapy can increase the efficacy of the therapy [16]. Moreover, in tumour cells defective in particular DNA repair pathway(s), targeted inhibition of the DNA repair pathway(s) that normally act(s) compensatorily to prevent the generation of lethal damaged lesions may be a promising approach to selectively kill tumour cells. On the basis of these principles, various treatment options using DNA repair inhibitors have been developed and are under investigation in clinical trials (Tab. 1).

DNA repair inhibitors used as a part of combination therapy

PARP inhibitors inhibiting multiple DNA repair pathways

Poly(ADP-ribose) polymerase (PARP) is an abundant nuclear enzyme that detects SSBs and stimulates the recruitment of DNA repair proteins to the site of damage, facilitating BER [17, 18]. Moreover, it also appears to play a role in the repair of other DNA lesions including DSBs [19]. Many small molecule PARP inhibitors have been synthesised to enhance the response of tumour cells to DNA damaging agents and led to clinical trials [20] (Tab. 1).

Combination of PARP inhibitors with platinum compounds

PARP inhibitors have been shown to preferentially kill neoplastic cells and induce complete or partial regression of a wide variety of human tumour xenografts in nude mice treated with platinum compounds [21]. Several clinical trials are ongoing, testing platinum compounds in combination with PARP inhibitors (Tab. 1).

Combination of PARP inhibitors with alkylating agents

The combination therapy of the alkylator temozolomide with PARP inhibitors is currently under investigation in several clinical trials (Tab. 1). Trials of GPI-21016, INO-1001, and AG-014699 show success of this treatment.

Combination of PARP inhibitors with histone deacetylase (HDAC) inhibitors

Recently, the combination therapy of the HDAC inhibitor PCI-24781 with the PARP inhibitor PJ34 was shown to cause a synergistic increase in apoptosis and a decrease in Rad51 expression in vitro and in vivo, suggesting that HDAC enzymes are critically important in HR [22]. Although clinical trials are awaited, these findings suggest a potential therapeutic utility of HDAC inhibitors in combination with chemotherapeutic agents that induce damage, which would be repaired by HR.

Inhibitors of DNA-PK as sensitisers to radiotherapy and DNA-damaging agents

The DNA-dependent protein kinase (DNA-PK) plays a key role in NHEJ. The inhibition of DNA-PK induces extreme sensitivity to ionising radiation [24]. In addition, it also sensitises tumour cells to DNA-damaging agents. NU7026 increased the sensitivity of irradiated tumour cells to the PARP-1 inhibitors [25]. Several DNA-PK inhibitors have been synthesised and evaluated in early clinical trials [26]. Their clinical use is, however, currently restricted because of their toxicities even to normal cells.

MGMT inhibitors as sensitisers to alkylating agents

Expression of MGMT in human cancers is known to have been associated with resistance to therapies using alkylating agents which may be overcome by the inhibition of MGMT. Lomeguatrib, the inhibitor of MGMT, has shown efficacy in combination with temozolomide in Phase I-II trials [27, 28]. O^6-benzylguanine, another inhibitor of MGMT, is currently under investigation in clinical trials (Tab. 1).

Tab. 1: Ongoing clinical trials of small molecule inhibitors of DNA repair and cell cycle checkpoints

Target	Agent	Combination therapy agent(s) or monotherapy	Indication(s)	Phase
PARP inhibitors	KU-0059436/AZD-2281 (KuDos Pharma/Astra Zeneca)	gemcitabine	advanced pancreatic cancer	Phase I
		dacarbazine	advanced melanoma not previously treated with systemic chemotherapy	Phase I
		carboplatin, or paclitaxel/ carboplatin	advanced solid tumours	Phase I
		topotecan	advanced solid tumours	Phase I
		bevacizumab	advanced solid tumours	Phase I
		doxorubicin	advanced BRCA1- or BRCA2-associated ovarian cancer	Phase II planned
		monotherapy	advanced BRCA1/2 mutant ovarian and breast cancer	Phase II
		monotherapy	advanced tumours	Phase I
		monotherapy	metastatic triple negative breast cancer	Phase I/II
		monotherapy	known BRCA or recurrent high grade serous/undifferentiated	Phase II
			ovarian carcinoma	
		monotherapy	platinum sensitive serous ovarian cancer following treatment	Phase II
			with two or more platinum containing regimens	
	AG014699 (Pfizer)	temolozomide	solid tumours	Phase I
		temolozomide	malignant melanoma	Phase II
		monotherapy	carriers of BRCA1 or BRCA2	Phase II
			mutations with locally advanced or metastatic cancers of the breast or ovaries	
	ABT-888 (Abbott)	monotherapy	metastatic melanoma, solid tumours, BRCA-deficient breast and ovarian cancer	Phase I
		topotecan, or topotecan/ carboplatin	relapsed or refractory acute leukaemia, high-risk myelodysplasia, or aggressive myeloproliferative disorders	Phase I
		whole brain radiation	cancer with brain metastases	Phase I planned
		temozolomide	solid tumours, metastatic melanoma, BRCA-deficient breast and ovarian cancer	Phase I
		cyclophosphamide	metastatic or unresectable solid tumours, non-Hodgkin lymphoma	Phase I
		carboplatin and paclitaxel	advanced solid cancer	Phase I
		topotecan	advanced or refractory solid tumours, lymphoma, or chronic lymphocytic leukaemia	Phase I
		irinotecan	lymphoma, or metastatic or unresectable solid tumours	Phase I planned
	BSI-201 (BiPar)	monotherapy, or with irinotecan	advanced solid tumours	Phase I/Ib
		gemcitabine, carboplatin	solid tumours	Phase I
		temozolomide	glioblastoma	Phase I/II
		topotecan, temozolomide, gemcitabine, carboplatin/ paclitaxel	advanced solid tumours	Phase I
		carboplatin, paclitaxel	uterine carcinosarcoma	Phase II
			advanced BRCA-1 or BRCA-2 associated	Phase II
		monotherapy	advanced epithelial ovarian, or peritoneal cancer	Phase II

Tab. 1 (*continued*)

Target	Agent	Combination therapy agent(s) or monotherapy	Indication(s)	Phase
	INO-1001 (Inotek)	temozolomide	melanoma and glioblastoma	Phase I
MGMT inhibitor	O^6-benzylguanine	temozolomide	metastatic melanoma	Phase I/II
		Gliadel wafer, conventional surgery	recurrent glioblastoma multiforme	Phase II
		temozolomide	recurrent or progressive gliomas or brain stem tumours	Phase II
		temozolomide	recurrent or progressive glioblastoma, gliosarcoma	Phase I
		temozolomide	temozolomide-resistant glioblastoma, gliosarcoma	Phase II
		radiotherapy, carmustine	newly diagnosed, or recurrent/progressive anaplastic glioma	Phase III
		carmustine	recurrent, metastatic, or locally advanced soft tissue sarcoma	Phase II
		temozolomide, conventional surgery	newly diagnosed, or recurrent/progressive cerebral anaplastic gliomas	Phase I
		temozolomide, irinotecan	recurrent/progressive cerebral anaplastic gliomas	Phase I
		temozolomide	temozolomide-resistant anaplastic glioma, astrocytoma, oligodendroglioma, oligoastrocytoma	Phase II
		carmustine	children with refractory CNS tumours	Phase I
		temozolomide, carmustine, radiotherapy, autologous stem cell transplantation	newly diagnosed glioblastoma multiforme or gliosarcoma	Phase I
		carmustine	recurrent or progressive gliomas of the brain	Phase I
		carmustine	newly diagnosed supratentorial glioblastoma multiforme	Phase II
		carmustine	stage I or stage II cutaneous T-cell lymphoma that has not responded to previous treatment	Phase I
		temozolomide, radiotherapy, blood cells modified by the insertion of a chemotherapy resistance gene, MGMTP140K	glioblastoma multiforme (WHO Grade IV) anaplastic astrocytoma (WHO Grade III)	Phase I
		temozolomide	glioblastoma multiforme that did not respond to previous temozolomide and radiation therapy	Phase II
Chk1 inhibitor	UCN-01	prednisone	refractory solid tumours and lymphoma	Phase I
		irinotecan	advanced solid tumours	Phase I
		monotherapy	relapsed or refractory lymphoma	Phase II
		topotecan	relapsed small cell lung cancer	Phase II
		perifosine	relapsed or refractory acute leukaemia, chronic myelogenous leukemia, or myelodysplastic syndromes	Phase I
		cytarabine	refractory or relapsed acute myelogenous leukaemia or myelodysplastic syndrome	Phase I
		monotherapy	unresectable stage III or stage IV kidney cancer	Phase II
		fludarabin	relapsed or refractory chronic lymphocytic leukaemia or lymphocytic lymphoma	Phase I/II
Chk1 and Chk2 inhibitor	XL844 (Exilixis)	gemcitabine	advanced solid tumours	Phase I

The current status and information of each clinical trial was referred to http://clinicaltrials.gov/, a service of the U.S. National Institute of Health

Inhibition of checkpoint signalling

Cell-cycle checkpoints are regulated by effector kinases, such as ataxia telangiectasia mutated (ATM) and ATM and Rad3-related (ATR), which regulate the activities of downstream checkpoint proteins, such as checkpoint kinases 1 (Chk1) and 2 (Chk2). Since the triggering of these checkpoints is crucial in DNA damage response, they are also widely investigated as a potential target for cancer therapy.

Combination of inhibitors of Chk1 and Chk2 with DNA-damaging agents

UCN-01 and XL844 are small-molecule inhibitors of Chk1, and both Chk1 and Chk2, respectively. UCN-01 was tried in combination with cisplatin and topotecan in patients with advanced solid tumours [29, 30], and these combinations have been relatively well tolerated with some preliminary evidence of efficacy. The two compounds are also currently tested in early clinical trials (Tab. 1).

ATM inhibitors

KU-55933 is a competitive ATP inhibitor that has high selectivity for ATM and low cytoxicity [31]. It increases the cellular cytotoxicity of ionising radiation and the chemotherapeutics camptothecin, etoposide, and doxorubicin. KU-55933 is currently in preclinical development.

DNA repair inhibitors used as single agents

Targeting the specific DNA repair defects in tumours

Recently, the application of DNA repair inhibitors has been extended to use them as single agents to target specific DNA repair pathways that would be lethal for particular tumours. The notable example is the recent development of treatment with PARP inhibitors alone in patients with inherited breast and ovarian cancers that lack wild-type copies of the *BRCA1* or *BRCA2* genes. Since BRCA1 or BRCA2 is inactivated in these tumour cells, the tumour cells are defective in HR. These HR-defective *BRCA1*- or *BRCA2*-mutated cells were shown to be more sensitive to PARP inhibitors than the heterozygote or the wild-type cell lines, indicating the potential to be exploited as specific treatments of BRCA1- or BRCA2-defective tumours [32, 33].

One explanation for this sensitivity is as follows. In the absence of PARP, the number of SSBs increases, leading to DSBs as a result of stalled replication forks. Although such lesions would be normally repaired compensatorily by HR, these lesions will be unrepaired in BRCA1- or BRCA2-deficient cancer cells because they are defective in HR repair, leading the tumour cells to death. The absence of significant cell death in non-tumour heterozygous mutant cells treated with PARP inhibitors was notable, since non-tumour cells in patients bearing *BRCA* mutations are heterozygous possessing one mutant allele and one wild-type allele. PARP inhibitors may, therefore, selectively kill the tumours that show loss of the wild-type *BRCA* allele.

Clinical trials using PARP inhibitors alone in the treatment of BRCA-associated cancer are ongoing (Tab. 1). Phase II clinical trials using the PARP inhibitor AZD2281 as a single agent so far show low toxicity and significant anti-tumour activity. A separate phase II trial with the PARP1 inhibitor AG014699 is carried out in carriers of *BRCA1* or *BRCA2* mutations with locally advanced or metastatic cancers of the breast or ovaries.

Resistance to DNA repair inhibitors

Resistance to chemotherapy is a major obstacle to effective cancer therapy. Recently, three studies showed that resistance to cisplatin or PARP inhibitors in cancer cells deficient in *BRCA1* or *BRCA2* correlated with restoration of the detectable levels of the BRCA1 or BRCA2 protein as a result of secondary mutations that restore the reading frame of the protein [34–36]. These new findings demonstrate the need for understanding the limitation together with the application of DNA repair inhibitors in cancer therapy.

Conclusions

DNA repair inhibitors have a great potential to be used in future cancer therapy, and are currently evaluated in early clinical trials. They can be used to enhance chemotherapy and radiotherapy, and also to selectively kill tumour cells exhibiting deficiencies in particular DNA repair pathway(s). Since individuals with defects in DNA repair proteins other than BRCA1 or BRCA2 are also predisposed to cancer, it is likely that other DNA repair proteins can be targeted in a similar manner. Better understanding of DNA repair processes would contribute to the identification of novel targets for cancer therapy.

Take-home message

Current DNA-damaging cancer treatments including chemotherapy and radiotherapy are not often successful to cure tumour-bearing patients because the responses to these therapies vary among individual patients. The use of DNA repair inhibitors will provide a good opportunity to resolve this problem and to realise targeted and individualised cancer therapy.

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