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REVIEW

Therapeutic implications of antiangiogenic agents and poly-adenosine diphosphate ribose polymerase (PARP) inhibitors in breast cancer: Current status and future perspectives

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Abstract Angiogenesis exhibits an integral role in cancer development and metastasis, therefore, antiangiogenic therapy forms the basis of several promising treatment strategies for breast cancer. Moreover, DNA damage has long been exploited in cancer chemotherapy and poly-adenosine diphosphate ribose polymerase (PARP) inhibitors constitute a novel group of drugs for the targeted disruption of DNA repair phenomenon attributed to breast cancer. Several antiangiogenic drugs and PARP inhibitors are effectively used as sole agents for the therapeutic management of early breast cancer and breast cancer gene mutation–induced breast cancer, respectively. Whereas, other antiangiogenic agents are employed for the ancillary therapy of metastatic breast cancer in conjunction with chemotherapeutic drugs. Likewise, some PARP inhibitors are recommended as adjuncts to chemotherapy against the triple-negative form of breast cancer. Combinations of PARP inhibitors with immunotherapy have also demonstrated favorable outcomes and offer an efficient treatment strategy for breast cancer. Currently, the combinations of antiangiogenic agents and PARP inhibitors are under investigation for prospective synergistic or additive effects in breast cancer. Despite being suggested for high-risk patients, the prophylactic use of PARP inhibitors has not been supported by means of preclinical or clinical studies. Finally, the identification of patient cohorts, determination of predictive biomarkers, optimization of dosing strategies, validation of long-term safety, and containment of resistance issues, necessitate proper attention for improving the clinical efficacy of potentially useful antiangiogenic agents and PARP inhibitors against breast cancer.

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PALABRAS CLAVE
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Implicaciones terapéuticas de los agentes antiangiogénicos y los inhibidores de poli-adenosina-difosfato-ribosa-polimerasa (PARP) Para el cáncer de mama: Estado actual y perspectivas futuras

Resumen La angiogénesis exhibe un papel integral en el desarrollo del cáncer y las metástasis y, por tanto, la terapia antiangiogénica establece la base de diversas estrategias terapéuticas prometedoras para el cáncer de mama. Asimismo, se ha explotado ampliamente el daño del ADN en la quimioterapia contra el cáncer, y los inhibidores de poli-adenosina-difosfato-ribosa-polimerasa (PARP) constituyen un grupo novel de fármacos para la alteración focalizada del fenómeno de reparación del ADN atribuida al cáncer de mama. Se utilizan de manera efectiva diversos fármacos antiangiogénicos e inhibidores de PARP como agentes únicos para el manejo terapéutico del cáncer de mama temprano y el cáncer de mama inducido por la mutación del gen BRCA, respectivamente, aunque se utilizan otros agentes antiangiogénicos para la terapia auxiliar del cáncer de mama metastásico, junto con fármacos quimioterapéuticos. De igual modo, se recomiendan algunos inhibidores de PARP como complementos a la quimioterapia contra la forma triple-negativa del cáncer de mama. Las combinaciones de los inhibidores de PARP y la inmunoterapia también han demostrado resultados favorables, ofreciendo una estrategia terapéutica eficiente para el cáncer de mama. Actualmente, las combinaciones de los agentes antiangiogénicos y los inhibidores de PARP están siendo investigadas en términos de efectos sinérgicos o aditivos prospectivos en el cáncer de mama. A pesar de haber sido sugeridos para las pacientes de alto riesgo, el uso profiláctico de los inhibidores de PARP no ha sido respaldado mediante estudios preclínicos o clínicos. Por último, deben estudiarse detenidamente la identificación de cohortes de pacientes, la determinación de biomarcadores predictivos, la optimización de las estrategias de dosificación, la validación de la seguridad a largo plazo, y la contención de cuestiones de resistencia, para mejorar la eficacia clínica de los agentes antiangiogénicos e inhibidores de PARP potencialmente útiles contra el cáncer de mama.

Introduction

Breast cancer is the second, most-frequent malignant tumor type and ranks fourth among cancers in relation to mortality.[1] Even with the most recent breakthroughs in diagnostics and therapeutics, prevention of metastasis and disease relapse continues to pose a hurdle for the oncologists. Appropriate treatment and prevention of breast cancer may eventually reduce the mortality and morbidity in affected women. Nevertheless, most of the currently available anticancer drugs are typically ineffective against the hormone receptor-negative and few other forms of breast cancer.[2] Therefore, alternative therapeutic and prophylactic strategies are requisite to replace the existing surgical options in breast cancer gene 1 (BRCA1) or breast cancer gene 2 (BRCA2) mutation-linked breast cancers.[3] Antiangiogenic agents are employed for preventing or downregulating the action of activating molecules, upregulating the action of inhibitory factors, obstructing the transduction pathways, and eventually suppressing the tumor expansion. The hazard of breast cancer development increases in individuals harboring a germline BRCA1 or BRCA2 heterozygous mutation if the inactivation of wild-type allele occurs due to an epigenetic event, second mutation or somatic loss. Emerging evidence reflects the prospective therapeutic significance of poly-adenosine diphosphate ribose polymerase (PARP) inhibition in a broader subcategory of infrequent breast cancers with the probable malfunctioning of homologous recombination-based DNA repair mechanisms. The BRCAness phenotype of both genetic and epigenetic origins in certain sporadic breast cancers may potentially take advantage of PARP inhibition-based therapeutic approach.

Therapeutic rationale for antiangiogenesis in breast cancer

Vascular endothelial growth factor (VEGF), a heparin-binding glycoprotein, constitutes the primary mediator of tumor angiogenesis and undergoes overexpression during breast cancer.[4] The human VEGF family encompasses various isoforms, identified as VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and VEGF-F.[5,6] VEGF is primarily exploited as an antiangiogenic target, on account of its early and continuous expression in breast cancer, and pivotal role in pathological angiogenesis. Simultaneous targeting of VEGF and human epidermal growth factor receptor 2 (HER2) has been recommended in case of HER2-positive breast cancer.[7] The development of first anti-VEGF humanized, monoclonal antibody, called bevacizumab, is considered as a milestone in the antiangiogenic therapy of cancer. The projected modes of action of bevacizumab include the deterioration of tumor vasculature and impediment of neovasculogenesis. Moreover, it also leads to reduction of interstitial fluid

pressure, vascular volume, tumor perfusion, and endothelial cell dissemination.[8] Several studies have evinced the effectiveness of bevacizumab in advanced breast cancer.[9] Sunitinib is a multitargeted tyrosine kinase antagonist that blocks several types of receptors including VEGFR-1, VEGFR-2, VEGFR-3, colony stimulating factor receptor-1, platelet-derived growth factor receptor-alpha (PDGFR-α), and PDGFR-β. It has revealed substantial antitumor effect in breast cancer xenograft models.[10] Sorafenib, another tyrosine kinase antagonist that inhibits angiogenesis and proliferation of tumors, has shown anticarcinogenic effect in various cell lines, together with breast cells.[11] Vandetanib inhibits neoplastic growth in many types of human cancer xenografts alongside the breast cancer. Lapatinib, a dual tyrosine kinase antagonist, is known for inhibiting both erythroblastic leukemia viral oncogene homolog (ErbB-1 and ErbB-2) receptors. Besides, several other anti-VEGF tyrosine kinase blockers including cediranib, motesanib, valatanib, and pazopanib have also been evaluated for the therapeutic management of metastatic breast cancer. So far, only lapatinib and neratinib have been approved by Food and Drug Administration (FDA) for the treatment of breast cancer (Fig. 1).

Causal role of PARP inhibitors in breast cancer therapy

A novel class of drugs termed as PARP inhibitors have been introduced for targeting the DNA-repair defects in neoplastic cells. Most of the currently known PARP inhibitors block both PARP1 and PARP2 enzymes. These agents prevent the repair of single-strand DNA breaks by inhibiting the catalytic activity of PARP enzymes and resultant autoPARylation reactions. Besides, the highly toxic dissociation process of PARP enzyme from DNA, termed as PARP trapping on DNA lesions and occurring in homologous recombination-deficient cells, is also precluded by PARP inhibitors.[12] PARP inhibition-based therapeutic strategies are currently employed in germline BRCA mutation-related and triple-negative forms of breast cancer. The first PARP inhibitor, olaparib received the regulatory approval in 2018, as a second-line treatment for HER2-negative metastatic breast cancer.[13] Talazoparib revealed maximum PARP1 trapping efficiency and was approved for women with advanced HER2-negative and germline BRCA-mutated types of breast cancer.[14,15]

PARP antagonists constitute a novel group of drugs for targeting cancers coupled with deficient DNA repair. Early preclinical studies revealed the high susceptibility of BRCA1 and BRCA2 tumors to PARP inhibitors on account of deficient homologous recombination. Based on this evidence, PARP inhibitors have been clinically examined as sole agents in BRCA1 or BRCA2 mutation-linked cancer as well as in conjunction with chemotherapeutic drugs in triple negative breast cancer (TNBC). The sensitization of tumor cells to DNA-impairing therapies by PARP inhibitors has been validated by means of preclinical studies.[16,17] Accordingly, PARP inhibitors are being clinically investigated for potentiating the cytotoxic potential of chemotherapeutic agents.[18] From mechanistic standpoint, the concurrent blockade of angiogenic and PARP pathways could theoretically result in improved antitumor activity.[19]

Limitations of antiangiogenic and PARP inhibition-based therapies in breast cancer

The impressive clinical efficacy of novel antiangiogenic drugs against breast cancer paved the ways towards the approval of bevacizumab, as the first-line therapy for metastatic breast cancer.[20] Nevertheless, despite the preliminary demonstration of enhanced progression-free survival in breast cancer patients, the overall clinical efficiency of antiangiogenic drugs has been lesser than the projected

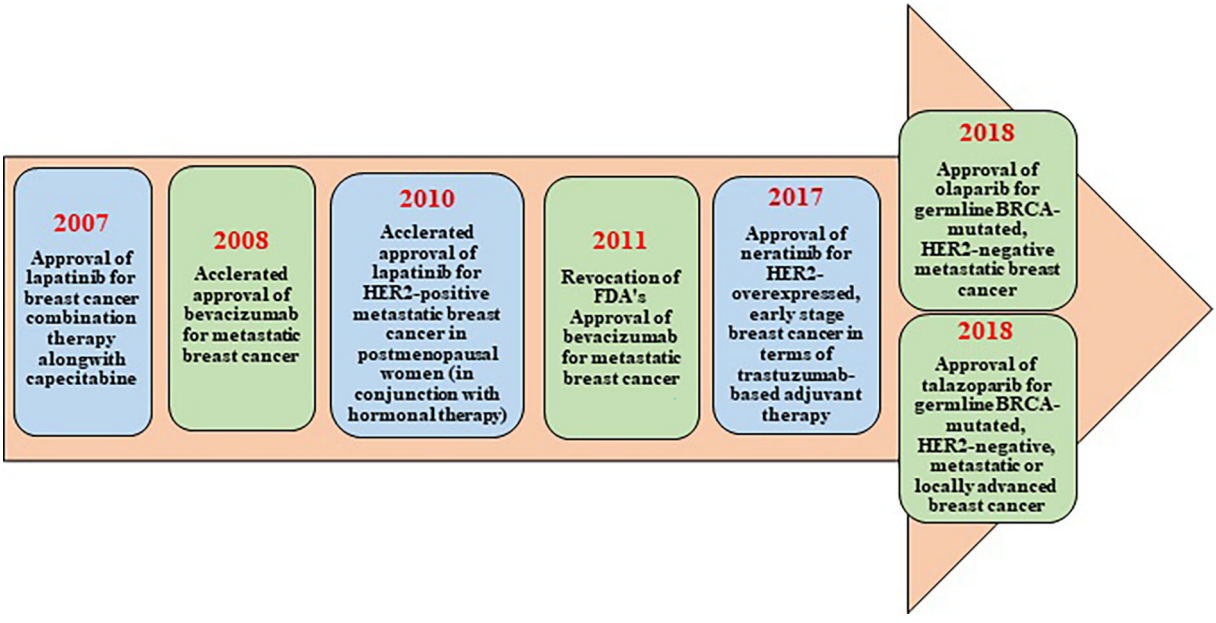

Fig. 1 FDA approval timeline of antiangiogenic agents and PARP inhibitors for breast cancer therapy.

level. Moreover, antiangiogenic therapy failed in providing a long-lasting survival advantage to women manifesting the advanced breast cancer.[21] The identification and validation of genetic or molecular biomarkers to select prospective patient cohorts for antiangiogenic therapy will give rise to considerable improvement in efficacy, and evasion of adverse effects.[22] Variations in the pathological, genetic, and immunohistochemical features of breast cancers may require the standardization of personalized antiangiogenic therapy systems.[21] Besides, the therapeutic role of multi-targeted VEGFR inhibitors in breast cancer has not been elucidated so far. Finally, the capability of cancerous cells to acquire resistance in terms of tumor angiogenesis, vascular mimicry, and vascular remodeling, may limit the therapeutic significance of antiangiogenic therapy in breast cancer.[21]

Currently, an adequate biomarker of response to PARP inhibitors therapy other than the germline BRCA mutation status is lacking. Despite the clinical verification of prognostic biomarkers of single agent PARP inhibitors responses, very little is known about projecting a favorable response to PARP inhibitors in combination therapy. Besides, standardized and appropriate biomarker of "BRCAness" is requisite for predicting the sensitivity of other malignancies to PARP inhibition.[23,24] The definite advantage of PARP inhibitors in women of germline BRCA mutation-linked breast cancer has substantiated the germline BRCA mutation as a prognostic bioindicator for PARP inhibitors response. The homologous recombination deficiency score has also been proposed to ascertain the breast cancer patients with malfunctioning DNA repair pathways,[25] and is therefore assessed for predicting the response to PARP inhibitors.[26,27]

Table 1 Ongoing clinical trials for new antiangiogenic agents and PARP inhibitors in breast cancer.

Drug(s)		NCT number	Phase	Number of patients	Key outcome
Antiangiogenic agents	Anlotinib	NCT05558722	II	30	pCR
		NCT06331169	I	42	ORR
	Apatinib	NCT05556200	II	58	pCR
	Capmatinib	NCT05243641	I/II	47	MTD
	Dasatinib	NCT06355037	II	10	ORR
	Famitinib	NCT06516289	II	130	DLT
	Nilotinib	NCT04205903	I	20	AEs
	Pyrotinib	NCT05910398	III	488	IDFS
	Tucatinib	NCT06016387	II	30	OS
		NCT06439693	II	72	DFS
		NCT05868226	I	54	AEs
		NCT05748834	II	36	ORR
PARP inhibitors	Fluzoparib	NCT05891093	III	766	IDFS
		NCT05761470	II	66	pCR
		NCT05759546	II	200	PFS
		NCT06612814	III	307	PFS
		NCT05834582	II	60	pCR
		NCT05085626	II	40	ORR
		NCT05656131	II	80	ORR
	Niraparib	NCT04641247	II	26	AEs
		NCT04915755	III	43	AEs
		NCT03368729	I/II	40	DLT
		NCT04837209	II	32	ORR
		NCT03945721	I	21	MTD
		NCT04481113	I	8	DLT
		NCT04673448	I	18	BOR
	Rucaparib	NCT03542175	I	31	MTD
		NCT03845296	II	64	ORR
	Veliparib	NCT01009788	II	64	ORR
		NCT01351909	I	35	PFS
		NCT01149083	II	71	ORR
		NCT01251874	I	44	AEs
Combinations of antiangiogenic agent and PARP inhibitor	Cediranib + Olaparib	NCT04090567	II	60	ORR
		NCT01116648	I/II	155	DLT
		NCT02484404	I/II	384	ORR
	Fluzoparib + Apatinib	NCT04296370	III	474	DLT

(retrieved from: www.clinicaltrials.gov).
AEs, adverse events; BOR, best objective response; DFS, disease-free survival, DLT, dose limiting toxicity; IDFS, invasive disease-free survival, MTD, maximum tolerated dose, ORR, overall response rate, OS, overall survival, pCR, pathological complete remission; PFS, progression-free survival.

PARP1 levels have been projected as a probable biomarker for response, and were found to be elevated in TNBC,[28] but this requires further validation. Although the estimation of PARP activity in tumor biopsy samples is achievable, but has not been adequately established until now. Other prospective biomarkers include the appraisal of HR proficiency via nuclear RAD51 foci synthesis,[24] the occurrence of miRNAs implicated in regulating the BRCA proteins,[29] and the estimation of 53BP1 expression level.[30]

Another challenge particularly associated with combination therapies is the escalation of adverse effects on account of drug–drug interactions. Thus, dosage regimen optimization becomes imperative for the clinical success of PARP inhibitors in combination therapies. The combined use of PARP inhibitors with cytotoxic agents may provide variable results in terms of treatment delays and dose-dependent toxicities. Some combination trials employed intermittent dosing of PARP inhibitors to avoid the hematologic toxicities, however, this strategy may possibly reduce the efficiency of combination regimen.[18] Identifying and controlling the tumor resistance to PARP inhibitors is another challenge. Upregulation of P-glycoprotein efflux pumps and resultant diminution in intracellular drug concentration represents the most usual mechanism underlying the resistance to PARP inhibitors.[31] Owing to the involvement of PARP inhibitors in stabilizing the cytotoxic PARP–DNA complexes, resistance can also arise from PARP1 malfunction and impaired inhibition of PARP.[32]

Future perspective of antiangiogenic agents and PARP inhibitors in breast cancer therapy

Following the pioneering work of Judah Folkman, considerable progress has been made in devising several antiangiogenic therapies against breast cancer.[33] Owing to the critical involvement of angiogenesis in breast cancer development and metastasis, the antiangiogenic drugs have been considerably focused by means of preclinical and clinical assessments during the past decade. The co-administration of bevacizumab and chemotherapeutic drugs caused the protraction of progression-free survival in metastatic breast cancer.[22] Nevertheless, the approval of bevacizumab for metastatic breast cancer was revoked by FDA in 2011, on account of resultant unsatisfactory survival benefit and critical tolerability concerns. Following the preliminary impressive results, various antiangiogenic drugs (including anlotinib, apatinib, cediranib, capmatinib, dasatinib, famitinib, nilotinib, pyrotinib, and tucatinib) and PARP inhibitors (such as fluzoparib, niraparib, olaparib, rucaparib, and veliparib) are recently undergoing the clinical investigation in breast cancer (Table 1). Based upon the initial promising clinical efficacy, PARP inhibitors are being rapidly developed as single agents in BRCA mutation-linked breast cancer, and combined with chemotherapeutic drugs in TNBC. Moreover, the combined use of PARP inhibitors along with immunotherapy, radiotherapy and targeted agents is also progressively rising in individuals with and without germline BRCA mutation.[34] PARP inhibition is a favorable therapeutic approach for germline BRCA1/2 mutation-related breast cancer. Novel strategies are being developed to broaden the therapeutic utility of PARP inhibitors in BRCA-associated tumors ahead of the breast and ovarian cancers. Evolving data indicate the therapeutic value of PARP inhibitors in BRCA-mutant pancreatic and prostate cancers.[35] Likewise, the capability of PARP inhibitors to penetrate the blood–brain barrier,[36,37] reflects their potential clinical effectiveness in TNBC susceptible to brain metastases.

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Ethical disclosures

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Declaration of competing interest

The authors declare no conflict of interest.

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