PARP阻害剤は難治性乳がん治療に有望である（Abstract #: CRA501 and P3）

PARP阻害剤と化学療法の組み合わせはtriple-negative乳がんの新たな治療選択肢となる可能性がある

PARP inhibitor plus chemotherapy may offer new treatment option for triple-negative breast cancer

新たなクラスの標的治療PARP阻害剤は難治性乳がん治療に対し有望であるとの二つのスタディの結果が第45回American Society of Clinical Oncology学会で発表された。PARPは”ポリ（ADPーリボース）ポリメラーゼ”の略称である。無作為化phase IIスタディの結果、治験薬PARP阻害剤BSI-201を従来の化学療法に加えて投与された転移性triple-negative乳がん患者は、通常の標準的な化学療法のみを受けた患者と比較し生存期間が有意に長く無増悪生存期間も長かったことが示された。BSI-201を投与された患者の約62%において臨床上の有益性が認められたのに対し、化学療法のみの群におけるその割合は21%であった。治療に対する全体の奏効率はBSI-201を含む併用療法群で標準的な化学療法のみの群よりも有意に高かった（それぞれ48%対16%）。BSI-201を投与された女性の生存期間中央値は9.2ヵ月であり無増悪生存期間中央値は6.9ヵ月であったのに対し、標準治療のみを受けた患者においてはそれぞれ5.7ヵ月と3.3ヵ月であった。さらに、小規模なphase II多国籍多施設スタディの結果、BRCA1またはBRCA2変異を有し前治療に抵抗性であった進行乳がんの女性の40%において、治験薬のPARP阻害剤olaparib投与後に腫瘍の縮小が認められた。

Full Text

Two new studies report results on the effect of a new class of targeted therapy called PARP inhibitors on traditionally difficult-to-treat breast cancers - so-called "triple negative" breast cancer and BRCA1-2 deficient breast cancers.

PARP is short for "poly (ADP-ribose) polymerase." Cancer cells use the PARP enzyme to repair DNA damage, including the damage inflicted by chemotherapy drugs. Researchers are examining whether drugs that inhibit the PARP enzyme will diminish this self-repair mechanism and make cancer cells more sensitive to treatment and promote cancer cell death.

A randomized Phase II study, featured in ASCO's plenary session, shows that women with metastatic triple-negative breast cancer who received the investigational PARP inhibitor BSI-201, in combination with conventional chemotherapy, lived significantly longer and experienced significantly better progression-free survival than women who received standard chemotherapy alone.

"The results of this study provide early evidence that BSI-201 is a promising treatment for women with triple-negative breast cancer, an aggressive form of the disease for which we need new, more effective therapies," said Joyce O'Shaughnessy, M.D., co-director of the Breast Cancer Research Program at Baylor- Charles A. Sammons Cancer Center in Dallas, Texas.

Triple-negative breast cancers are particularly hard to treat since they lack receptors for estrogen, progesterone and HER2, which are targeted by widely available and effective drugs.

In this study, clinical benefit rate (defined by complete and partial responses and stable disease of at least 6 months), response rate, progression-free survival, and overall survival were compared among 116 women with metastatic triple-negative breast cancer who were randomly assigned to receive a standard chemotherapy treatment (gemcitabine and carboplatin) plus BSI- 201, or standard treatment alone.

Approximately 62 percent of patients receiving BSI-201 showed clinical benefit, compared with 21 percent in the chemotherapy only group. The overall response rate to treatment with the drug combination containing BSI-201 was significantly greater (48 percent) than in the group receiving only standard chemotherapy (16 percent). Women who received BSI-201 had a median survival of 9.2 months and median progression-free survival of 6.9 months compared with 5.7 months and 3.3 months, respectively, in women who received standard treatment alone.

The incidence of side effects was similar between the two groups. BSI-201 itself was well-tolerated and did not contribute any new side effects nor add to the known side effects of gemcitabine and carboplatin.

A small, Phase II international multi-center study reports that more than a third of women with BRCA1 or BRCA2 mutations and advanced breast cancer that persisted despite prior treatment experienced tumor shrinkage after receiving the investigational PARP inhibitor olaparib.

"The findings of our study provide very promising evidence that the potent PARP inhibitor olaparib may be useful for treating BRCA-deficient breast cancers," said lead author Andrew Tutt, MB ChB, Ph.D., director of the Breakthrough Breast Cancer Research Unit at Kings College in London. "However, this drug is in a very early stage of development, and additional clinical trials are necessary to determine the best way to use olaparib in women with BRCA-deficient breast cancer. We are actively discussing the design of future PARP inhibitor studies for women with BRCA1 and BRCA2 mutations."

This study is the first to evaluate olaparib when used alone in women with BRCA-deficient breast cancer. A prior Phase II study showed that some women with BRCA-deficient ovarian cancers responded to olaparib. Tumors that arise in patients with BRCA mutations have a defect in their ability to repair DNA.

By adding olaparib, the tumor cells are deprived of another DNA repair mechanism. It is thought that this added inhibition of DNA repair with olaprib then leads to cancer cell death.

In this study, Dr. Tutt and his colleagues examined the response rate to olaparib (as evidenced by tumor shrinkage) in 54 women with breast cancer that was deficient in BRCA1 or BRCA2 and that persisted despite several rounds of standard chemotherapy. Forty percent of the patients responded to olaparib (experienced tumor shrinkage) at the higher of the two doses used in the study.

Olaparib was well tolerated, with the most common side effects being mild fatigue, nausea and vomiting.

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