抗体药物偶联物治疗顺铂耐药的卵巢癌初见疗效

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基因泰克(Genentech)研发的新药DMUC5754A是一类抗体药物偶联物（ADCs,antibody-drug conjugates）。在今年的AACR会议上，该公司报道了该药的I期临床研究结果。

DMUC5754A由靶向MUC16(又被称为CA-125)蛋白的单克隆抗体、毒素及连接它们的可裂解链接子组成。大约80%卵巢癌患者的肿瘤细胞高表达MUC16蛋白。该药的组成毒素名为MMAE(monomethyl auristatin E)一种微管破坏剂。

DMUC5754A的I期研究在晚期卵巢癌及前列腺癌患者中评估不同给药剂量的安全性。DMUC5754A的给药剂量从0.3 mg/kg增至3.2 mg/kg，每三周给药1次。 共有46例晚期的复发的顺铂耐药卵巢癌患者入组，其中1例完全缓解，4例部分缓解。这5例治疗有效病例接受的DMUC5754A治疗剂量为2.4mg/kg且高表达MUC16蛋白。

DMUC5754A治疗最常见的不良事件为疲乏（发生率>50%）。其它常见的不良事件包括呕吐、食欲减弱、恶心、腹泻及外周神经病变。

AACR: Antibody-Drug Conjugate Shows Promise in Platinum-Resistant Ovarian Cancer

By Anna Azvolinsky, PhD1 | 2013年4月9日

Washington, DC—A novel therapy has shown activity in treatment of difficult-to-treat, advanced, platinum-resistant ovarian cancer. The drug, DMUC5754A (Genentech), is part of a new class of drugs called antibody-drug conjugates. The phase I trial results were presented at the American Association for Cancer Research (AACR) Annual Meeting, held April 6 – 10 in Washington, DC by Joyce F. Liu, MD, MPH, of the Dana-Farber Cancer Institute and Harvard Medical School in Boston.

“Overall the drug was well tolerated, with a toxicity profile that is comparable to other therapeutics currently used in clinical practice,” Liu told Cancer Network. “We think the results are very encouraging in a patient population where response to other therapies is limited.”

DMUC5754A consists of a monoclonal antibody against the protein MUC16, found on ovarian cancer cells at high levels, and a toxin linked by a cleavable linker. Approximately 80% of ovarian cancer patients have tumors that have high expression of MUC16 (also known as CA-125), according to Liu. The toxin is the microtubule-disrupting agent mono

methyl auristatin E (MMAE). The antibody directs the toxin specifically to ovarian cancer cells to kill them. Because the antibody delivers the toxin specifically to the ovarian tumor, an especially potent toxin can be used, one that would be too toxic as a general cytotoxic agent that would also affect healthy tissue.

The results from the phase I trial also showed that those patients who had the highest expr ession of MUC16, the target of the antibody portion of the drug, derived the most benefit from the treatment. This is likely to facilitate the selection of only those patients who are m ost likely to benefit from treatment in future trials.

Platinum-resistant, advanced ovarian cancer has an unmet need and is difficult to treat. Pa tients currently have few treatment options. Platinum-based chemotherapy remains the sta ndard way to treat ovarian cancer, and platinum resistance is a major treatment challenge.

The phase I trial evaluated various doses of DMUC5754A in advanced ovarian and panc reatic cancer patients. DMUC5754A was administered at doses ranging from 0.3 mg/kg to 3.2 mg/kg every 3 weeks. Forty-four patients with advanced, recurrent, platinum-resist ant ovarian cancer enrolled; of those, one complete response and four partial responses were reported. All patients who responded were treated with a 2.4 mg/kg dose of the dr ug and had high MUC16 expression in their tumor cells. Six additional patients had minor responses.

Fatigue was the most common adverse event at all dose levels, occurring in more than hal f of all patients. Other common adverse events were vomiting, decreased appetite, nause a, diarrhea, and peripheral neuropathy. Peripheral neuropathy was manageable and rever sible in most patients through dose delay and dose reductions, according to the researche rs.

Grade 3 adverse events included fatigue and neutropenia, both occurring in 9% of patient s. Neutropenia and uric acid release were the only dose-limiting toxicities during the stud y. Both occurred at the maximum 3.2 mg/kg dose. Other serious drug-related adverse ev ents were small intestine obstruction in two patients, hypocalcemia in a single patient, and neutropenia in a single patient.

“Neuropathy, which was an anticipated potential toxicity of the drug, did occur, but was manageable and typically reversible with dose reductions or delays,” said Liu.

The role of MUC16 in cancer development and progression is not yet clear. The protein i s a large transmembrane protein that is found in abundance on ovarian cancer cells but no t healthy tissue. Researchers speculate that the protein may help ovarian tumor cells bind t o mesothelial cells that line the peritoneal cavity.

The encouraging activity and safety profile of the antibody-drug conjugate warrants furthe r trials in ovarian cancer patients, according to the study researchers. “I think the major remaining question is how this therapy compares against the standard treatments that we u se in platinum-resistant ovarian cancer,” said Liu.

Discussions for further development of DMUC5754A, including a phase II ovarian cance r trial, are ongoing.

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