Harley's Angels

Kelly K. Hunt, M.D., F.A.C.S.

Professor

Department of Surgical Oncology

THE UNIVERSITY OF TEXAS
MD Anderson
Cancer Center
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PROGRESS REPORT

BACKGROUND

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer. Due to the limited treatment options for TNBC, patients have a high rate of recurrence and reduced survival. TNBC is an invasive breast cancer that lacks estrogen receptor (ER), progesterone receptor (PR) and HER-2 expression. TNBC is more likely to affect younger women and present at a more advanced stage. These tumors, which account for up to 17% of breast cancers and represent an aggressive phenotype, are often of high histologic grade, have larger tumor size at diagnosis, are found more often in premenopausal women, and have decreased overall survival compared to other types of breast cancers. This decreased survival is due, in part, to the lack of specific therapies for this subset of breast cancer patients. While cytotoxic chemotherapy is effective in some patients, most TNBC patients are more likely to fail standard therapy and develop recurrence within the first five years of follow-up. Due to the cumulative toxicity of chemotherapeutic agents, there is a need to establish logical combinations with targeted therapies in order to avoid prolonged chemotherapy administration for the treatment of TNBC.

RESULTS

There is an urgent need to identify successful drugs and combinations of drugs early in the development pipeline in order to reduce the cost and time spent getting therapies to the clinic. To identify drugs that are cytotoxic and synergistic when used in combination, we developed an in vitro high-throughput survival assay (HTSA). This assay accurately screens multiple drugs against multiple cell lines in 96 well plates, making it a robust assay for drug development. Compared to short-term assays, which we have shown to inaccurately measure cell arrest as cell death, the HTSA (a 12-day long assay) can differentiate between cells that are killed by a drug (i.e., cytotoxic) versus those that are temporarily arrested (i.e., cytostatic). The HTSA can more accurately predict in vivo response.

Additionally, the HTSA can be used to test drugs in various sequences to optimize the timing of cross talk between target pathways. This assay allows investigators to analyze multiple drug treatments and cell lines at the same time in one experiment with automated data acquisition and analysis. This rapid and robust assay allows the user to determine whether the effects of combination treatment strategies are synergistic, additive, or antagonistic in different cell lines and advance those combinations that are synergistic for further drug development. The accuracy and efficiency of the HTSA makes it an invaluable tool in the screening of drugs for clinical trials and will help to decrease the failure rate of drugs going through the development pipeline. We have used this assay in TNBC cell lines and have identified several drug combinations that are synergistic when used to treat TNBC cells. Using this assay, we discovered one such combination, Dinaciclib + Epirubicin, which is currently in clinical trials.

Our ongoing laboratory work has elucidated that this combination is synergistic through the deregulation of tumor cell cycle checkpoints. However, since combination of targeted therapy (Dincaciclib) with systemic chemotherapy (Epirubicin) can cause toxicity to patients, we need to identify additional combination therapies that utilize targeted agents and not chemotherapy.

To identify novel combination therapy, we have to first take advantage of the genetics of TNBC cells. About 84% of TNBC harbor p53 mutations, which leads to partial deregulation of two main checkpoints of the cell cycle. Therefore, these cancer cells are particularly vulnerable to disruptions in the cell cycle and rely on other checkpoint regulators to protect them from massive DNA damage, such as Rb for the G1/S checkpoint and Wee1 kinase for the G2/M checkpoint. The sequential combination treatment of Dinaciclib followed by Wee1 kinase inhibitor can target dual checkpoints to cause mitotic catastrophe in these TNBC cells. The treatment of Dinaciclib can block the cell cycle at the G1/S checkpoint by inhibition of cdk2 in the cell with wild-type Rb, and then follow-up treatment of MK-1775 will force these cells to prematurely enter mitosis by inhibiting Wee1 kinase. Such aberrant cell cycle dynamics will generate massive DNA damage and eventually cause cell death. As 90% of p53 mutated TNBC maintain wild-type Rb, the sequential combination treatment has the potential to benefit the majority of TNBC patients. Additionally, the sequential therapeutic strategy can not only reach the therapeutic effect of each drug, but also prevent the overlapping toxicities if both drugs are to be administered concomitantly.

In the upcoming year, we will evaluate the efficacy of the combination therapeutic strategy in vitro in multiple TNBC cell lines with different genetic backgrounds. The mechanism of synergy and mitotic catastrophe will be investigated. Understanding the biological and molecular mechanisms of the combination treatment will provide valuable information to design and conduct preclinical animal studies and further translation to a clinical trial. The knowledge of mechanism will also uncover relevant biomarkers that can be used to further stratify patients who are likely to respond to this novel treatment strategy and also offer insights to other possible combination strategies to benefit a similar patient population.

SUMMARY

The successful translation of this novel combination from our proposed pre-clinical study to clinical trials will provide those TNBC patients with metastatic disease a new treatment option. Using two targeted therapies based on scientific knowledge and understanding the patient population most likely to benefit avoids the use of cytotoxic and non-specific chemotherapeutic agents.

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PUBLICATIONS

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