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Inhibiting fatty acid synthase in operable triple negative breast cancer.

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Abstract Disclosures

Research Funding:
Breast Cancer Research Foundation

Background:
Fatty acid synthase (FASN) is overexpressed in 70% of newly diagnosed triple negative breast cancer (TNBC) and is associated with poor prognosis. *In vitro*, FASN overexpression induces drug resistance to DNA damaging agents. Proton pump inhibitors (PPI) selectively inhibit FASN activity and induce apoptosis in breast cancer cell lines with minimal effect on non-malignant cells. We report the results of a single arm phase II study of high dose omeprazole (OMP) in combination with anthracycline-taxane (AC-T) based neoadjuvant chemotherapy.

Methods:
Patients (pts) with operable TNBC independent of baseline FASN expression; and no prior PPI use within 12 months were enrolled. Pts began OMP 80 mg PO BID for 4-7 days prior to AC-T; carboplatin was allowed per physician discretion. OMP was continued until surgery. Paired biopsy samples were obtained before and after OMP monotherapy. The primary endpoint was pathologic complete response (pCR), defined as no residual invasive disease in breast or axilla, in pts with baseline FASN expression (FASN+) assessed using immunohistochemistry. Relevant secondary endpoints included

pCR in the intent to treat population, change in FASN expression, enzyme activity and downstream target gene expression after OMP monotherapy; safety and limited OMP pharmacokinetics. We targeted a pCR rate of 60% in FASN+ pts (null pCR ~ 40%) with 80% power and alpha of 0.10.

Results:

A total of 42 pts were recruited from 5 US sites. Median age was 51y (28-72). Most pts had >cT2 (33, 79%) and ≥N1 (22, 52%) disease. 14 (33%) were African American. FASN expression prior to AC-T was identified in 28 (85%) samples available for analysis. The pCR rate was 71.4% (95% CI 51.3 to 86.8) in FASN+ pts and 71.8 %(95% CI 55.1 to 85.0) in all enrolled pts. Fifteen pts (36%) received carboplatin with AC-T; pCR in this subset was 73%. Peak OMP concentration was significantly higher than IC_{50} observed during preclinical testing; FASN positivity significantly decreased with OMP monotherapy from 0.53(SD 0.25) at baseline to 0.38(SD 0.30; p = 0.02). OMP was well tolerated with no known grade (G) 3 or 4 toxicities. Chemotherapy toxicity was similar to prior studies using AC-T with G3 or 4 neutropenia (19%), febrile neutropenia (7%) and peripheral neuropathy (7%) being the most common.

Conclusions:

Consistent with previous studies, FASN is frequently expressed in early stage TNBC. OMP can be safely administered in doses that inhibit FASN. The addition of high dose OMP to neoadjuvant AC-T yields a promising pCR rate without adding toxicity. Funded by the Breast Cancer Research Foundation. Clinical trial information: NCT02595372.