Comparative Effectiveness Analysis of Monotherapy With Cytotoxic Agents in Triple-negative Metastatic Breast Cancer in a Community Setting

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ABSTRACT

Purpose: There has been considerable progress in the treatment of metastatic breast cancer. However, the identification of optimal cytotoxic agents in patients with triple-negative breast cancer (TNBC) (negative for hormone receptors and human epidermal growth factor receptor 2) remains a therapeutic challenge. We conducted a comparative effectiveness analysis of 4 cytotoxic agents in patients with TNBC.

Methods: We retrospectively identified patients who received single-agent chemotherapy with eribulin, capecitabine, gemcitabine, or vinorelbine from 19 community oncology clinics across the United States. Data collection included baseline patient and disease characteristics, prior therapies, performance status, duration of current therapy, growth-factor use and other supportive care, and dose-limiting toxicities and associated dose reductions or delays or skipped doses. Time to treatment failure (TTF) was measured from the first cycle of chemotherapy until disease progression, discontinuation due to toxicity, or death. TTF was estimated using the Kaplan-Meier method and Cox proportional hazards modeling adjusted for clustering on the practice site. To control for selection bias, which is inherent in observational studies, a propensity score–weighted TTF analysis was also conducted.

Findings: Data from 225 patients were included in the analysis (eribulin, 47 patients; capecitabine, 69; gemcitabine, 56; and vinorelbine, 53). The median age of each group was <60 years, with the exception of the gemcitabine group (63 years). The 4 groups were comparable with respect to age, performance status, duration of disease-free survival, presence of comorbidities, and hemoglobin level before the start of chemotherapy. Median lines of therapy of eribulin, capecitabine, gemcitabine, and vinorelbine and were 4th, 2nd, 3rd, and 3rd, respectively. The median durations of treatment were $\sim$2 months with eribulin, capecitabine, and gemcitabine compared with 1.6 months with vinorelbine. Using eribulin as the reference drug, and with adjustment for line of therapy and associated prognostic factors, the propensity score–weighted Cox regression analysis did not identify significant between-treatment differences in TTF (hazard ratios [95% CI] vs eribulin: capecitabine, 1.15 [0.75–1.76]; gemcitabine, 0.62 [0.34–1.13]; and vinorelbine, 1.0 [0.67–1.67]).

Implications: In this assessment of patients with TNBC treated in a community oncology setting, eribulin was utilized in later lines compared with the other agents. However, comparable drug activity was reported among the 4 agents. (*Clin Ther.* 2015;37:134–144)

Key words: eribulin, capecitabine, gemcitabine, metastatic breast cancer, triple negative, vinorelbine.

INTRODUCTION

Despite recent advances in its early detection and treatment, breast cancer remains one of the leading causes of death in women. In 2013 the United States

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alone, there were 232,340 new cases of breast cancer diagnosed and 39,620 deaths from the disease.[1] However, 5-year survival rates after a diagnosis of early stage breast cancer have increased, from 75% in the 1970s to approximately 90% in 2013.[1] This increase has been largely due to improved options focused on specific tumor biology, with availability and widespread use of hormonal and cytotoxic therapies, as well as targeted agents (TAs), with treatment benefit extending into the metastatic setting.[2–4]

On closer inspection of the data, gains in survival have primarily been realized in patients whose tumors express hormone receptors or human epidermal growth factor receptor (HER)-2. In contrast, options are more limited for patients whose tumors are negative for hormone receptors and HER-2 (triple-negative breast cancer [TNBC]), in whom hormone and HER-2 TAs are ineffective. This heterogeneous group encompasses ~15% of all new diagnoses.[5] One of the distinctive characteristics of TNBC is the rapid development of, or de novo, resistance to chemotherapy, leading to shorter disease-free and overall survival (OS).[5,6] In a cohort study in 1601 patients with breast cancer who were followed up for a median of 8.1 years, patients with TNBC were at a higher risk for distant recurrences (hazard ratio [HR] = 2.6; $P < 0.05$) and death (HR = 3.2; $P < 0.05$) within 5 years of the initial diagnosis.[7] After a diagnosis of metastatic disease, patients in the TNBC cohort had a significantly shorter OS compared with the reference population (9 vs 22 months; $P < 0.05$).[7] Clearly, the treatment of TNBC represents a major therapeutic challenge and is an active area of clinical research.

Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor. There is some experience with bevacizumab in combination with chemotherapy in TNBC. In a subgroup analysis of data from RIBBON-2 (A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination With Chemotherapy for Second-Line Treatment of Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer),[8] which evaluated various cytotoxic agents with and without bevacizumab in metastatic disease, patients with TNBC had a statistically significant improvement in progression-free survival (6.0 vs 2.7 months; $P < 0.001$) and a numerically greater but statistically similar OS. However, these results have yet to be confirmed in an adequately powered Phase III randomized comparative trial. Therefore, it is unlikely that bevacizumab will address the current unmet need that is TNBC. Other agents being investigated in clinical trials include anti–vascular endothelial growth factor receptor tyrosine kinase inhibitors, anti–epidermal growth factor receptor therapies, poly (adenosine diphosphate ribose) polymerase inhibitors, Src tyrosine kinase inhibitors, and oral mammalian target of rapamycin inhibitors.[5,9] The most advanced of these agents is iniparib, with a randomized Phase II trial reporting statistically significant improvements in objective response, progression-free survival, and most importantly OS (7.7 vs 12.3 months; HR = 0.57; $P = 0.01$).[10] Iniparib was then taken into Phase III development in a trial that mimicked the Phase II study. In that randomized, controlled trial (RCT), the drug failed to meet its progression-free survival and OS end points, and further development of iniparib was halted.[11]

Because there are no specifically targeted chemotherapeutic drugs with proven clinical benefit in TNBC, patients typically are treated with the same agents used in other breast cancer subgroups. Patients with metastatic TNBC would be offered single-agent or combination chemotherapy containing an anthracycline or taxane agents, capecitabine, gemcitabine, vinorelbine, or carbo- or cisplatin.[6,9] However, some results with eribulin were reported in a subset analysis of data from the Phase III EMBRACE (Eribulin Monotherapy Versus Treatment of Physician's Choice in Patients With Metastatic Breast Cancer) trial.[12] In that global study, which enrolled 762 patients into an eribulin arm or a physician's-choice comparator arm, the experimental therapy was reported to have had an OS benefit (HR = 0.81; $P = 0.041$); 74% of enrolled patients were HER-2 negative, and 19% had TNBC. Eribulin was more effective in both hormone-negative and TNBC patients than in the control group. However, these intriguing findings have yet to be confirmed in an RCT.

Although ongoing and planned trials are evaluating a variety of TAs for the treatment of patients with metastatic TNBC, clinicians need immediate information that will help to guide medical decision making. Comparative effectiveness studies, through observational data, are a reasonable approach to assessing treatment effects in a clinical practice setting.[13,14] Several examples illustrate the concordance between