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Notes on Clinical Trial Interpretation

Reevaluating Adjuvant Capecitabine for Resected Biliary Tract Cancer

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Key words: biliary tract cancer; adjuvant; capecitabine; BILCAP.

Despite surgical resection, biliary tract cancer (BTC) carries a significant risk of recurrence.[1] As such, several clinical trials have attempted to identify a therapy that mitigates the risk of relapse and prolongs survival. Although capecitabine, gemcitabine, and oxaliplatin have demonstrated benefit in the metastatic setting, 3 phase III trials (BILCAP, BCAT, and PRODIGE 12-ACCORD 18-UNICANCER GI) evaluating these antineoplastic agents in the adjuvant setting did not demonstrate a statistically significant improvement in recurrence-free survival nor in overall survival (OS).[2-4] Updated analyses of outcomes from BILCAP have also not demonstrated a statistically significant improvement in survival.[5] Specifically, the *P*-value in BILCAP for OS is .097, which failed to achieve the prespecified cutoff of 0.05. Nevertheless, clinical practice guidelines from the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) both recommend adjuvant capecitabine for resected BTC.[6,7] The rationale for this recommendation is that resected BTC is a dire malignancy with no treatment options, and that among all 3 studies, BILCAP is the closest to traditional nominal significance. However, this stance does not account for analysis of all 3 studies; here, we place BILCAP in context.

PRODIGE 12-ACCORD 18-UNICANCER GI which compared gemcitabine plus oxaliplatin (GEMOX) to observation reported a median OS of 75.8 months versus 50.8 months (HR 1.08; 95%CI, 0.70-1.66; *P* = .74), respectively. Despite a numerical improvement in OS of 25 months, the authors concluded that there was no benefit with GEMOX due to the lack of statistical significance. In comparison, BILCAP (which randomized individuals to either capecitabine or placebo) did not meet its primary endpoint of improved OS, with a median OS of 51.1 months versus 36.4 months and an adjusted hazard ratio (HR 0.81; 95%CI, 0.63-1.04; *P* = .097). Similar to the GEMOX study demonstrating a numerical improvement in OS that was not statistically significant, the study authors of BILCAP instead concluded adjuvant capecitabine "could be considered as standard of care." The study's conclusion and its subsequent adoption by several prominent practice guidelines are concerning given its implications for the oncology field.

Table 1 shows all 3 studies and *P*-values found for OS. *P*-value is the probability of observing these results or more extreme results if we draw random patients from the same population. In other words, if there was no therapeutic effect, approximately in 10% of instances, a result such as BILCAP would occur. When taking into consideration that the 3 studies were run concurrently, and ^a priori no particular agent was favored, the probability that 1 of the 3 trials would have a result like BILCAP rises to nearly 1 in 3. In other words, if none of these drugs worked, it is entirely plausible to anticipate trial results as shown in Table 1. In fact, this would occur nearly a third of the time, a false-positive rate that has never been accepted in oncology to our knowledge.

While the study authors of BILCAP contend that the "safety profile in manageable," 21% of individuals who received capecitabine experienced serious adverse effects. These toxicities are not trivial and may translate to extensive consequences for patients and patients' families, including quality of life, financial toxicity, and time toxicity from clinical visits, interventions, lab testing, and potentially hospitalization.

Several ongoing clinical trials may ultimately identify a therapeutic agent that significantly improves DFS or OS for resected BTC.[8] If so, capecitabine will likely be abandoned as a commonly accepted and advocated adjuvant therapy. If not, however, adjuvant capecitabine and its widely accepted use may reinforce the acceptance of adjuvant oncologic therapies with no proven benefit in the future.

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Conflict of Interest

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Table 1. Phase III adjuvant clinical trials for resected biliary tract cancer.

Trial name	Study drug(s)	Hazard ratio	*P*-value
BILCAP	Capecitabine	0.81	.097
BCAT	Gemcitabine	1.01	.964
PRODIGE 12-ACCORD 18-UNICANCER GI	Gemcitabine, Oxaliplatin	1.08	.74

from Evicore and New Century Health, and a Plenary Session podcast with Patreon backers.

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