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EDITORIAL – PANCREATIC TUMORS

Editorial Comment to "High Expression of Bloom Syndrome Helicase is a Key Factor for Poor Prognosis and Advanced Malignancy in Patients with Pancreatic Cancer: A Retrospective Study"

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The number of patients with pancreatic cancer is increasing by 0.5–1.0% per year, and pancreatic cancer is projected to become the second leading cause of cancer-related mortality by 2030.[1] Pancreatic ductal adenocarcinoma (PDAC) accounts for the majority (90%) of pancreatic cancers, and is characterized by poor prognosis because of rapid growth, invasive progression, and chemoresistance, which make treatment difficult. Recently, comprehensive germline and somatic genomic sequencing have been performed to select subgroups of patients who may benefit from targeted treatment opportunities. The study by Lan and colleagues retrospectively evaluated Bloom syndrome helicase (BLM) expression in 182 patients with PDAC to determine the role of BLM expression in this cohort.[2] BLM is a key member of the RecQ subset of DNA helicases that contribute to genome maintenance and stability.[3] The BLM protein has an ATP-dependent, 3'–5' DNA helicase activity and plays important roles in the initiation and regulation of homologous recombination repair of double-strand breaks and in the restarting of stalled forks, while suppressing the firing of new origins in response to replication stress.[4] High expression of BLM reportedly promotes tumor progression and reduces chemosensitivity in cancers of the lung, prostate, breast, and bile duct.[5]

In their study, Lan and colleagues found high expression of BLM at both the messenger RNA (mRNA) and protein levels in PDAC, and high BLM expression was independently associated with poor overall and recurrence-free survival after curative resection. They performed in vitro assays using BLM-expressing pancreatic cancer cell lines and found that BLM suppression reduced tumor proliferation, invasion, migration, and chemoresistance activities. Based on the results presented, the authors proposed that BLM is a potential prognostic marker and a potential anticancer drug target for patients with PDAC.

One of the most important pathogenic germline gene variants that increases susceptibility to PDAC is *BRCA1/2*, whose prevalence is approximately 5–7% among all PDAC.[1] The results of this study showed that 66 of 182 patients (36%) were highly positive for BLM expression by immunohistochemistry. The subgroup analysis demonstrated that high BLM expression was associated with shorter overall survival among patients with younger age ($\leq$ 70 years), male sex, high cancer antigen 19-9 level ($>$ 37 U/mL), advanced tumor stage (T 3/4), lymph node metastasis, nerve invasion, and adjuvant chemotherapy. A limitation of the present study is that only 35 of 182 patients (19%) received neoadjuvant chemotherapy, and a relationship between BLM expression and response to neoadjuvant chemotherapy was lacking. Furthermore, adjuvant chemotherapy was performed mostly with tegafur/gimeracil/oteracil (S-1; 113 of 143 patients, 79%) or gemcitabine (28 patients, 20%); thus, data on the

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relationship between BLM expression and response to other fluorouracil-based or platinum-based based therapies, such as FOLFIRINOX, are not available. A previous report showed that *BRCA* expression levels are inversely correlated with those of *BLM*, suggesting a possible compensatory or direct transcriptional effect on *BLM* in the setting of low or insufficient *BRCA*.[4] Another recent study showed that patients who had a germline *BRCA* mutation and metastatic pancreatic cancer that had not progressed during first-line platinum-based chemotherapy had significantly longer progression-free survival with maintenance poly(adenosine diphosphate–ribose) polymerase 1 (PARP1) inhibitor than with placebo.[6] Further studies regarding BLM expression and sensitivity to platinum-containing chemotherapy and inhibitors of PARP1 are anticipated.

While the investigators highlight BLM expression as a useful biomarker of poor prognosis, one must initially ask whether this could be a promising therapeutic target for PDAC. BLM has been studied as an attractive anticancer drug target, and inhibitors of BLM are currently in preclinical development.[7] The authors of the current study showed successful inhibition of proliferation, invasion, and migration activity of BLM-positive cell lines by using BLM-specific small interfering RNAs (siRNAs). A combination of gemcitabine and a BLM-specific siRNA demonstrated a stronger antiproliferative effect against gemcitabine-sensitive pancreatic cancer cell lines than gemcitabine alone. However, it is important to note that this study examined a limited number of pancreatic cancer cell lines that are highly positive for BLM expression, and again, sensitivity to other types of chemotherapy, such as fluorouracil-based or platinum-containing chemotherapy, was not tested. Furthermore, the mechanism of action of BLM-specific siRNA is still not fully understood. Bioinformatics analysis successfully identified E2F targets as a possible molecular pathway involved in BLM expression, and its downregulation was confirmed by western blot analysis. Although there are several challenges to considering a BLM-targeting compound as an anticancer agent, this study sheds light on a new target for PDAC treatment.

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