ADJUVANT THERAPY FOR BILIARY CANCER

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Cancers of the biliary tract (gallbladder and intra and extra hepatic cholangiocarcinomas) are relatively rare, with approximately 10,000 new cases diagnosed in the US annually[1]. These cancers have a poor prognosis with five year survival rates in the range of 5-20%[2,3]. Surgical resection offers the only potentially curative option but less than 35% are resectable at presentation and relapse rates are high[4,5]. The pattern of recurrence following curative resection is typically local[6], although first relapse at a distant site is quite common also.[6,7]. With such high rates of relapse, a strategy aimed at optimizing local control with postoperative radiation alone or in combination with chemotherapy, or optimizing systemic recurrence with chemotherapy may provide benefit and impact long term survival outcomes from this disease. Data supporting an adjuvant approach is sparse. With relatively few patients resectable at presentation, it is particularly difficult to complete a large randomized adjuvant trial powered to show improvements in overall survival. Moreover, prior to recent data in metastatic disease[8], there was a lack of global consensus regarding the optimal chemotherapy regimen which could be brought forward for adjuvant evaluation. Consequently, the existing literature consists mainly of uncontrolled institutional series and registry analyses. Based on these retrospective data, an adjuvant approach is still largely favored and surveys suggest it is utilized in up to 70% of centers worldwide[9,10.] Reflecting this lack of level 1 evidence the NCCN guidelines make broad recommendations for adjuvant approaches which include considerations of fluoropyrimidine-based chemoradiotherapy, or fluoropyrimidine or gemcitabine based chemotherapy alone or observation alone. And enrollment in clinical trials strongly supported [11]. A recent systematic review and meta-analysis of over 6,000 patients examined the benefits of adjuvant therapies concluded that an overall survival benefit of adjuvant chemotherapy was seen in higher risk patients with lymph node positive disease (OR,0.49; p=.004) and and/or R1 resections (OR, 0.36; P=.002)[12]. This analysis provides support for the use of adjuvant therapy for resected disease, particularly in patients with these high risk features until better data is provided and will contribute to the rational design of prospective studies. Such studies will require international collaboration to be successful. We are also encouraged that a number of randomized trials evaluating adjuvant therapy are now underway and these designs will be reviewed.

References:

1. Jemal A, Siegel R, Xu J, et al: Cancer statistics, 2010. CA Cancer J Clin 60:277-300

2. Anderson CD, Pinson CW, Berlin J, et al: Diagnosis and treatment of cholangiocarcinoma. Oncologist 9:43-57, 2004

3. Howlader N NA, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.:

4. de Groen PC, Gores GJ, LaRusso NF, et al: Biliary tract cancers. N Engl J Med 341:1368-78, 1999

5. Wade TP, Prasad CN, Virgo KS, et al: Experience with distal bile duct cancers in U.S. Veterans Affairs hospitals: 1987-1991. J Surg Oncol 64:242-5, 1997

6. Jarnagin WR, Ruo L, Little SA, et al: Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer 98:1689-700, 2003

7. Hasegawa S, Ikai I, Fujii H, et al: Surgical resection of hilar cholangiocarcinoma: analysis of survival and postoperative complications. World J Surg 31:1256-63, 2007

8. Valle J, Wasan H, Palmer DH, et al: Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362:1273-81

9. Pitt HA BC, Fong Y, Gouma DJ, Lau JW, Nagorney DM, et al. : Adjuvant therapy for biliary malignancies: international trends and possibilities. . J Gastrointest Surg 7;309A, 2003

10. Nakeeb A, Pitt HA: Radiation therapy, chemotherapy and chemoradiation in hilar cholangiocarcinoma. HPB (Oxford) 7:278-82, 2005

11. Benson AB, 3rd, Abrams TA, Ben-Josef E, et al: NCCN clinical practice guidelines in oncology:hepatobiliary cancers. J Natl Compr Canc Netw 7:350-91,2009.

12. Horgan AM, Amir E, Walter T and Knox J: Adjuvant therapy in the treatment of of biliary tract cancer:a systematic review and meta-analysis. J Clin Oncol 30:1934-40, 2012.

A Phase 2, Randomized Trial of GVAX Pancreas and CRS-207 Immunotherapy versus GVAX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: Ongoing Safety and Efficacy Results

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Background: Novel immunotherapies augment presentation of tumor-associated antigens (TAAs) in the context of stimulatory signals and induce anti-tumor immunity. GVAX pancreas is comprised of two GM-CSF-secreting allogeneic human pancreatic cell lines which are irradiated and injected intradermally, and preceded by the intravenous administration of low-dose cyclophosphamide (CY) to inhibit regulatory T-cells. CRS-207 is a live-attenuated, double-deleted (LADD) Listeria monocytogenes (Lm) engineered to express mesothelin, a TAA over-expressed by nearly all pancreatic ductal adenocarcinomas (PDA). CRS-207 as a bacterial vector is designed to stimulate both innate and adaptive immunity. CRS-207 has shown synergy with GVAX in mouse tumor models and the Phase 1 study of CRS-207 showed induction of mesothelin-specific CD8+ T-cell immunity and significant survival benefits anecdotally in patients previously treated with GVAX.

Methods: Metastatic PDA patients (ECOG 0-1 with adequate organ function) who had received (or refused) one or more chemotherapy regimens were randomized 2:1 to receive 2 doses of CY/GVAX followed by 4 doses of CRS-207 (Arm A) or 6 doses of CY/GVAX (Arm B) every 3 weeks for a 20-week course. Courses could be repeated in patients deriving clinical benefit. The primary endpoint was overall survival (OS) between the treatment arms. Secondary endpoints included safety, clinical and immune responses.

Results: 90 patients (comprising the Full Analysis Set [FAS]: Arm A: 61; Arm B 29) with median age 63 and 51% having received 2 or more chemotherapy regimens for metastatic disease were treated. An interim analysis at 42 deaths (in 88 patients) showed a median OS of 6.0 months in Arm A versus 3.4 months in Arm B (hazard ratio for death [HR], 0.45; 95%CI, 0.24 to 0.85; p=0.01, two-sided). This met the predetermined stopping criterion for efficacy ($p<0.0263$, one-sided). Subsequent OS analysis on the FAS based on 58 deaths among 90 patients (64.4%) (Arm A: 36/61, 59%; Arm B: 22/29, 76%) showed median OS was 6.1 months (95% CI, 4.2 to 9.7) in Arm A as compared to 3.9 months in Arm B (95% CI, 2.8 to 4.9) (HR, 0.55; 95%CI, 0.32 to 0.94; p=0.03, two-sided). OS analysis in the per protocol analysis set (patients who received >3 doses; at least two doses of CY/GVAX and 1 dose of CRS-207 in Arm A or >3 doses of CY/GVAX in Arm B) based on 35 deaths among 66 patients (53%) (Arm A: 21/45, 47%; Arm B: