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Case Report

Adjuvant Systemic Therapy for Intestinal Type Invasive IPMNs: A Case Series and Brief Literature Review

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ABSTRACT

Intraductal Papillary Mucinous Neoplasms (IPMNs) are epithelial neoplasms that can progress to invasive pancreatic malignancies. While the Sendai guidelines can assist us regarding which IPMNs are likely to be invasive and therefore need resection, there are limited data about management after resection. The adjuvant therapy for resected Invasive IPMNs (I-IPMNs) is currently based off of limited retrospective analyses and expert opinion extrapolating primarily from pancreatic exocrine regimens. The heterogeneity in both pathology and treatment response as seen in a recent systematic review suggests that we should consider delineating between the broad categories of intestinal/colloid type and pancreatobiliary/tubular type I-IPMNs to guide adjuvant systemic therapy similar to what is done with ampullary malignancies. Without prospective studies to guide our treatment decisions, we performed a literature review focused on the subgroup analyses of retrospective studies to modify and individualize the adjuvant systemic treatment of resected intestinal type I-IPMNs. Six months of adjuvant 5-fluorouracil based therapy appears to be a reasonable approach for fit, high-risk patients.

Keywords: Invasive; Intestinal; Pancreatic; Neoplasm; Chemotherapy

INTRODUCTION

Intraductal Papillary Mucinous Neoplasms of the pancreas (IPMNs) are a relatively recently defined member of the Pancreatic Cystic Neoplasms (PCN) with evolving pathogenesis and treatment guidelines [1]. IPMNs are believed to develop in 1% to 5% of the general population [2]. The reported incidence of invasive malignancy varies from 57% to 92% in main duct IPMNs and from 6% to 46% in branch duct IPMNs [3]. The Sendai guidelines aid decision making regarding resection of IPMNs and focus on such attributes as symptoms, diameter>3 cm, solid components, involvement of the main pancreatic duct or malignant cells on cytology [4].

Adjuvant management of resected IPMNs, if they are found to be invasive, is challenging given the lack of prospective trials. A comprehensive systematic review of adjuvant therapy in invasive IPMNs (I-IPMNs) published in 2019 included a total of 2652 patients with I-IPMNs resected between 2010 and 2019. This study revealed significant geographical and institutional differences in adjuvant therapy including various chemotherapy and radiation therapy regimens. This review also found improvements in disease specific survival in 7 of the 8 included trials with the use of adjuvant therapy. The variable use of systemic therapy after resection of 1-IPMN highlights the need for prospective clinical trials to confirm the benefits attributed to systemic therapy in this population [5].

I-IPMNs can be categorized into at least three groups based on differences in histomorphologic phenotypes: tubular (typically consisting of pancreatobiliary), colloid (typically consisting of intestinal or gastric-foveolar), and the rare intraductal oncocytic neoplasms as differentiated by particular mucin expression patterns of MUC6, MUC1, MUC5AC and MUC2 [6]. As of 2009 it has been documented in retrospective analyses that 5-year overall survival with non-intestinal or pancreatobiliary type I-IPMNs is as poor as conventional pancreatic ductal adenocarcinoma whereas intestinal types have a more favorable prognosis [7]. Marchegiani et al. have suggested that like ampullary cancers, which also have intestinal and biliary subtypes, the different subgroups may derive differing amounts of value from adjuvant therapy and may benefit from tailored systemic therapy regimens [8,9].

CASE SERIES

Case 1

A 67-year-old female originally presented 04/2020 with persistent

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cough and a chest CT incidentally indicated hepatic steatosis. Subsequent MRI in 05/2020 revealed pancreatic ductal prominence of the body and tail. Follow up CA 19-9 (9.0 ng/mL), CEA and LFTs were within normal limits. An Endoscopic Ultrasound (EUS) illustrated a hypoechoic density in the neck of the pancreas measuring 1.1 × 0.8 cm. FNA revealed an IPMN with high grade dysplasia. Robot-assisted pancreatectomy and splenectomy was performed. Pathological analysis demonstrated grade 2 moderately differentiated colloid carcinoma associated with intestinal type IPMN. There was a 0.7 cm invasive component, and 1/27 lymph nodes were positive (Figure 1). Immunohistochemical (IHC) staining indicated that DNA Mismatch Repair (MMR) proteins MLH1, MSH2, MSH6, PMS2 were retained and the tumor was CDX2 positive. The pathologic stage was pT1bN1. Adjuvant mFOLFOX was then offered given the intestinal type and nodal involvement. The patient has tolerated the first two cycles well with a plan to complete 6 months of total adjuvant systemic therapy.

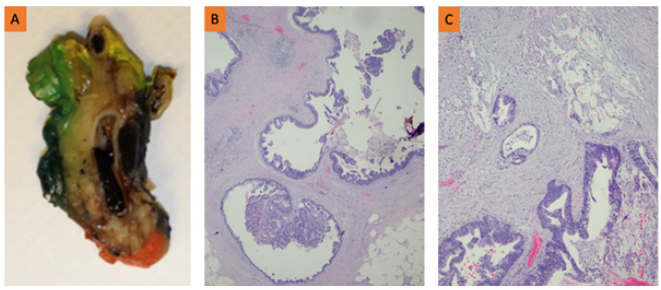

Figure 1: (A) A multiloculated lesion macroscopically; (B) high grade intestinal type IPMN composed of pseudostraified columnar cells mimicking colonic tubular adenoma; (C) In transition of inflitrating colloid adenocarcinoma.

Case 2

A 64-year-old female presented in 2019 with persistent epigastric pain. Her previous history was significant for ampullary villous adenoma status post pancreaticoduodenectomy and subsequent laparoscopic lysis of adhesions secondary to small bowel obstruction. EGD with EUS demonstrated a dilated main pancreatic duct with stenosis at the pancreaticojejunostomy and a suspicious pancreatic tail lesion. CA 19-9 was within normal limits at the time of surgery. Completion Pancreatectomy and splenectomy were performed and revealed a 3.2 cm invasive moderately differentiated adenocarcinoma with mucinous features, perineural invasion, negative margins and 0/55 involved lymph nodes. Histological analysis further indicated the mass was positive for CK20 and CDX2 and negative for CK7, consistent with derivation from an intestinal type IPMN. The patient was pathologically staged as pT2N0. IHC showed proficient MMR proteins. Adjuvant mFOLFOX was offered given the higher T stage. The patient tolerated 6 cycles of adjuvant therapy which was complicated by hair thinning, cold paresthesias and weight loss. Given the lack of nodal involvement and progressive toxicities we opted for an abbreviated three-month course rather than a six-month course similar to certain colon cancer regimens.

Case 3

An 80-year-old male originally presented for follow up of a hepatic abscess noted on imaging in 2018 which was incidentally found during a workup of chronic cough. Abdominal MRI and MRCP indicated a posterior mass in the right hepatic lobe that measured 4.8 × 3.7 cm as well as noting multiple cystic lesions including 0.8 and 1.2 cm cystic lesions in the pancreatic tail and a 1.3 × 0.8 cm lesion in the pancreatic head. AFP was normal at <2 ng/mL and CA19-9 was normal at 14 U/mL. Biopsy of the liver lesion indicated granulomatous inflammatory changes. In 07/2020 an EGD and EUS were performed illustrating multiple pancreatic cysts at the head, body and tail, with a cyst at the tail being described as hypoechoic and irregular with a solid component measuring 17 × 13 mm. FNA was then performed on the tail cyst which indicated adenocarcinoma. The patient then underwent robot-assisted distal pancreatectomy and splenectomy, with pathology demonstrating moderately differentiated pancreatic ductal adenocarcinoma in association with branch duct and gastric foveolar type IPMN. This histology, like the intestinal subtype, is part of the colloid or non-pancreatobiliary grouping. Peri-pancreatic invasion of 1.6 cm was noted and all 35 lymph nodes were negative. The patient's pathological stage was thus pT1cN0. Given the negative nodes, low T stage, patient's age and discussion of risk and benefits, we opted for observation rather than adjuvant chemotherapy.

DISCUSSION

Here we describe the management of systemic therapy in three patients with I-IPMN following surgical resection. There are no prospective studies to guide adjuvant treatment decisions. A single systematic review by Aronsson et al. [5] addressed this topic and revealed disease specific survival benefits with adjuvant systemic therapy in patients with node positive disease, higher TNM stage, positive resection margins, tubular subtype and poorly differentiated tumors. Based on these findings, adjuvant systemic therapy was recommended for our first patient due to node positivity and for our second patient with T2 disease. Patient three did not have any of the features likely to benefit from chemotherapy and therefore was recommended observation. All three patients are alive and continuing with their treatment plans as delineated.

Following a decision to treat I-IPMN with adjuvant chemotherapy, the decision of which regimen to use remains a challenge. We focused on the intestinal/colloid subtype nature of our patients' disease to guide systemic therapy choice. We selected a fluoropyrimidine based regimen since 5-FU forms the backbone of adjuvant systemic therapy in many other intestinal malignancies, particularly colon cancer. Giovanni et al. revealed that a disease specific survival benefit with primarily gemcitabine-based regimens (83.4% vs. 2% utilizing 5-FU based regimens) was only noted for the tubular or non-intestinal subtypes of I-IPMNs [9]. Similarly, another study by Schiergens et al of patients with ampullary cancers demonstrated a worse prognosis but positive response to gemcitabine in non-intestinal subtype ampulla of Vater cancers and a possible harmful effect in those with the intestinal subtype [8]. Based on these available studies and extrapolating from other intestinal malignancies, we felt that the data supported a 5FU based regimen over a gemcitabine-based regimen in our patients with intestinal subtype I-IPMN.

Given the lack of prospective trials in this area, we chose a 6-month duration of adjuvant systemic therapy based on extrapolation from adjuvant data and consensus guidelines in pancreatic ductal adenocarcinomas and in high-risk colon adenocarcinomas [10]. However, in the case of patient two, given progressive toxicities, we felt an abbreviated three-month course was reasonable to mitigate toxicity, particularly as her only high-risk feature was T2 disease.

None of our patients were noted to have deficient MMR proteins via

IHC suggesting a low likelihood of Microsatellite Instability (MSI). The incidence of loss of MMR proteins or MSI among IPMNs is unknown and in pancreatic adenocarcinoma it remains rare with estimates of <1% [11]. While the incidence of dMMR or MSI-H in I-IPMN is likely low, it is worth exploring given the potential treatment implications. The treatment landscape is evolving for GI malignancies with dMMR, MSI-H, or a high tumor mutation burden to include the use of immune checkpoint inhibitors, especially in metastatic disease [12]. Finally, it is worth noting that patients with minimally invasive IPMN's (≤ 0.5 cm invasive component) are unlikely to benefit from adjuvant therapy [13].

CONCLUSION

Based on available literature, 6 months of adjuvant fluoropyrimidine based chemotherapy for fit high risk intestinal subtype I-IPMNs seems reasonable. Further research, including prospective studies, are needed to confirm if treatment decisions based on the tumor pathological subtype is an appropriate strategy and to determine the optimal type and duration of adjuvant systemic therapy. Similarly, evaluation of the role of immunotherapy or other targeted therapies in I-IPMNs both in the adjuvant and metastatic setting remains an area of unmet need.

REFERENCES

1. Farrell JJ. Prevalence, Diagnosis and management of pancreatic cystic neoplasms: Current status and future directions. Gut Liver. 2015;9: 571-589.
2. Laffan TA, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, et al. Prevalence of unsuspected pancreatic cysts on MDCT. AJR Am J Roentgenol. 2008;19:802-807.
3. Machado NO, Al Qadhi H, Al Wahibi K. Intraductal papillary mucinous neoplasm of the pancreas. N Am J Med Sci. 2015;7:160-175.
4. Tanaka M, Chari S, Adsay V, Castillo CF, Falconi M, Shimizu M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6:17-32.
5. Aronsson L, Marinko S, Ansari D, Andersson R. Adjuvant therapy in invasive intraductal papillary mucinous neoplasm (IPMN) of the pancreas: A systematic review. Ann Transl Med. 2019;7:689.
6. DeVita, VT, Lawrence TS, Rosenberg SA. Colon and other gastrointestinal cancers: Principles and practice of oncology. Lippincott Williams & Wilkins, 2016.
7. Sadakari Y, Ohuchida K, Nakata K, Ohtsuka T, Aishima S, Takahata S, et al. Invasive carcinoma derived from the nonintestinal type intraductal papillary mucinous neoplasm of the pancreas has a poorer prognosis than that derived from the intestinal type. Surgery. 2010;10:720-725.
8. Schiergens TS, Reu S, Neumann J, Renz B, Niess H , Boeck S, et al. Histomorphologic and molecular phenotypes predict gemcitabine response and overall survival in adenocarcinoma of the ampulla of vater. Surgery. 2015;158:151-161.
9. Giovanni M, Andrianello S, Dal Borgo C, Secchettin E, Melisi D, Malleo G, et al. Adjuvant chemotherapy is associated with improved postoperative survival in specific subtypes of invasive intraductal papillary mucinous neoplasms (IPMN) of the pancreas: It is time for randomized controlled data. HPB. 2019;21:596-603.
10. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D et al. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 20;26:56-68.
11. Hu ZI, Shia J, Stadler ZK, Varghese AM,Capanu M, Salo-Mullen E, et al. Evaluating mismatch repair deficiency in pancreatic adenocarcinoma: Challenges and recommendations. Clin Cancer Res. 2018;24:1326-1336.
12. Center for Drug Evaluation and Research. FDA approves Pembrolizumab for First-Line Treatment of MSI-H/DMMR Colo. U.S. Food and Drug Administration, FDA, 2020.
13. Nara S, Shimada K, Kosuge T, Kanai Y, Hiraoka N. Minimally Invasive Intraductal Papillary-Mucinous Carcinoma of the Pancreas: Clinicopathologic Study of 104 Intraductal Papillary-Mucinous Neoplasms. Am J Surg Pathol. 2008;32:243-255.