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Adjuvant and Neoadjuvant Systemic Therapy for Pancreas Adenocarcinoma

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Abstract

The last two decades of research in the adjuvant setting of pancreas adenocarcinoma have established the value of adjuvant systemic therapy as being able to delay recurrence and increase overall survival. International standards of care in the adjuvant setting include either 6 months of gemcitabine or 5-flurouracil and leucovorin. The added value of additional agents in the adjuvant setting is being evaluated in several large adjuvant studies. The role of a targeted agent in the adjuvant setting remains investigational. Other major areas of exploration include the integration of adjuvant immunotherapeutic approaches, which provide promise in a setting of micrometastatic disease volumes where such approaches may have greatest value.

Pancreas adenocarcinoma is a malignancy with a rising incidence and with an overall 5-year survivorship rate of approximately 6%.[1] Currently the only accepted potentially curative modality is surgery for patients with localized resectable pancreas adenocarcinoma. For most patients with resected disease, the risk of relapse remains substantial. Local-regional recurrence rates from 50%– 80% and systemic recurrence rates of greater than 70% have been reported previously.[2] There has been no significant improvement in long-term survival even during the past decade.[3] As a result, adjuvant treatment following surgery is routinely recommended to reduce the risk of and delay recurrence and to prolong survival. While a variety of options for adjuvant therapy such as chemotherapy, combined chemotherapy and radiation, and chemoradiation plus chemotherapy have been evaluated, the optimum treatment still remains controversial; however, the value of adjuvant systemic therapy has been clearly established. This review will summarize the major adjuvant studies for pancreas adenocarcinoma with a particular focus on adjuvant systemic therapy, as well as discuss new directions in adjuvant therapy and the optimal timing of initiation of adjuvant therapy, and highlight some of the biomarker selection factors that are under evaluation in the adjuvant setting.

OLDER ADJUVANT SYSTEMIC TRIALS

One of the first phase III trials exploring the role of adjuvant therapy in pancreas adenocarcinoma was the Gastrointestinal Tumor Study Group (GITSG) trial originally

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published in 1985.[4] This study enrolled 49 patients from 1974–1982. A total of 43 evaluable patients with surgically resected pancreas adenocarcinoma were randomized to receive adjuvant treatment with either 5-fluorouracil (5-FU) concurrent with radiation (21 patients) versus observation (22 patients). Patients receiving adjuvant treatment in this study were treated with bolus 5-FU 500 mg/m^2 on the first 3 days of weeks 1 and 5 of radiation, which was given as a split course of 50 Gy with a 2-week break in the middle. Patients on the experimental arm were then placed on maintenance 5-FU given on a weekly basis for 2 years or until tumor recurrence. Median survival was found to be significantly longer for the adjuvant treatment group at. 20 months compared to 11 months for the observation group (P = .035). Criticisms of this study include having a small patient population and inadequate quality assurance of radiation therapy. Furthermore, while patients in this study derived a survival benefit with adjuvant treatment, it is unclear if the benefit was actually from the systemic chemotherapy or the chemoradiation or both.

While the GITSG study has been used by some as a basis for 5-FU–based chemoradiation in the adjuvant setting, other studies have challenged the value of chemoradiation. The European Organization for Research and Treatment of Cancer (EORTC) 40891 trial was a large multicenter phase III study of patients with resected pancreatic head cancer and periampullary tumors.[5] Patients recruited between 1987–1995 were randomized to either observation or postoperative chemoradiation with infusional 5-FU at a dose of 25 mg/kg/d on days 1–5 on weeks 1 and 5 with concurrent split course radiation totaling 40 Gy with a 2-week break between radiation blocks. There was no maintenance systemic therapy in this study. A total of 120 patients (approximately > 50% of the total study population) with resected pancreatic head cancer were evaluated as a part of this study. While the first analysis at a median follow-up of 7.3 years suggested a trend toward an advantage for adjuvant chemoradiation in the patients with pancreatic head cancer with a median overall survival of 17.1 months in the treatment group versus 12.6 months in the observation group (P = .099), the long-term follow-up analysis at a median follow-up of 11.7 years showed no significant difference in survival, even when only the pancreatic head cancer group was evaluated.[6]

Along with EORTC 40891, the European Study Group of Pancreatic Cancer (ESPAC)-1 trial[7,8] provided a further challenge to the value of chemoradiation and rather suggested that chemotherapy alone provided a survival benefit in the adjuvant setting. This study used a complex 2 × 2 factorial study design to randomize patients undergoing curative resection for pancreas adenocarcinoma stratified by center, tumor type and resection margins. The four treatment arms in this study included (1) chemoradiation consisting of an intravenous bolus of 5-FU at 500 mg/m^2 on the first 3 days of weeks 1 and 5 of radiation, which was given as a split course of 40 Gy with a 2-week break in the middle; (2) chemotherapy consisting of an intravenous bolus of leucovorin at. 20 mg/m^2 followed by intravenous bolus of 5-FU at a dose of 425 mg/m^2 for 5 consecutive days every 28 days with a total of 6 months of therapy; (3) combination therapy consisting of chemoradiation followed by chemotherapy as described above; and (4) observation. A total of 289 patients from 53 hospitals in Europe underwent randomization between 1994–2000. With a median follow-up of 47 months, the authors reported that the 5-year survival rate was 21% among patients treated with chemotherapy versus 8% among patients not treated with chemotherapy (P = .009). In

addition, the estimated 5-year survival rate was 10% for patients treated with chemoradiation compared to. 20% for patients who did not receive chemoradiation ($P = .05$). This negative impact of chemoradiation has been challenged by others due to the quality of radiation therapy provided and various protocol violations, all of which could have possibly contributed to a greater than 62% local recurrence rate in the study.[9–11] Despite the various limitations of the study, ESPAC-1 lead to a trend away from chemoradiation in Europe and beyond in favor of systemic chemotherapy alone as the main adjuvant treatment choice for resected pancreas adenocarcinoma. Regardless, these results remain a source of ongoing controversy and the value of chemoradiation in the adjuvant setting in North America remains in question.

THE RECENT ERA OF ADJUVANT SYSTEMIC THERAPY

While ESPAC-1 demonstrated the benefit of adjuvant systemic chemotherapy alone in pancreas adenocarcinoma with intravenous 5-FU, researchers continued to evaluate if other or additional systemic chemotherapy agents would provide greater benefit in this setting. The CONKO-001 (Charite Onkologie 001) trial was designed to compare adjuvant intravenous gemcitabine with observation alone in patients undergoing complete curative resection for pancreatic cancer.[12,13] A total of 368 patients were enrolled between 1998–2004, stratified based on nodal status, tumor stage, and margin status. Patients were required to have a CA 19-9 level within 2.5 times the upper limit of normal. Eligible patients were then randomized to either observation or to receive six cycles of gemcitabine given every 4 weeks consisting of 3 weekly infusions of 1,000 mg/m^2, followed by a 1-week break. The primary endpoint was disease-free survival and the secondary endpoint was overall survival. The main result of the trial was that there was a significant improvement in disease-free survival of 13.4 months in the treatment group versus 6.7 months in the observation group ($P < .001$). In addition, patients in the treatment group were found to have significantly prolonged overall survival compared to those being observed ($P = .01$), with 5-year overall survival of. 20.7% versus 10.4% and 10-year overall survival of 12.2% versus 7.7%, respectively.[13] Furthermore, the treatment effect was found to be consistent and uniform throughout all prognostic strata based on tumor stage, nodal status, and margin status. The findings from the CONKO-001 therefore provided strong level 1 evidence supporting the use of gemcitabine as a routine chemotherapy agent in the adjuvant setting.

At the approximately the same time as the CONKO-001 study was being conducted in Germany and Austria, investigators in North America conducted the Radiation Therapy Oncology Group (RTOG) 97-04 study.[14] RTOG 97-04 was a phase III trial to determine if the addition of gemcitabine to adjuvant 5-FU chemoradiation improved survival in patients with resected pancreatic adenocarcinoma. A total of 451 patients were enrolled in this study from 1998–2002. Patients were randomized to chemotherapy with either 5-FU (continuous infusion of 250 mg/m^2 per day) or gemcitabine (1,000 mg/m^2 once per week) for 3 weeks prior to chemoradiation therapy and for 12 weeks following chemoradiation therapy. The chemoradiation (continuous infusion of 5-FU at 250 mg/m^2 daily throughout radiation therapy with a total dose of 50.4 Gy of radiation) between the two groups was the same and therefore this was not a study designed to investigate the role of chemoradiation in the adjuvant setting. Interestingly, 86% of patients enrolled in the study had pancreatic head

tumors and the study was mainly powered to analyze the survival among these patients. This distinction was made because investigators reasoned that patients with resected pancreatic body or tail tumors generally have different clinical presentations and operations, as well as an overall worse prognosis compared to those with head tumors.[15,16] Therefore, by using the key primary endpoint of overall survival for patients with pancreatic head tumors, the investigators reported a median survival of. 20.5 months in the gemcitabine group versus a median survival of 16.9 months in the 5-FU group ($P = .09$). While not statistically significant, the authors concluded that the addition of gemcitabine given before and after chemoradiation was associated with a survival benefit in the adjuvant setting. Interestingly, a follow-up study by Abrams et al[17] on the RTOG 97-04 study noted that upon multivariate analysis for patients with pancreatic head tumors, adherence to radiation therapy per protocol and gemcitabine treatment were both correlated with improved median survival ($P = .016$ and $P = .043$, respectively). Therefore, the authors further concluded that it was a failure to adhere to specified radiation therapy guidelines during the trial that was associated with reduced survival.

In addition to CONKO-001 and RTOG 97-04, the ESPAC investigators also began to build on results from their ESPAC-1 trial. The ESPAC-3 trial was developed as an initial three-arm study randomizing patients with resected pancreas adenocarcinoma to adjuvant 5-FU and leucovorin versus gemcitabine versus observation. Chemoradiation was not evaluated in this study. Ultimately, as the ESPAC-1 trial results were finalized showing a benefit to adjuvant 5-FU, the observation arm for ESPAC-3 was removed. Therefore, ESPAC-3 (v2) accrued a total of 1,088 patients from. 2000–2007.[18] Patients received either 5-FU plus leucovorin (leucovorin. 20 mg/m^2 intravenous bolus followed by 5-FU 425 mg/m^2 intravenous bolus given on days 1–5 every 28 days) or gemcitabine (1000 mg/m^2 intravenous infusion once a week for 3 of every 4 weeks) chemotherapy for 6 months in the adjuvant setting. The primary endpoint of the study was 2-year overall survival. The final analysis was performed after a median follow-up of 34.2 months and revealed equivalency between the two different chemotherapy agents with a median survival of 23.0 months for patients treated with 5-FU plus leucovorin and 23.6 months for those patients treated with gemcitabine ($P = .39$). The study also reported that 14% of patients treated with 5-FU plus leucovorin developed serious (> grade 3) treatment-related adverse events compared to only 7.5% of patients treated with gemcitabine ($P < .001$). Based on these results, the use of gemcitabine chemotherapy alone became favored as the predominant therapy in the adjuvant setting. However, these data provide support for the use of 5-FU/leucovorin in the setting where gemcitabine cannot be safely continued or administered (eg, history of gemcitabine-related pneumonitis, hemolytic-uremic syndrome and idiopathic pulmonary fibrosis where the risk of gemcitabine-related pneumonitis is high).

ADJUVANT CHEMORADIATION TRIALS

Based on results from the six above mentioned prominent adjuvant prospective randomized phase III trials (GITSG, EORTC, ESPAC-1, CONKO-001, ESPAC-3, and RTOG 97-04) for pancreas adenocarcinoma, chemotherapy with gemcitabine or 5-FU plus leucovorin for 6 months currently represents a standard of care. The data for and against adjuvant chemoradiation remain mixed from these studies. Even additional retrospective data, phase

II studies and a recent meta-analysis continue to provide evidence for and against the use of chemoradiation in the adjuvant setting. Merchant et al[19] performed an analysis of pooled data from seven academic centers where a total of 299 patients underwent surgery followed by chemoradiation versus 347 patients who had surgery alone. The median overall survival was. 20 months for patients receiving adjuvant chemoradiation versus 14.5 months for patients with no adjuvant therapy ($P = .001$). The investigators also found that chemoradiation provided a significant survival advantage only in lymph node positive disease. Additional large-institution retrospective reviews have been performed at both the Mayo Clinic and the Johns Hopkins Hospital reporting similar results of an overall survival benefit favoring the use of adjuvant chemoradiation.[20–22]

While many of the retrospective reviews have focused on comparing chemoradiation to observation in the adjuvant setting, the EORTC 40013 phase II trial evaluated gemcitabine chemotherapy alone (four cycles at a dose of 1,000 mg/m^2 each week for 3 weeks followed by 1 week of rest) versus gemcitabine for two cycles followed by weekly gemcitabine with concurrent radiation (gemcitabine 300 mg/m^2 by infusion once per week given 4 hours before radiation 50.4 Gy total for 5–6 weeks).[23,24] The co-primary endpoints of the study were to exclude a > 40% rate of grade IV toxicity and < 60% treatment completion. A total of 90 patients with head of pancreas adenocarcinoma were randomized. Eighty-seven percent of patients in the gemcitabinealone arm and 73% of patients in the chemoradiation arm completed treatment. There were low levels of grade IV toxicity with 0% in the chemotherapy-alone arm versus 4.4% in the chemotherapy followed by chemoradiation arm. Median overall survival was the same for the two arms at 24 months. Interestingly, while the rate of distant metastasis was similar between both arms of the study, the rate of local recurrence alone at first progression was 24% for the chemotherapy alone arm and 11% in the chemoradiation arm, suggesting that the addition of chemoradiation may provide better local control with only a slight increase in toxicity compared to gemcitabine alone.

ADJUVANT THERAPY SYSTEMATIC REVIEWS

However, a recent systematic review of different adjuvant treatments for resected pancreas adenocarcinoma (5-FU ν gemcitabine ν chemoradiation ν chemoradiation plus 5-FU or gemcitabine) with Bayesian network meta-analysis demonstrated that chemotherapy alone with either 5-FU (hazard ratio [HR] 0.65, 0.49–0.84) or gemcitabine (HR 0.59, 0.41–0.83) was the optimum adjuvant treatment by providing a significant overall survival benefit over observation alone.[25] In contrast, chemoradiation was associated with a worse overall survival when compared with 5-FU (HR 1.69, 1.12–2.54) and gemcitabine (HR 1.86, 1.04–3.23). While chemoradiation plus 5-FU or gemcitabine did not provide a significant survival advantage over either 5-FU or gemcitabine chemotherapy alone, the addition of chemoradiation to chemotherapy was associated with more significant toxicity. Therefore, based on all of these studies, the role of the addition of chemoradiation to chemotherapy in the adjuvant setting remains very unclear.

While gemcitabine chemotherapy alone is often recommended as the current standard adjuvant chemotherapy for resected pancreas adenocarcinoma, many of the current trials are focused on adding either different chemotherapy or biologic agents to gemcitabine or the use

of other agents. Recently, the results of the Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC)-01 trial suggested that S-1, an oral fluoropyrimidine designed with the aim of improving antitumor activity and reducing the toxicity of 5-FU,[26] appears to be not only non-inferior to gemcitabine and but also superior to gemcitabine in the adjuvant setting for the Japanese patient subpopulation.[27] This study enrolled 385 resected pancreas adenocarcinoma patients from 33 hospitals in Japan from. 2007–2010. Patients were randomized to six cycles of intravenous gemcitabine (1,000 mg/m^2 for 3 weeks followed by 1 week of rest) or four cycles of oral S-1 (80–120 mg/d based on body surface area for 4 weeks followed by 2 weeks of rest). The study was a non-inferiority study with 80% power with the primary endpoint of overall survival. The investigators reported that overall survivals at 2 years were 53% for the gemcitabine group and 70% for the S-1 group ($P < .0001$ for non-inferiority, $P < .0001$ for superiority). While the results are impressive, it is unclear if the survival benefit with adjuvant S-1 will translate to a broader population. Specifically, Caucasians receiving S-1 have been known to develop more severe gastrointestinal toxicities compared to Asians possibly due to metabolic and pharmacogenomic differences between the populations. Therefore, lower doses of S-1 may be required if S-1 is introduced to a broader patient population, which could affect the overall efficacy of the drug in the adjuvant setting.

NEW DIRECTIONS IN ADJUVANT THERAPY

The three main approaches being explored in the adjuvant setting to improve outcomes are: (1) the value of combination cytotoxic therapy, (2) the value to the addition of a targeted agent, and (3) the value of immunotherapeutic approaches.

ESPAC-4 (ISRCTN96397434) is a large randomized phase III trial comparing the addition of capecitabine plus gemcitabine to gemcitabine. The study is powered for a primary endpoint of overall survival with a target of 1,080 patients. This study will further build on results of ESPAC-1 and ESPAC-3 and will take several more years before results will become available.

Regarding targeted therapy, erlotinib is the agent that is being investigated most extensively in the adjuvant setting. Several additional adjuvant studies have been designed based on positive results reported in the locally advanced and metastatic treatment settings for pancreas adenocarcinoma. For example, the National Cancer Institute of Canada Clinical Trials Group (NCIC) PA.3 randomized phase III trial showed that the addition of erlotinib, an oral tyrosine kinase inhibitor, to gemcitabine demonstrated a statistically significant survival advantage when compared to gemcitabine alone in patients with locally advanced or metastatic pancreas adenocarcinoma.[28] While the improvement in median overall survival was minimal to modest between the two arms of the study (6.24 months for gemcitabine plus erlotinib ν 5.91 months for gemcitabine alone), there were significant 1-year survival and progression-free survival advantages in the erlotinib plus gemcitabine group, leading to US Food and Drug Administration approval of this combination for advanced pancreas adenocarcinoma in. 2005. As debate continues regarding the significance of the cost/benefit for erlotinib-treated patients in the advanced setting,[29] both Europe and North America have current phase III trials evaluating the addition of erlotinib to gemcitabine in the adjuvant

setting. The CONKO-005 (DRKS00000247) trial has completed recruitment, evaluating gemcitabine plus erlotinib compared to gemcitabine alone in patients with R0 resected pancreas cancer. The primary endpoint of the study will be relapse-free survival based on 436 patients. The trial is currently in the follow-up phase. In addition to CONKO-005, RTOG 0848 (NCT01013549) is an active North American phase III trial also evaluating the role of the addition of erlotinib in the adjuvant setting. A target of 952 patients with resected head of pancreas adenocarcinoma with post-resection CA 19-9 < 180 IU/L will be stratified by margin and lymph node status and the country of origin. Patients are randomized to receive gemcitabine or gemcitabine plus erlotinib to complete a total of 6 months of adjuvant systemic therapy. However, patients in this study also will undergo restaging after 5 months of chemotherapy and if found to have no recurrence, they will undergo a second randomization with the addition of chemoradiation versus no added therapy. This study design will allow investigators to not only evaluate the role of the addition of erlotinib in the adjuvant setting but also will attempt to answer the question of the value of combined chemoradiation to systemic chemotherapy in the adjuvant setting. Given the large target sample size and complexity of the trial, results from this study will likely not be available until at least. 2020. Interestingly, results from the LAP-07 phase III trial were recently presented[30] demonstrating that the addition of radiation did not improve outcomes following 4 months of systemic therapy in patients with locally advanced pancreas adenocarcinoma. In this study 442 patients were first randomized to receive gemcitabine alone versus gemcitabine plus erlotinib 100 mg per day for 4 months. Of these 442 patients, 269 patients reached the second stage where patients were randomized to 2 additional months of chemotherapy versus chemoradiation with 54 Gy of radiation therapy with capecitabine 1,600 mg/m^2/d. The primary objective was median overall survival after the second randomization, which was 16.5 months for the chemotherapy group versus 15.3 months for the chemoradiation group. Therefore, the investigators concluded that administering chemoradiation is not superior to continuing chemotherapy in patients with locally advanced pancreas cancer after 4 months of chemotherapy. Overall, these findings have implications on the future of the RTOG 0848 study moving forward. An amendment was recently completed that removed the randomization to erlotinib. The current study design involves one randomization only to plus or minus the addition of fluoropyrimidine-based radiation to the single-agent gemcitabine cytotoxic backbone.

In metastatic pancreas adenocarcinoma, large phase III trials have demonstrated a significant survival benefit with both FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin) and the combination of gemcitabine plus nab-paclitaxel (Abraxane, Celgene, Summit, NJ) when compared to singleagent gemcitabine.[31,32] Given these findings, investigators from the group PRODIGE which conducted the prior FOLFIRINOX study in the metastatic setting have now developed PRODIGE 24/ACCORD 24 (NCT01526135), a phase III trial comparing adjuvant chemotherapy with gemcitabine versus modified FOLFIRINOX (omission of bolus 5-FU) to treat resected pancreatic adenocarcinoma. The estimated enrollment will be 490 patients with the primary outcome being disease-free survival at 3 years. The study began in January 2012 and is due to mature by. 2020. Similarly, development of phase III trials such as ABI-007-PANC-003 (NCT01964430) will compare the efficacy of nab-paclitaxel in combination with gemcitabine to gemcitabine alone as

adjuvant treatment in patients with surgically resected pancreatic adenocarcinoma. This study will plan to recruit 800 patients with the primary outcome of disease-free survival and is also estimated to be completed by approximately 2020.

ADJUVANT IMMUNOTHERAPEUTIC APPROACHES

Another area of increasing research interest in the adjuvant treatment for pancreas adenocarcinoma has been the development of the use of vaccinations and immunotherapy. For instance, *KRAS* mutations are frequently seen in pancreas adenocarcinoma. A small phase I–II trial of 23 patients treated with a *KRAS* vaccine in the adjuvant setting demonstrated an immune response to the vaccine in 85% of patients with a median survival of 28 months.[33] Our group at Memorial Sloan-Kettering Cancer Center also developed a study and treated 24 patients with resected pancreas adenocarcinoma with a univalent vaccine targeted at *KRAS* mutations but unfortunately only noted limited immunogenicity with median overall survival of. 20.3 months.[34] Besides targeting *KRAS*, telomerase has been shown to be involved in cancer development and therefore, a telomerase peptide vaccine GV1001 targeting the catalytic subunit of hTERT was developed.[35] However, a recent phase III randomized trial of 1,062 patients with locally advanced or metastatic pancreatic cancer treated with gemcitabine and capecitabine with or without the GV1001 found that there was no significant overall survival benefit with the addition of GV1001 to chemotherapy, compared to chemotherapy alone.[36] Another concept in vaccine development involves the use of shared antigens across pancreatic adenocarcinomas. By using this concept, investigators at the Johns Hopkins University developed an allogeneic whole cell vaccine (GVAX) where three out of 14 patients initially treated with the vaccine in addition to conventional therapy in the adjuvant setting developed specific immunity and achieved 10-year survivorship.[37] However, a follow-up single arm phase II trial of approximately 60 patients treated with GVAX in the adjuvant setting found that there was no improvement in survival compared with a contemporary patient cohort treated without the vaccine at the same institution.[38]

Therefore, while no vaccine or immunotherapies have shown significant improvements in overall survival in phase III clinical trials of resected pancreas adenocarcinoma patients, multiple newer approaches continue under development. For example, using the concept of hyperacute rejection, a vaccine (algenpantucel-L) has been developed using genetically modified pancreas cancer cells with a mouse gene leading to foreign protein expression of alpha (1,3)-galactosyl (αGal). Pre-existing anti-αGal antibodies then trigger a significant immune response leading to cell destruction of any tumor cells in patients undergoing treatment with this form of immunotherapy.[39,40] Interestingly, a phase II study evaluating the role of this form of algenpantucel-L immunotherapy in addition to therapy with gemcitabine with 5-FU–based chemoradiation in patients with resected pancreas adenocarcinoma showed an impressive 1-year disease-free survival of 63% and overall survival of 86%, which compares favorably to historical controls.[41] As a result a phase III trial of chemotherapy and chemoradiotherapy with or without algenpantucel-L immunotherapy in 722 subjects with surgically resected pancreatic cancer has recently completed recruitment and results are eagerly awaited (NCT01072981).

NEOADJUVANT THERAPY FOR RESECTABLE PANCREAS ADENOCARCINOMA

Based on the many large phase III trials above, adjuvant chemotherapy provides a proven survival benefit compared to pancreatic resection alone. However, due to the significant morbidity risk associated with pancreatic surgery, many patients often are unable to receive adjuvant chemotherapy within the therapeutic window provided after surgery. Therefore, the neoadjuvant sequence of therapy has a strong theoretical rationale with the potential advantages of neoadjuvant therapy including but not limited to, early delivery of systemic therapy to more patients with consequently better micro-metastatic disease control, improved tolerability of therapy, the potential for improved rates of R0 resection margins at time of surgery and an assessment of chemosensitivity. Neoadjuvant chemotherapy in resectable patients has yet to be fully defined with regard to value as results from prior phase II studies have been limited and mostly are based on single-institution experiences. For example, a single small phase II prospective trial evaluating neoadjuvant gemcitabine and cisplatin for resectable head of pancreas adenocarcinoma demonstrated feasibility with favorable overall and disease-free survival.[42] However, data from a large pooled meta-analysis review in. 2010 does not suggest a significant advantage of neoadjuvant therapy with respect to resectability and survival rates when compared to upfront surgical resection followed by adjuvant therapy.[43] A multicenter nonrandomized phase II trial evaluating neoadjuvant/adjuvant gemcitabine and erlotinib (American College of Surgeons Oncology Group [ACOSOG] Z5041; NCT003733746) has completed recruitment and may provide additional valuable results regarding the delivery of systemic therapy in the neoadjuvant setting. This study has proved the feasibility of multi-center participation in a neoadjuvant study. Furthermore, a phase III trial of 310 patients exploring the role of neoadjuvant gemcitabine with oxaliplatin in addition to adjuvant gemcitabine compared to adjuvant gemcitabine alone in resectable pancreatic cancer with the primary endpoint of progression free survival (NEOPAC [NEOadjuvant Gemcitabine/Oxaliplatin Plus Adjuvant Gemcitabine in Resectable PAcreatic Cancer]; NCT01521702) is projected to be completed by December 2015.

TIMING AND DURATION OF ADJUVANT THERAPY

The exact timing of when to begin adjuvant treatment after surgical resection also remains relatively uncertain. In many malignancies such as colon cancer, adjuvant chemotherapy is often started within 4–6 weeks of surgical resection. Guetz et al performed a meta-analysis of eight studies including 13,158 patients with stage III colorectal cancer and overall survival was compared between groups of patients receiving chemotherapy within 8 weeks and those delaying chemotherapy for more than 8 weeks.[44] Delaying chemotherapy more than 8 weeks was associated with worse overall survival (relative risk 1.20, 95% confidence interval 1.15–1.26) but surprisingly not relapse-free survival. Therefore, this discrepancy may be due to other factors rather than directly related to cancer. In pancreas adenocarcinoma, computer modeling had previously demonstrated that earlier initiation of adjuvant therapy might lead to better survival compared to later initiation.[45] However, Valle et al evaluated this question in patients who had been randomly assigned to the

chemotherapy group of the ESPAC-3 phase III study and performed an overall survival analysis based on the start time of chemotherapy.[46] A total of 985 patients were analyzed (486 received gemcitabine and 499 received 5-FU) and 675 patients were found to have completed all six cycles of chemotherapy while 293 patients completed one to five cycles. All patients receiving chemotherapy also were compared based on starting chemotherapy within 8 weeks of surgery versus those who were delayed in starting chemotherapy after 8 weeks. Overall survival favored patients who completed the full six cycles of treatment when compared to those who did not (HR 0.516, $P < .001$). Surprisingly, the time to starting chemotherapy did not influence overall survival rates for the entire study population (HR 0.985, $P = .32$), but the timing was noted by the authors to be an important survival factor only for the cohort of patients who did not complete the full course of chemotherapy, in favor of the later treatment group (HR 0.919, $P = .004$). Similar results also were reported for recurrence-free survival in this study. Therefore, it appears that completion of all six cycles of adjuvant chemotherapy was the more significant prognostic factor after pancreas adenocarcinoma resection rather than the timing of initiating adjuvant chemotherapy. While it still remains unclear what the true cutoff time for delaying adjuvant chemotherapy may be for resected pancreas adenocarcinoma, it is certainly possible that permitting patients to have adequate time to recover postoperatively may lead to better tolerability of chemotherapy allowing patients to potentially complete a full course of treatment.

BIOMARKERS AND PATIENT SELECTION FOR ADJUVANT THERAPY

The use of biomarker stratification and prognostication is an emerging area of research in pancreas adenocarcinoma. For example, a high flux transporter named human equilibrative nucleoside transporter-1 (hENT1) appears to play a major role in transporting gemcitabine into cells,[47] which may have a significant role in adjuvant chemotherapy delivery in pancreas adenocarcinoma. Farrell et al[14] demonstrated a significant correlation between hENT1 expression level and disease-free and overall survival (HR 0.36 [$P = .003$] and 0.47 [$P = .04$], respectively) in patients treated with gemcitabine after surgical resection in the RTOG 9704 adjuvant study. Furthermore, a recent study by Greenhalf et al used samples collected from the adjuvant ESPAC-1 and -3 randomized trials and demonstrated that patients with low hENT1 expression had a significantly lower median survival (17.1 ν 26.2 months) compared to patients with high hENT1 expression for those who received adjuvant gemcitabine after undergoing surgical resection for pancreatic cancer.[48] However, recently the Low hENT1 Adenocarcinoma of the Pancreas (LEAP) trial was the first study to evaluate in a prospective fashion, the role of hENT1 as a biomarker in patients with metastatic pancreatic cancer. Unfortunately, the researchers for this study found no significant overall survival difference between the hENT1 high and low subgroups of patients treated with gemcitabine.[49] Therefore, the possibility that hENT1 may have greater prognostic value in the adjuvant setting rather than the metastatic setting will require further prospective testing in the future.

In addition to hENT1, additional biomarkers that may play a role in the adjuvant setting for pancreas adenocarcinoma include molecules involved in DNA synthesis and repair such as ribonucleotide reductase subunits 1 and 2 (RRM1 and RRM2), and also the excision repair cross-complementing gene-1 (*ERCC1*). By using a prospective database, Fisher et al

performed immunohistochemical analysis on 95 randomly selected patients with resected pancreas adenocarcinoma and demonstrated that high RRM2 and high *ERCC1* expression was associated with reduced recurrence-free survival, as well as overall survival.[50] Additional potential mediators of adjuvant therapy resistance may be S100A4 and S100A2, both of which are calcium-binding proteins involved in the cell cycle.[51] In one study of 601 tumor samples from patients with operable and locally advanced pancreas cancer,[52] patients with tumors expressing high levels of S100A2 and S10A4 were found to have poor outcomes after surgery, whereas patients with S100A2 negative tumors had a survival benefit following surgery (overall survival of 19.4 months ν 8.8 months, $P < .001$). An analysis of 184 samples from the RTOG 9704 trial has since been performed and demonstrated a 2-year disease-specific survival of 59% for the S100A4-negative patients versus 37% for the S100A4-positive patients.[53] While not statistically significant, this finding suggests that S100A4 may potentially predict for resistance in patients treated with adjuvant gemcitabine.

CONCLUSIONS

The last two decades of research in the adjuvant setting of pancreas adenocarcinoma have clearly established the value of adjuvant systemic therapy as being able to delay recurrence and increase overall survival. The benefits accrued are similar to the relative benefits of adjuvant therapy in other solidorgan malignancies, although the absolute risk of recurrence is much higher in pancreas adenocarcinoma. International standards of care in the adjuvant setting in. 2014 include either 6 months of gemcitabine or 5-FU and leucovorin. The added value of a second or more agents in the adjuvant setting is currently being evaluated in several large adjuvant studies and results are likely to accrue in the next 3–5 years. The role of a targeted agent in the adjuvant setting remains investigational, with most of the focus being on the potential integration of erlotinib in the adjuvant setting, although recent data suggest that the value is likely to be limited in an unselected patient population. A North American randomized phase II trial did not identify a value to the addition of either bevacizumab or cetuximab to gemcitabine and fluoropyrimidine-based radiation in the adjuvant setting. Other major areas of exploration include the integration of adjuvant immunotherapeutic approaches, which provide promise in a setting of micrometastatic disease volumes where such approaches may have greatest value. In the current era of improved systemic therapy in the advanced disease setting with the advent of FOLFIRINOX and gemcitabine and nab-paclitaxel, the time is ripe for a wider scale evaluation of neoadjuvant therapy, which we believe is likely to benefit patients not least of all with regard to improved patient selection for surgical therapy.

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