JOP. J Pancreas (Online) 2013 July 10; 14(4):337-339.

HIGHLIGHT ARTICLE

Locally Advanced Pancreatic Cancer. Looking Beyond Traditional Chemotherapy and Radiation

Highlights from the "2013 ASCO Annual Meeting". Chicago, IL, USA; May 30 - June 4, 2013

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Summary

About a third of all pancreatic cancer is found to be locally advanced at the time of diagnosis, where the tumor is inoperable but remains localized to the pancreas and regional lymphatics. Sadly, this remains a universally deadly disease with progression to distant disease being the predominant mode of failure and average survival under one year. Optimal treatment of these patients continues to be an area of controversy, with chemotherapy alone being the treatment preference in Europe, and chemotherapy followed by chemoradiation in selected patients, preferred in the USA. The aim of this paper is to summarize the key abstracts presented at the 2013 ASCO Annual Meeting that address evolving approaches to the management of locally advanced pancreatic cancer. The late breaking abstract (#LBA4003) provided additional European data showing non-superiority of chemoradiation compared to chemotherapy in locally advanced pancreatic cancer patients without distant progression following 4 months of chemotherapy. Another late breaking abstract, (#LBA4004), unfortunately showed a promising new complement to gemcitabine and capecitabine using immunotherapy in the form of a T-helper vaccine did not translate to improved survival in the phase III setting.

About a third of all pancreatic cancer is found to be locally advanced at the time of diagnosis, where the tumor is inoperable but remains localized to the pancreas and regional lymphatics [1]. Sadly, this remains a universally deadly disease with progression to distant disease being the predominant mode of failure and average survival under one year [2]. Optimal treatment of these patients continues to be an area of controversy, with chemotherapy alone being the treatment preference in Europe, and chemotherapy followed by chemoradiation in selected patients, preferred in the USA.

What We Knew Before the 2013 ASCO Annual Meeting

The debate between chemotherapy alone *versus* chemoradiation for the treatment of locally advanced pancreatic cancer is based on trials that have been historically underpowered, using outdated modes of chemotherapy and radiation. Two key Gastrointestinal Study Group (GITSG) trials published in the 1980's led to the adoption of concurrent chemoradiation with 5-FU in the USA. GITSG 9273 consisted of 193 patients, split course radiation, and bolus 5-FU with maintenance 5-FU until progression, with results showing median survival time of 9 months with 5-FU/external beam radiation therapy (XRT) *vs*. 5 months with radiation alone [3]. GITSG 9283 compared multidrug 5-FU based chemotherapy *vs*. XRT with concurrent 5-FU based chemotherapy, with improved median survival seen in the concurrent chemoradiation arm: 9.7 *vs*. 7.4 months, respectively [4]. These trials were small, fraught with criticism, and not duplicated by prospective Eastern Cooperative Oncology Group (ECOG) trials published in the 1980's, with ECOG 8232 showing no benefit of 5-FU, mitomycin and concurrent XRT *vs*. radiation alone, and ECOG 1985 showing no survival benefit of 5-FU/XRT *vs*. 5-FU alone (8.3 *vs*. 8.2 months) [5, 6]. When gemcitabine was found to be more effective in the metastatic setting [7], its use was adopted in the management of localized disease, and its role in the concurrent chemoradiation *vs*. chemotherapy alone debate was played out in several prospective trials. The Federation Francophone de Cancerologie Digestive and Societe Francaise de Radiotherapie Oncologique (FFCD-SFRO) trial published in 2005

Key words Chemoradiation; Immunotherapy; Neoadjuvant Therapy

Abbreviations XRT: external beam radiation therapy

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showed improved survival in the gemcitabine alone arm *vs*. concurrent radiotherapy plus 5-FU (13 *vs*. 8.6 months) [8]. The ECOG E4201 study published in 2011 showed improved overall survival in the XRT plus gemcitabine compared to gemcitabine alone (11.1 *vs*. 9.2 months), with a slightly worse toxicity profile [9]. Gemcitabine plus XRT *vs*. 5-FU plus XRT was compared in the Taipei trial, with benefit in the gemcitabine arm (14.5 *vs*. 6.7 months) [10]. However, the outcome in the 5-FU arm was criticized for its inferior results compared to already published data.

In all of the above trials, treatment was palliative, with no long-term survival benefit achieved, and with not insignificant toxicity profiles. Variation in treatment strategy was undertaken in the Selective Chemoradiation in Advanced Localised Pancreatic Cancer (SCALOP) multicenter phase II trial that adopted neoadjuvant chemotherapy with concurrent chemoradiation using capecitabine *vs*. gemcitabine, with results showing overall survival benefit of 15.2 *vs*. 13.4 months in the capecitabine arm, with an improved toxicity profile [11]. The LAP-07 trial was the first phase III trial to investigate the method of neoadjuvant chemotherapy followed by concurrent chemoradiation. This trial's accrual and trial scheme were presented in a prior ASCO meeting, with the highly anticipated outcomes having been presented at this year's meeting.

What We Learned at the 2013 ASCO Annual Meeting

LAP-07 Phase III Trial (Abstracts #LBA4003 [12])

Hammel *et al*. presented results from a multi-institutional phase III study where 442 patients were randomized to neoadjuvant gemcitabine plus/minus erlotinib 100 mg/day, given over 4 months. If disease was controlled, patients were then randomized to either two additional months of chemotherapy, or to concurrent chemoradiation that consisted of 54 Gy and capecitabine 1,600 mg/m^2/day. If patients were initially randomized to the erlotinib arm, they were maintained on erlotinib after the second randomization treatment was completed. The primary outcome was overall survival, with secondary outcome of overall survival in the erlotinib arm, tolerance, predictive markers, and circulating tumor cells (with a separate abstract published reporting this result). Overall 269 patients reached the second randomization, with 136 patients randomized to continued chemotherapy, and 133 randomized to capecitabine based chemo/XRT. The median follow-up was 36 months; with results showing no difference in overall survival between capecitabine based concurrent chemoradiation *vs*. chemotherapy alone in those patients who had not progressed after 4 months of chemotherapy (16.5 *vs*. 15.3 months, P=0.83).

A Phase III Randomized Trial of Chemo-Immunotherapy Comprising Gemcitabine and Capecitabine with or without Telomerase Vaccine GV1001 in Patients with Locally Advanced or Metastatic Pancreatic Cancer (Abstract #LBA4004 [13])

Middleton *et al*. presented the results of a phase III randomized prospective multi-institutional study looking at the benefit of the vaccine targeting cancer pervasive telomerase peptides, GV1001, when used either concurrently or in sequence with combination chemotherapy. The trial had three arms; one received gemcitabine and capecitabine alone; the second received gemcitabine and capecitabine followed by GV1001, with maintenance gemcitabine/capecitabine if there was no progression; and the third arm received concurrent gemcitabine/capecitabine and GV1001. The primary endpoint was overall survival. One thousand and sixty-two patients were randomized with follow-up of 6 months. Overall survival was not statistically significant between the three arms, and overall there was no improved outcome adding the vaccine to concurrent chemotherapy.

Discussion

LAP-07 trial is the first modern phase III trial that compares neoadjuvant chemotherapy followed by concurrent chemoradiation, and these results agree with prior European data showing that the addition of conventional radiation to management in locally advanced disease does not lead to improved outcome when compared to gemcitabine alone. This is despite selection of patients who have not progressed following 4 months of chemotherapy; which presumably would enrich for patients who would benefit from local therapy with radiation. Unfortunately, this did not translate into identifying a group of patients who benefit from chemoradiation. The ancillary study presented at this meeting investigating circulating tumor cells as a correlate of systemic disease and prognosis is one example in the heavily sought after path of discovering a marker that will help select patients for improved individualized treatment outcome in the future. Further investigation is greatly needed to look beyond clinical or pathologic indicators that have failed to identify patients who benefit from the addition of local therapy. Ongoing studies that utilize chemoradiation for treatment of locally advanced pancreatic cancer are obligated to include exploration of novel predictive molecular markers. Finally, improvements in the delivery of local therapy are required and there is ongoing work on the development of techniques that will allow for

dose escalation that limits toxicity to the surrounding tissues.

On the other end of the spectrum was the large phase III randomized trial that investigated the use of a telomerase vaccine as an adjunct to chemotherapy for the treatment of locally advanced pancreatic cancer. This trial also had disappointing results in light of promising phase I/II data showing a robust immune response to GV1001 in patients with pancreatic cancer. As is the case for many agents that do well in phase I/II trials and fail to show benefit in the randomized setting, the earlier trials are likely fraught with imbalance. Further development of immunotherapy will continue to focus on identifying active antigens to promote an even more robust immune response and superior choice of adjuvant therapies that enhance the anti-tumor effects of vaccination.

Conflicts of interest The authors have no potential conflicts of interest

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