Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial.


Collaborators (65)

Abstract

IMPORTANCE:
In locally advanced pancreatic cancer, the role of chemoradiotherapy is controversial and the efficacy of erlotinib is unknown.

OBJECTIVES:
To assess whether chemoradiotherapy improves overall survival of patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine-based induction chemotherapy and to assess the effect of erlotinib on survival.

DESIGN, SETTING, AND PARTICIPANTS:
In LAP07, an international, open-label, phase 3 randomized trial, 449 patients were enrolled between 2008 and 2011. Follow-up ended in February 2013.

INTERVENTIONS:
In the first randomization, 223 patients received 1000 mg/m2 weekly of gemcitabine alone and 219 patients received 1000 mg/m2 of gemcitabine plus 100 mg/d of erlotinib. In the second randomization involving patients with progression-free disease after 4 months, 136
patients received 2 months of the same chemotherapy and 133 underwent chemoradiotherapy (54 Gy plus capecitabine).

**MAIN OUTCOMES AND MEASURES:**

The primary outcome was overall survival from the date of the first randomization. Secondary outcomes were the effect of erlotinib and quality assurance of radiotherapy on overall survival, progression-free survival of gemcitabine-erlotinib and erlotinib maintenance with gemcitabine alone at the second randomization, and toxic effects.

**RESULTS:**

A total of 442 of the 449 patients (232 men; median age, 63.3 years) enrolled underwent the first randomization. Of these, 269 underwent the second randomization. Interim analysis was performed when 221 patients died (109 in the chemoradiotherapy group and 112 in the chemotherapy group), reaching the early stopping boundaries for futility. With a median follow-up of 36.7 months, the median overall survival from the date of the first randomization was not significantly different between chemotherapy at 16.5 months (95% CI, 14.5-18.5 months) and chemoradiotherapy at 15.2 months (95% CI, 13.9-17.3 months; hazard ratio [HR], 1.03; 95% CI, 0.79-1.34; P = .83). Median overall survival from the date of the first randomization for the 223 patients receiving gemcitabine was 13.6 months (95% CI, 12.3-15.3 months) and was 11.9 months (95% CI, 10.4-13.5 months) for the 219 patients receiving gemcitabine plus erlotinib (HR, 1.19; 95% CI, 0.97-1.45; P = .09; 188 deaths vs 191 deaths). Chemoradiotherapy was associated with decreased local progression (32% vs 46%, P = .03) and no increase in grade 3 to 4 toxicity, except for nausea.

**CONCLUSIONS AND RELEVANCE:**

In this open-label, randomized trial involving patients with locally advanced pancreatic cancer with disease controlled after 4 months of induction chemotherapy, there was no significant difference in overall survival with chemoradiotherapy compared with chemotherapy alone and there was no significant difference in overall survival with gemcitabine compared with gemcitabine plus erlotinib used as maintenance therapy.

**TRIAL REGISTRATION:**

clinicaltrials.gov Identifier: NCT00634725.

**Comment in**

- Optimizing Treatment for Locally Advanced Pancreas Cancer: Progress but No Precision. [JAMA. 2016]
- Radiation Therapy Deviations in Trial of Locally Advanced Pancreatic Cancer [corrected]. [JAMA. 2016]

PMID: 27139057
Chemoradiation unnecessary for locally advanced pancreas cancer

An international phase 3 trial of patients with locally advanced, chemo-contained pancreatic cancer has found no significant difference in overall survival with chemoradiotherapy—a controversial treatment for this application—compared with chemotherapy alone.

The same study found no significant difference in overall survival with the drug gemcitabine compared with gemcitabine plus erlotinib (trade name Tarceva) used as maintenance therapy.

*JAMA* published the findings online May 3.

Pascal Hammel, MD, PhD, of Beaujon Hospital in France and colleagues drew from the LAP07 study, an unblinded randomized trial conducted by the French-led European Cooperative group GERCOR.

Homing in on patients with locally advanced pancreatic cancer controlled after four months of gemcitabine-based induction chemotherapy, the researchers analyzed two randomizations.

One compared 223 patients who received 1,000 mg/m² weekly of gemcitabine alone with 219 patients who received 1000 mg/m² of gemcitabine plus 100 mg/d of erlotinib.

The other compared 136 patients who received randomized chemotherapy with 133 patients who underwent chemoradiotherapy (54 Gy plus capecitabine).

The team’s key findings:

- With a median follow-up of 36.7 months, the median overall survival from the date of the first randomization was not significantly different between chemotherapy at 16.5 months and chemoradiotherapy at 15.2 months (hazard ratio, 1.03).
- Median overall survival from the date of the randomization for the 223 patients receiving gemcitabine was 13.6 months and 11.9 months for the 219 patients receiving gemcitabine plus erlotinib (hazard ratio, 1.19; 188 deaths vs. 191 deaths).

Meanwhile, chemoradiotherapy was associated with marginally superior local control (32 percent vs. 46 percent) and no increase in grade 3 to 4 toxicity, except for nausea.

The lack of superiority of chemoradiotherapy “cannot be explained by insufficient power of the study,” the authors write in their discussion. “The trial was stopped after the independent...
data monitoring committee concluded that the planned intermediate analysis could be the final one to answer the primary objective of the study. Quality of radiation therapy could be questioned because deviations from the protocol can impact negatively on the outcome of patients receiving chemoradiotherapy.

“Although LAP07 [previously] confirmed the safety of radiation therapy with concurrent capecitabine,” they add, “a further intensification of the chemoradiotherapy regimen seems to be needed.”

In accompanying commentary, Deborah Schrag, MD, MPH, of the Dana Farber Cancer Institute in Boston predicts that proponents of chemoradiation will find reasons to perpetuate its use despite the “clear negative result” previously shown from the LAP07 trial.

Such proponents “will note that deviations from optimal radiation technique could have compromised efficacy,” she writes. “However, most protocol violations were minor and adherence appears to have been more carefully monitored than in prior trials.”

Schrag further states, “advocates of chemoradiation will note that, even though the [Hammel] study does not demonstrate superiority for chemoradiation, it also does not demonstrate superiority for chemotherapy, with near identical outcomes between treatments.”

“Ideally, future pancreatic cancer trials will identify molecular markers that better predict responsiveness to specific treatments including radiation and will allow for more focused approaches to treatment selection,” Schrag concludes. “In the meantime, chemoradiation need not constitute an essential component of the therapeutic backbone.”

No Survival Benefit Reported With Chemoradiotherapy vs Continued Chemotherapy in Controlled Locally Advanced Pancreatic Cancer


In the phase III GERCOR LAP07 trial reported by Pascal Hammel, MD, of Beaujon Hospital, Clichy, France, and colleagues in JAMA, there was no survival benefit of chemoradiotherapy vs continued chemotherapy in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib (Tarceva).¹

In this open-label trial, 442 patients from 80 sites in France, Australia, New Zealand, Belgium, and Sweden were randomized between February 2008 and December 2011 to four monthly
cycles of induction with gemcitabine at 1,000 mg/m² weekly (n = 223) or gemcitabine plus erlotinib at 100 mg/d (n = 219). Patients without disease progression after 4 months underwent a second randomization to continue chemotherapy or to receive chemoradiotherapy consisting of radiotherapy at 54 Gy plus capecitabine for 2 months. During maintenance, the erlotinib dose was increased to 150 mg/d.

For the gemcitabine and gemcitabine/erlotinib groups in the first randomization, median age was 64 and 63 years, 52% and 51% were men, and nodal status was N0 in 60% and 57%, respectively. A total of 269 patients without disease progression at 4 months were randomized to continue chemotherapy (n = 136) or to undergo chemoradiotherapy (n = 133). Among these patients, median age was 63 and 62 years, 56% and 44% were men, and 58% and 57% had N0 nodal status.

**Survival Outcomes**

Study accrual was terminated early after interim analysis by the data and safety monitoring committee indicated that prespecified futility criteria were met. Median follow-up was 36.7 months. Median overall survival from first randomization was 16.5 months (95% confidence interval [CI] = 14.5–18.5 months) in the chemotherapy group vs 15.2 months (95% CI = 13.9–17.3 months) in the chemoradiotherapy group (hazard ratio [HR] = 1.03, P = .83). Median progression-free survival was 8.4 vs 9.9 months (HR = 0.78, P = .06). Locoregional progression was observed in 46% vs 32%, and metastatic progression was observed in 44% vs 60% of patients.

Median overall survival from first randomization was 13.6 months (95% CI = 12.3–15.3 months) among all 223 patients randomized to receive gemcitabine vs 11.9 months (95% CI = 10.4–13.5 months) among all 219 receiving gemcitabine/erlotinib (HR = 1.19, P = .09). There was also no significant difference in median progression-free survival (7.8 vs 6.5 months, HR = 1.12, P = .26).

Overall, chemotherapy, radiotherapy, or both were reintroduced in 190 patients (43%) after protocol completion. Median time to subsequent treatment was 6.1 months in the chemoradiotherapy group vs 3.7 months in the chemotherapy group (P = .02). Second-line chemotherapy consisted mostly of fluorouracil/platinum-based treatment and was balanced across the two groups.

**Toxicity**

During induction chemotherapy, the gemcitabine/erlotinib group had more frequent grade 3 or 4 anemia (P = .05), febrile neutropenia (P = .03), diarrhea (P = .006), and acneiform rash (P = .007). Among grade 3 or 4 adverse events, only nausea (6% vs 0%, P = .008) was more common with chemoradiotherapy vs chemotherapy.

The investigators concluded: “In this open-label, randomized trial involving patients with locally advanced pancreatic cancer with disease controlled after 4 months of induction chemotherapy, there was no significant difference in overall survival with chemoradiotherapy compared with chemotherapy alone and there was no significant difference in overall survival with gemcitabine compared with gemcitabine plus erlotinib used as maintenance therapy.”
Chemoradiotherapy Does Not Improve Survival for Patients with Locally Advanced Pancreatic Cancer Compared With Chemotherapy

EMBARGOED FOR RELEASE: 11 A.M. (ET) TUESDAY, MAY 3, 2016

Media Advisory: To contact Pascal Hammel, M.D., email pascal.hammel@aphp.fr.

To place an electronic embedded link to this study in your story This link will be live at the embargo time: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2016.4324

In a study appearing in the May 3 issue of JAMA, Pascal Hammel, M.D., of Beaujon Hospital, Clichy, France and colleagues assessed whether chemoradiotherapy improves overall survival of patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine-based induction chemotherapy, and assessed the effect of erlotinib on survival. Gemcitabine and erlotinib are drugs used to treat cancer.

In locally advanced pancreatic cancer, the role of chemoradiotherapy is controversial and the efficacy of erlotinib is unknown. For this study, the researchers first randomly assigned 449 patients to receive gemcitabine alone (n = 223) and 219 patients received gemcitabine plus erlotinib. In the second randomization involving patients with progression-free disease after 4 months, 136 patients received 2 months of the same chemotherapy and 133 underwent chemoradiotherapy (54 Gy [a measure of radiation dose] plus the chemotherapy drug capecitabine).

A total of 442 of the 449 patients enrolled underwent the first randomization. Of these, 269 underwent the second randomization. With a median follow-up of 36.7 months, the researchers found no survival benefit of chemoradiotherapy compared with chemotherapy, with median overall survival from the date of the first randomization of 15.2 months and 16.5
months, respectively. Also, there was no significant difference in overall survival with gemcitabine (13.6 months) compared with gemcitabine plus erlotinib (11.9 months).

(doi:10.1001/jama.2016.4324; this study is available pre-embargo at the For The Media website.)

Editor’s Note: This trial was supported by Roche and the French National Institute of Cancer. Please see the article for additional information, including other authors, author contributions and affiliations, financial disclosures, etc.

LAP07 study results published in JAMA

May 9, 2016 http://agitg.org.au/ lap07-study-results-published-in-jama/

Compared with chemotherapy alone, chemoradiotherapy does not improve survival for patients with locally advanced pancreatic cancer, according to the LAP07 study published in the May 3 issue of the Journal of American Medical Association (JAMA).

“I am pleased that this prestigious journal has recognised the LAP07 study results,” commented Professor David Goldstein, Prince of Wales Hospital, Co-Chair AGITG LAP07 study. “Pancreatic cancer continues to have a low survival rate at only 7% over 5 years, publishing this study with an accompanying editorial will hopefully renew focus on this disease.”

The LAP07 clinical trial was closed to new recruitment in Australia and New Zealand in 2012 and recruited 32 patients in our region. Two ongoing AGITG Sub studies include:

Radiotherapy Quality Assurance – ensuring uniform delivery of trial standard radiotherapy to patients at all sites;

Surgical – examining surgical interventions for both curative purposes and management of symptoms; and

Conjoint Clinical Professor David Goldstein co-chaired the LAP07 study with Dr Jenny Shannon, Nepean Cancer Care Centre. The analysis led by, Pascal Hammel, MD, Beaujon Hospital, Clichy, France, from the GERCOR French trails group, in close collaboration with the AGITG and other trials groups, assessed whether chemoradiotherapy improves overall survival of patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine-based induction chemotherapy, and assessed the effect of erlotinib on survival.

The role of chemoradiotherapy is controversial in locally advanced pancreatic cancer and the efficacy of erlotinib is unknown.

Worldwide, for the current study, the researchers randomised 449 patients to receive gemcitabine alone (n = 223) or gemcitabine plus erlotinib (n = 219). In the second
randomisation involving patients with progression-free disease after 4 months, 136 patients received 2 months of the same chemotherapy and 133 underwent chemoradiotherapy (54 Gy plus capecitabine).

A total of 442 of the 449 patients enrolled underwent the first randomisation. Of these, 269 underwent the second randomisation.

With a median follow-up of 36.7 months, the researchers found no survival benefit of chemoradiotherapy compared with chemotherapy, with median overall survival from the date of the first randomisation of 15.2 months and 16.5 months, respectively. This is the largest such study ever done and will influence both current practice and future trial design as stated in the accompanying editorial.

There was no significant difference in overall survival with gemcitabine (13.6 months) compared with gemcitabine plus erlotinib (11.9 months). We congratulate all of the sites that contributed to this important study where once again Australia has made a significant contribution and all of the patients and their families for willingly contributing to its successful completion.

Click here to read the full article in JAMA

Chemoradiotherapy, erlotinib gave no survival boost to advanced pancreatic cancer patients

Author(s): Jessica Craig

Key clinical point: Compared with chemotherapy, chemoradiotherapy did not improve survival outcomes in patients with advanced pancreatic cancer. Supplementing gemcitabine with erlotinib also did not improve survival outcomes.

Major finding: There was no significant difference in overall survival between patients receiving gemcitabine or gemcitabine plus erlotinib (HR, 1.19; 95% CI, 0.97-1.45; P = .09) nor was there a significant difference in progression-free survival (HR, 1.12; 95% CI, 0.92-1.36; P = .26). There was also no significant difference in overall survival between patients receiving chemotherapy or chemoradiotherapy (HR, 1.03; 95% CI, 0.79-1.34; P = .83), and there was no significant difference in progression-free survival (HR, 0.78; 95% CI, 0.61-1.01; P = .06).

Data source: An international, multicenter, open-label, unblinded, randomized phase III clinical trial involving 449 patients with advanced pancreatic cancer.
Disclosures: This study was supported by Roche and the French National Institute of Cancer. Dr. Hammel reported receiving consulting fees from Celgene. Dr. Hammel’s associates reported receiving personal fees, nonfinancial support, grant support, personal fees, or honoraria from Amgen, Merck Serono, Lilly, Roche, Celgene, Sanofi, Novartis, Integragen, Eisai, Invectys, and Nestle.

Chemoradiotherapy does not improve overall or progression-free survival in patients with advanced pancreatic cancer, compared with chemotherapy alone. Gemcitabine plus erlotinib also does not improve overall or progression-free survival when compared with patients who received only gemcitabine.

“This open-label, randomized clinical trial showed no survival benefit of chemoradiotherapy compared with chemotherapy in patients with locally advanced pancreatic cancer... the addition of erlotinib to gemcitabine, despite excellent adherence (92%), failed to improve survival and yet was associated with increased grade 3 hematologic, digestive, and skin toxicities,” wrote Dr. Pascal Hammel of Beaujon Hospital, France, and associates (JAMA. 2016 May 3. doi: 10.1001/jama.2016.4324). “This suggests that in patients with locally advanced pancreatic cancer, more efficient systemic treatments are needed to treat any early micrometastatic spread and to downstage tumors,” they said.

Investigators enrolled 449 patients with advanced pancreatic cancer in the international, LAP07 phase III trial; 442 met the demographic criteria and were randomly divided into two groups, 223 of which received gemcitabine and 219 of which received gemcitabine plus erlotinib, during the first of two randomization steps. Patients in both groups received their designated drug regime intravenously for three weeks followed by a one week resting period for a total of four cycles.

During step one, 135 of the 223 patients who received gemcitabine, and 134 of the 219 patients who received gemcitabine plus erlotinib, survived the 16-week period progression free and were eligible for step two randomization; 136 patients were then randomly selected to receive chemotherapy and 133 patients were randomly selected to receive chemoradiotherapy.

After the two randomization steps, 68 patients received gemcitabine with chemotherapy, 68 patients received gemcitabine plus erlotinib with chemotherapy, 67 patients received gemcitabine with chemoradiotherapy, and 66 patients received gemcitabine plus erlotinib with chemoradiotherapy.

By the end of the clinical trial, 379 patients had died and 385 had experienced tumor progression. There was no significant difference in overall survival between patients receiving gemcitabine or gemcitabine plus erlotinib (hazard ratio, 1.19; 95% confidence interval, 0.97-1.45; P = .09), and there was no significant difference in progression-free survival (HR, 1.12;
95% CI, 0.92-1.36; \( P = .26 \)). Patients who received erlotinib were at a significantly elevated risk for experiencing anemia, neutropenia, diarrhea, and acneiform rash when compared with patients who did not receive erlotinib.

There was no significant difference in overall survival between patients receiving chemotherapy or chemoradiotherapy (HR, 1.03; 95% CI, 0.79-1.34; \( P = .83 \)), and there was no significant difference in progression-free survival (HR, .78; 95% CI, 0.61-1.01; \( P = .06 \)).

There was also no significant difference in survival when first-step randomization status was combined with second-randomization status (\( P = .24 \)).

This study was supported by Roche and the French National Institute of Cancer. Dr. Hammel reported receiving consulting fees from Celgene. Seven of the other thirteen investigators reported receiving personal fees, nonfinancial support, grant support, personal fees, or honoraria from Amgen, Merck Serono, Eli Lilly, Roche, Celgene, Sanofi, Novartis, Integragen, Eisai, Invectys, or Nestle.

jcraig@frontlinemedcom.com

FROM JAMA

Progress but not precision

Clinical trials that find no difference between groups never garner as much excitement as trials with positive findings. However, clear negative results chart the path forward by informing the design of next-generation studies and hastening retirement of ineffective therapies.

The results of the LAP07 trial are persuasive that contemporary chemoradiation does not add a survival advantage to chemotherapy alone. However, the heterogeneity in response to both chemotherapy and radiation is unclear. What if any features distinguished tumors resistant to treatment and, conversely, those that responded? What features distinguish tumors with propensity to spread locally versus diffusely? Tumors in the former category stand to benefit from regionally focused treatment such as chemoradiation.

The LAP07 trial is progress, but it does not achieve the goal of precision medicine.

The LAP07 trial contributes important new information to help guide treatment decisions for patients with locally advanced pancreas cancer. Ideally, future pancreatic cancer trials will identify molecular markers that better predict responsiveness to specific treatments including radiation and will allow for more focused approaches to treatment selection. In the meantime, chemoradiation need not constitute an essential component of the therapeutic backbone.

Dr. Deborah Schrag is at the Dana Farber Cancer Institute in Boston. Dr. Schrag made these remarks in an editorial accompanying Dr. Hammel’s report (JAMA. 2016 May 3. doi: 10.1001/jama.2016.4284), and she reported having no conflict of interest disclosures.