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Evidence-Based Series 2-18- EDUCATION AND INFORMATION 2014

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO

The Use of FOLFIRINOX as First-Line Treatment for Metastatic Pancreatic Adenocarcinoma

N. Hammad, R. Cosby, J. Biagi, M. Mackenzie
and the Gastrointestinal Cancer Disease Site Group

Report Date: June 23, 2011

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Section 1: Guideline Recommendations
Section 2: Evidentiary Base

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Evidence-Based Series 2-18: Section 1

The Use of FOLFIRINOX as First-Line Treatment for Metastatic Pancreatic Adenocarcinoma: Guideline Recommendations

N. Hammad, R. Cosby, J. Biagi, M. Mackenzie
and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: June 23, 2011

QUESTION

Does FOLFIRINOX (folinic acid, 5FU, irinotecan and oxaliplatin) improve overall survival, progression free survival (PFS), response rate, and/or quality of life (QOL), with acceptable levels of adverse events, for adult patients with metastatic pancreatic adenocarcinoma (MPA)?

TARGET POPULATION

These recommendations apply to adult patients with MPA who have not received prior systemic treatment for it.

INTENDED USERS

These guidelines are intended for use by clinicians and healthcare providers involved in the management of patients with MPA.

RECOMMENDATION

- The FOLFIRINOX regimen is recommended as first-line treatment for adult patients with MPA who have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 and bilirubin <1.5 upper limit of normal (ULN) (26 mmol/l), to prolong survival and to decrease the likelihood of deterioration in global health status and QOL.

KEY EVIDENCE

- The Prodige 4/ACCORD11 Phase III (1) reports a significant improvement with FOLFIRONOX compared to gemcitabine for median overall survival (11.1 versus [vs.] 6.8 months; hazard

ratio [HR], 0.57; 95% confidence interval [CI], 0.45 to 0.73; p<0.0001), one-year survival (48.4% vs. 20.6%), and PFS (6.4 vs. 3.3 months; HR, 0.47; 95% CI, 0.37 to 0.59; p<0.001).
- Time to QOL deterioration significantly favoured FOLFIRINOX at six months (HR, 0.47; 95% CI, 0.30 to 0.70; p<0.001) (1).
- There is a greater incidence of several grade 3 and 4 toxicities (diarrhea, nausea, vomiting, fatigue, neutropenia, and febrile neutropenia) with FOLFIRINOX compared to gemcitabine. Despite these toxicities, FOLFIRINOX has shown greater clinical benefit than gemcitabine when coupled with adequate patient selection and effective management of toxic side effects.

QUALIFYING STATEMENTS
- The frequency of grade 3 and 4 febrile neutropenia is 5.4% with FOLFIRINOX. Secondary prophylaxis with filgrastim could be considered for high-risk patients such as those with recurrent Grade 3/4 neutropenia despite first-dose reduction or following febrile neutropenia. In the trial, the proportion of patients who received filgrastim was 42.5% in the FOLFIRINOX arm and 5.3% in the gemcitabine arm (p<0.001) (1).
- A modified version of FOLFIRINOX, in which the bolus 5-fluorouracil (5FU) was omitted, was used in the Prodige 4/ACCORD11 trial because of myelosuppression. Post hoc analysis (data unpublished) demonstrated that the response rate was the same in those that received the full dose and those that received the modified version of FOLFIRINOX. This modified version of the FOLFIRINOX regimen will be used on a go-forward basis in upcoming adjuvant trials. Therefore, the use of modified FOLFIRINOX is a reasonable alternative to offer patients.
- Patients who had biliary stents were eligible; thus, FOLFIRINOX may be considered safe in these patients with biliary stents.
- There is currently no evidence for or against the administration of FOLFIRINOX in locally advanced pancreatic cancer or in the neoadjuvant or adjuvant settings in pancreatic cancer.

FUTURE RESEARCH

Future research will be required to assess the use of FOLFIRINOX in the locally advanced and adjuvant settings and in potentially resectable patients. A study looking at the use of FOLFIRINOX as second-line treatment for those who have failed first-line gemcitabine in the metastatic setting would also be useful. A dose-tolerance study would be important in order to safely generalize the FOLFIRINOX regimen to an expanded MPA patient population.

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Evidence-Based Series 2-18: Section 2

The Use of FOLFIRINOX as First-Line Treatment for Metastatic Pancreatic Adenocarcinoma: Evidentiary Base

N. Hammad, R. Cosby, J. Biagi, M. Mackenzie
and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: June 23, 2011

QUESTION

Does FOLFIRINOX (folinic acid, 5FU, irinotecan, and oxaliplatin) improve overall survival, progression free survival (PFS), response rate, and/or quality of life (QOL), with acceptable levels of adverse events, for adult patients with metastatic pancreatic adenocarcinoma (MPA)?

INTRODUCTION

The majority of patients with pancreatic cancer present with advanced disease. This disease is one of the most lethal solid malignancies and is difficult to treat. The estimated number of new incident cases of pancreatic cancer in Canada was approximately 4000 in 2010, whereas the estimated numbers of deaths owing to pancreatic cancer was just under 4000 for the same time period (1). Pancreatic ductal adenocarcinoma make up the majority of cases (>90%) (2). Since the late 1990s, the standard treatment for advanced pancreatic cancer has been chemotherapy with single-agent gemcitabine (3), which was shown to significantly improve median and one-year survival over single-agent 5FU. However, even with this improvement in treatment, the prognosis is grim. Subsequent efforts to find a more efficacious regimen have largely been unsuccessful. In the past several years, the use of oxaliplatin in treating advanced pancreatic has begun to be explored both in first-line and second-line settings (4-7). Recently, in Phase II (8) and Phase III (9) testing, a regimen consisting of folinic acid, 5FU, irinotecan and oxaliplatin (FOLFIRINOX) has demonstrated improved outcomes in advanced pancreatic adenocarcinoma. Given these findings, the

Gastrointestinal Disease Site Group (GI DSG) determined that a guideline exploring the use of this regimen was warranted to inform current clinical practice.

METHODS

The evidence-based series (EBS) guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (10). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on the use of FOLFIRINOX in MPA. The body of evidence in this review is primarily comprised of Phase II and III randomized controlled trial (RCT) data. That evidence forms the basis of the recommendations developed by the FOLFIRINOX Working Group (Appendix 1) of the GI DSG (Appendix 2). The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE (2003 through May week 1 2011), Medline In-Process (May 13, 2011) and EMBASE (2003 through week 19 2011) databases were searched for relevant evidence. The full literature search strategies can be found in Appendix 3. The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) Annual Conference Proceedings from 2003 through 2011 were searched as well.

Study Selection Criteria

Articles were selected for inclusion in the systematic review if they:

- were published abstracts or fully published reports of Phase II or III RCTs comparing FOLFIRINOX to gemcitabine (the current standard of care). Syntheses of RCTs in the form of systematic reviews or meta-analyses were also included.
- included at least one of the outcomes of interest.

Articles were excluded if they:

- were published in a language other than English, owing to the unavailability of translation services,
- were abstract reports of studies that were subsequently fully published,
- were published in the form of a letter, editorial, note, retrospective study, or non-systematic review.

Synthesizing the Evidence

As indicated by the literature search below, owing to the lack of fully published RCTs, data were not pooled using meta-analytic techniques.

RESULTS

Literature Search Results

The MEDLINE search yielded 10 hits, three of which were potentially relevant and ordered for full review; two met the selection criteria. These were a Phase II (8) and a Phase III (9) trial of FOLFIRINOX versus gemcitabine by the same authors. As the Phase III trial included all patients from the Phase II trail, only the Phase III trial will be reported. The EMBASE search yielded 401 hits, of which 12 were potentially relevant, excluding duplicates from the MEDLINE search; none met the selection criteria. The search of ASCO conference

proceedings yielded six abstracts which were potentially relevant, but none were retained. The search of ESMO conference proceedings did not yield any relevant abstracts. A search of the reference lists of included studies yielded no hits. A flow diagram illustrating the literature search results can be found in Appendix 4.

Study/Trial Design and Quality

The one eligible trial was evaluated using various characteristics (see Table 1). Overall, this is a well-powered trial with balanced arms that used an intent-to-treat analysis. Allocation concealment, blinding, and loss to follow up are not reported.

Table 1. Methodological quality characteristics of identified randomized controlled trials s identified for inclusion in this guidance document.

Methodological Quality Characteristic	Conroy 2011 (9)
Generation of Allocation Sequence Reported	Yes
Allocation Concealment	NR
Blinding	NR
Intention-to-Treat Analysis	Yes
Withdrawals Described	No
Industry Funding	Yes
Statistical Power and Target Sample Size	80% power to detect an increase in median overall survival from 7 to 10 months with 360 patients and 250 events. Actual accrual 342 patients.
Loss to Follow Up	NR
Baseline Characteristics Balanced	Fewer measureable lung metastases in the FOLFIRINOX arm
Terminated Early	Stopped for benefit

Abbreviation: NR=not reported

Outcomes

One RCT, the PRODIGE 4/ACCORD 11 trial (9), met the inclusion criteria. That trial is a Phase III RCT of FOLFIRINOX versus single-agent gemcitabine in chemotherapy-naive patients with MPA (Table 2). The trial enrolled 342 patients evenly distributed between the two arms. Accrual was stopped early for benefit on the recommendation of the Independent Data Monitoring Committee (IDMC) after a preplanned interim analysis met the a priori stopping rule. The analysis was an intent-to-treat analysis. Baseline patient and disease characteristics were similar in the two arms.

Table 2. Dose and schedule of treatment in the PRODIGE 4/ACCORD 11 trial.

ARM	DOSE/SCHEDULE
FOLFIRINOX	Oxaliplatin: 85 mg/m^2, IV, d1 Leucovorin: 400 mg/m^2, IV, d1 Irinotecan: 180 mg/m^2, IV, d1 Fluorouracil: 400 mg/m^2, IV bolus, d1 Fluorouracil: 2400 mg/m^2, CIV over 46 hours after bolus dose of fluorouracil Regimen given biweekly
Gemcitabine	Gemcitabine: 1000 mg/m^2, IV weekly x 7, I week rest, then weekly 3q4w
Planned duration of chemotherapy in both arms was 6 months.	

Abbreviations: IV=intravenously; w=week(s).

Survival

Median overall survival was 11.1 versus 6.8 months for the FOLFIRINOX and gemcitabine arms respectively (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.45 to 0.73; p<0.001). One-year survival was 48.4 versus 20.6% in favour of the FOLFIRINOX arm. Median PFS was also significantly greater in the FOLFIRINOX arm (6.4 vs. 3.3 months; HR, 0.47; 95% CI, 0.37 to 0.59; p<0.001). These remarkable survival results are despite almost 50% of the gemcitabine patients went on to receive FOLFOX in the second-line setting.

Response Rate

Complete response (CR) was obtained in 0.6% versus 0.0% of patients in the FOLFIRINOX and gemcitabine arms, respectively. Partial response (PR) was obtained in more patients in the FOLFIRINOX arm (31% vs. 9.4%). Overall, the objective response rate (CR + PR) was 31.6% vs. 9.4%, p<0.001 and the disease control rate (CR + PR + stable disease [SD]) was 70.2% versus 50.9% (p <0.001).

Adverse Events

Several grade 3/4 hematological adverse events were significantly higher in the FOLFIRINOX arm including neutropenia (45.7% vs. 21%, p<0.001), febrile neutropenia (5.4% vs. 1.2%, p=0.03), and thrombocytopenia (9.1% vs. 3.6%, p=0.04). There was no significant difference between the two arms with respect to anemia (7.8% vs. 6%). There was one toxic death in each arm. Filgrastim was used mainly as a secondary prophylaxis in 42.5% of patients in the FOLFIRINOX arm compared with 5.3% in the gemcitabine arm (p<0.001).

Several grade 3/4 non-hematological adverse events were also significantly higher in the FOLFIRINOX arm. These included peripheral neuropathy (9% vs. 0%, p<0.001), and diarrhea (12.7% vs. 1.8%, p<0.001). Grade 3/4 elevated ALT (alanine transaminase) levels were seen significantly more often in the gemcitabine arm (p<0.001).

A small proportion of patients had a biliary stents; 15.8% and 12.9% in the FOLFIRINOX and gemcitabine arms, respectively. Hematological toxicity and the risk of infection were similar in both groups, with or without a biliary stent.

Quality of Life (QOL)

QOL was measured by administering the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire every two weeks. There was no difference between the arms at baseline. During the study, there was also no difference between the study arms on the global QOL score or any of the individual domains, with the exception of diarrhea. There were higher scores of diarrhea in the FOLFIRINOX arm during the first eight cycles. The time to QOL deterioration significantly favoured FOLFIRINOX at six months (HR, 0.47; 95/% CI, 0.30 to 0.70; p < 0.001), as was the case for the scales related to appetite loss, dyspnea, and constipation.

Ongoing Trials

The NCI® database (http://www.cancer.gov/clinicaltrials/search) of ongoing clinical trials was searched on May 16, 2011. Currently, there are no other ongoing trials of FOLFIRINOX in advanced pancreatic adenocarcinoma.

DISCUSSION

Approximately 85% of patients with pancreatic cancer present with advanced disease that precludes curative surgery. Prognosis in these patients is extremely poor, and the impact of standard therapy is minimal. In the years 2009/2010, there were 658 cases of

pancreatic cancer treated with gemcitabine on the Ontario New Drug Funding Plan, with a total number of 5601 treatments. An estimated 80 to 85% of these patients had MPA. In 1997, gemcitabine was established as the standard first-line treatment for advanced pancreatic cancer (3). With the exception of erlotinib, which increased median overall survival by only 10 days, no new therapies have significantly improved the outcome since gemcitabine was established as the standard.

FOLFRINOX is the first regimen to significantly improve PFS, overall survival, and response rate in patients with metastatic pancreatic cancer when compared to gemcitabine. Moreover, the proportion of patients who experienced deterioration in their QOL was significantly lower compared to those who received gemcitabine, with the exception of the effect on diarrhea. It should also be noted that FOLFIRNOX resulted in a greater incidence of several grade 3 and 4 toxicities (diarrhea, nausea, vomiting, fatigue, neutropenia, and febrile neutropenia) than did gemcitabine. Despite these toxicities, FOLFIRINOX has shown greater clinical benefit than gemcitabine when coupled with adequate patient selection and effective management of toxic side effects.

CONCLUSIONS

FOLFIRINOX significantly improves overall survival in patients with MPA and also better preserves the QOL in this challenging disease. It is important to note, firstly, that the patients enrolled in the phase III trial were younger than 76 years and had a good performance status (ECOG 0 or 1), no cardiac ischemia, and normal or nearly normal bilirubin levels. Secondly, FOLFIRINOX was shown to have higher rates of toxicity than gemcitabine, but these adverse events can be medically managed effectively. Patient selection and monitoring on therapy are important medical considerations in the use of this regimen. Clinicians must be attentive to whether this therapy can be generalized to the population level outside of the specific population described in the trial. In recommending FOLFIRINOX to patients, clinicians must fully discuss the risks and benefits. The GI DSG strongly endorses a recommendation that the FOLFIRINOX regimen be made available to patients with MPA.

CONFLICT OF INTEREST

GI DSG members involved in the development of this guidance document were polled for potential conflicts of interest. Three authors (NH, RC, JB) declared they had no conflicts of interest. One author (MM) reported being a principal investigator for CRC3, a trial for stage II colon cancer that involved oxaliplatin.

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For a complete list of the GI DSG members, please visit the CCO Web site at http://www.cancercare.on.ca/

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Appendix 1. Members of the FOLFIRINOX Working Group.

Chair:	Nazik Hammad	Medical Oncologist

Panel Members:

Jim Biagi	Medical Oncologist
Roxanne Cosby	Methodologist
Mary Mackenzie	Medical Oncologist

Appendix 2. Members of the Gastrointestinal Disease Site Group.

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Jim Biagi	Medical Oncologist
Rebecca Wong	Radiation Oncologist

Members:

Tim Asmis	Medical Oncologist
Scott Berry	Medical Oncologist
Christine Brezden-Masley	Medical Oncologist
Kelvin Chan	Medical Oncologist
Charles Cho	Radiation Oncologist
Murray Citron	Patient Representative
Natalie Coburn	Surgical Oncologist
Roxanne Cosby	Research Coordinator
Craig Earle	Medical Oncologist
Barbara Fisher	Radiation Oncologist
Nazik Hammad	Medical Oncologist
Derek Jonker	Medical Oncologist
Juhu Kamra	Radiation Oncologist
Sindu Kanjeekal	Medical Oncologist
Gregory Knight	Medical Oncologist
Monika Krzyzanowska	Medical Oncologist
Calvin Law	Surgical Oncologist
Mary Mackenzie	Medical Oncologist
Richard Malthaner	Surgical Oncologist
Jason Pantarotto	Radiation Oncologist
Mark Rother	Medical Oncologist
Marko Simunovic	Surgical Oncologist
Simron Singh	Medical Oncologist
Andy Smith	Surgical Oncologist
Stephen Welch	Medical Oncologist
Raimond Wong	Radiation Oncologist
Youssef Youssef	Radiation Oncologist
Kevin Zbuk	Medical Oncologist

Appendix 3. Literature search strategy.

MEDLINE

1 exp Carcinoma/
2 exp Neoplasms/
3 1 or 2
4 exp Pancreas/
5 3 and 4
6 exp Pancreatic Neoplasms/
7 (Pancrea: adj3 (cancer or carcinoma or tum: or neoplasm:)).mp
8 or/5-7
9 folfirinox.mp
10 5FU.mp or exp Fluorouracil/
11 folinic acid.mp or exp Leucovorin/
12 camptosar.mp
13 irinotecan.mp
14 12 or 13
15 oxaliplatin.mp
16 eloxatin.mp
17 15 or 16
18 10 and 11 and 14 and 17
19 9 or 18
20 8 and 19
21 Limit 20 to yr="2003–2011"

EMBASE

1 exp CARCINOMA/
2 exp NEOPLASM/
3 1 or 2
4 exp PANCREAS/
5 3 and 4
6 exp pancreas tumor/
7 exp pancreas carcinoma/
8 (pancreas: adj3 (cancer or carcinoma or tum: or neoplasm:)).mp
9 or/5-8
10 folfirinox.mp
11 exp FLUOROURACIL
12 5FU.mp
13 11 or 12
14 leucovorin.mp or exp folinic acid/
15 camptosar.mp or exp irinotecan/
16 eloxatin.mp or exp oxaliplatin/
17 13 and 14 and 15 and 16
18 10 or 17
19 9 and 18
20 Limit 19 to yr="2003-2011"

Appendix 4. Literature search results flow diagram.