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Original Article

Uptake and Effectiveness of FOLFIRINOX for Advanced Pancreatic Cancer: a Population-based Study

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Abstract

Aims: Although FOLFIRINOX is a standard treatment option for advanced pancreas cancer, there are few data describing utilisation and effectiveness in routine clinical practice. Here we report practice patterns and outcomes in the general population of Ontario, Canada.

Materials and methods: Using the Ontario Cancer Registry and New Drug Funding Program, we identified all patients with pancreas cancer treated with palliative intent gemcitabine or FOLFIRINOX in Ontario during 2006–2014. FOLFIRINOX became available in Ontario's single-payer health system in November 2011. Gemcitabine cases were classified as pre-FOLFIRINOX era (2006–2010) or post-FOLFIRINOX era (2011–2014). Cases treated with perioperative chemotherapy were excluded. Comparisons of proportions between study groups were made using the chi-square test. Overall survival was measured from the date of chemotherapy initiation.

Results: During 2006–2014, 3826 patients in Ontario were treated with gemcitabine ($n = 3042$) or FOLFIRINOX ($n = 784$) chemotherapy for advanced pancreas cancer. Uptake of FOLFIRINOX increased from 41% (206/505) of treated cases in 2012 to 56% (274/486) of treated cases in 2014. The median overall survival of patients treated with gemcitabine was 5.0 months in 2006–2010 and 4.8 months in 2011–2014. The median overall survival of FOLFIRINOX patients treated in 2011–2014 was 8.2 months.

Conclusion: The use of FOLFIRINOX in the general population has increased since 2011. Survival outcomes show a substantial efficacy–effectiveness gap between the pivotal Prodige 4/ACCORD 11 clinical trial and routine practice.

Key words: Chemotherapy; FOLFORINOX; metastatic; pancreatic cancer

Introduction

Pancreatic cancer is associated with a very poor prognosis, highlighted by the close parallel between disease incidence and mortality [1]. Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the USA and Canada [1,2]. It is estimated that in 2015 in the USA, 49 000 cases of pancreatic cancer were diagnosed and that there were 41 000 deaths [3]. Prognosis is very poor, with 5 year survival rates of about 9% [2]. Surgery remains the only curative option, but only up to 20% of patients with localised disease will be eligible for resection. Unfortunately, due to high recurrence rates, 5 year survival in these patients is at best 25% [2]. In patients with unresectable or metastatic disease, standard treatment involves palliative chemotherapy and supportive care.

Until recently, palliative chemotherapy for pancreatic adenocarcinoma has been unable to extend survival beyond 6 months. Fluorouracil-based chemotherapy was the mainstay of treatment for pancreatic adenocarcinoma since the 1950s. Gemcitabine was the first therapeutic agent that was shown to be superior to 5-fluorouracil in terms of overall survival and clinical benefit. However, the benefit was modest, with a median overall survival improvement of approximately 1 month and a response rate of 5%. Clinical

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benefit, defined by a pain score, Karnofsky performance score and body weight, was superior with gemcitabine (23.8% versus 4.2%) [4]. Since then two chemotherapy regimens have shown improved overall survival compared with gemcitabine. In 2011, Conroy *et al.* [5] showed that FOLFIRINOX improved survival by about 5 months compared with gemcitabine alone (11.1 versus 6.8 months, hazard ratio 0.57, 95% confidence interval 0.45–0.73). In 2013, nab-paclitaxel in combination with gemcitabine was shown to improve overall survival by about 2 months compared with gemcitabine alone (8.5 versus 6.7 months, hazard ratio 0.72, 95% confidence interval 0.62–0.83) [6]. These two regimens have since been adopted as first-line therapy for patients with advanced disease and a good performance status.

It is well known that efficacy may not translate into effectiveness in the general population [7]. This may relate to the fact that patients, practitioners and health delivery systems in routine practice are very different from clinical trials [8]. There is very little published literature on the use of FOLFIRINOX in routine clinical practice. Two small multi-institutional Canadian studies (presented in abstract form) reported a median survival of 7.8 and 7.5 months among cohorts of 150 and 132 treated patients, respectively [9,10]. Several single institution studies have reported a median survival of between 9 and 14 months [11–14]. Population-based outcome studies may be useful in evaluating the external validity of the results of clinical trials [15]. We undertook a population-based study to describe the adoption and outcomes of FOLFIRINOX for advanced pancreas cancer in the general population of Ontario. The study objectives were: (i) to describe uptake of FOLFIRINOX and treatment delivery in routine practice; and (ii) to evaluate whether the outcomes achieved with FOLFIRINOX showed in the pivotal randomised controlled trial (RCT) are translated into effectiveness in the general population.

Materials and methods

Study design and population

This was a population-based, retrospective cohort study to determine the uptake and effectiveness of FOLFIRINOX chemotherapy for patients with advanced pancreatic adenocarcinoma in the Canadian province of Ontario. Ontario has a population of about 13.5 million people and a single-payer universal health insurance programme. The study population included all patients with pancreatic adenocarcinoma who received palliative chemotherapy with either gemcitabine or FOLFIRINOX from 2006 to 2014. FOLFIRINOX became available in Ontario's single-payer health system in November 2011. The study cohort was identified using Ontario Cancer Registry (OCR) and linked electronic treatment records, including the New Drug Funding Program (NDFP). The NDFP provides provincial reimbursement for gemcitabine, oxaliplatin and irinotecan used in the treatment of pancreas cancer. Gemcitabine cases were classified as in the pre-FOLFIRINOX era (2006–2010) or the post-FOLFIRINOX era (2011–2014). Patients who received chemotherapy before surgical resection of pancreatic cancer and those who received chemotherapy within 4 months after surgical resection were excluded in order to include only cases with unresectable or metastatic disease. The study was approved by the Research Ethics Board of Queen's University.

Data sources and linkage

The OCR is a passive, population-based cancer registry that captures diagnostic and demographic information on at least 98% of all incident cases of cancer in the province of Ontario [16]. The OCR also provides information about vital status and cause of death. A variety of electronic administrative health databases are linked to the OCR. Records from the Canadian Institute for Health Information were used to provide information about hospitalisations and surgical interventions; these records are known to be complete [17]. Data from NDFP provided information regarding the use of FOLFIRINOX and gemcitabine chemotherapy.

Measures and outcomes

Geographic region of residence was assigned based on postal code at the time of diagnosis. Patients were assigned into one of Ontario's 14 Local Health Integration Networks based on predetermined geographic boundaries as determined by the Ontario Ministry of Health and Long-Term Care. Chemotherapy delivery was described using data from the NDFP. This data source captures date, drug and dose delivered for all gemcitabine, oxaliplatin and irinotecan in the Canadian province of Ontario. Treatment records were used to identify the regimen delivered, number of cycles and dose reduction. To avoid underestimation, only those patients with a minimum of 4 months of follow-up were included in the calculation of the median number of cycles. Up-front dose reductions were unable to be calculated as ideal body surface area was not available. Therefore, dose reduction was defined as any subsequent dose beyond the first cycle of chemotherapy that was lower than the initial dose. The primary outcome in the study was median survival, which was measured from the date of treatment initiation to the date of death. Secondary outcomes of interest included admissions to hospital within 30 days of chemotherapy and death within 30 days of chemotherapy.

Statistical analysis

Comparisons of proportions between study groups were made using the chi-square test. Survival was determined using the Kaplan–Meier method. Results were considered statistically significant at P-value < 0.05. All analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC) and Microsoft Excel 2010.

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