Metastatic Pancreatic Adenocarcinoma Treatment Patterns, Health Care Resource Use, and Outcomes in France and the United Kingdom Between 2009 and 2012: A Retrospective Study

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ABSTRACT

Purpose: In Europe, pancreatic cancer (PC) accounts for approximately 2.6% of all new cancer cases and is the fourth leading cause of cancer-related death. Despite substantial morbidity and mortality, limited data are available describing real-world treatment patterns and health care resource use in any European country. We evaluated PC-related treatment patterns and associated health care resource use among patients with metastatic PC in the United Kingdom and France.

Methods: One hundred three oncology specialists (53 in France and 50 in the United Kingdom) abstracted data from medical records of 400 patients whom they treated for metastatic PC. Eligible patients had a diagnosis of metastatic PC at age 18 years or older between January 1, 2009, and December 31, 2012; had ≥3 months of follow-up time beginning at metastatic diagnosis; and received at least 1 cancer-directed therapy for metastatic disease. Information on patient demographics, Eastern Cooperative Oncology Group performance status, location of primary tumor, presence of comorbidities, adverse events, and complications were collected. Data on cancer-directed treatments and supportive care measures were evaluated. All analyses were descriptive.

Findings: Approximately two thirds of patients were men, and median age at metastatic disease diagnosis was 62.2 years. Nearly all patients (97.3%) received chemotherapy to treat metastatic disease, 9.3% received radiation therapy, and 7.8% received a targeted therapy. Overall, the most frequently administered first-line regimens for metastatic disease were gemcitabine alone (46.0%), a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX; 20.1%); gemcitabine/capecitabine (10.8%); and gemcitabine/oxaliplatin (9.5%). Approximately 40% of patients in France and 15% of patients in the United Kingdom received second-line systemic therapy, whereas 20% of patients in France and 3.4% of patients in the United Kingdom received third-line systemic therapy for metastatic disease. Overall, 52.5% of patients experienced at least one complication of PC. More than two thirds of patients had ≥1 office visit unrelated to chemotherapy administration, 54.0% had ≥1 inpatient hospitalization, 36.8% had ≥1 emergency department visit, and 25.3% had ≥1 pain management clinic visit. A total of 26.5% of patients in France and 42.5% in the United Kingdom entered hospice or long-term care.

Implications: This study provides new, detailed information for patients with metastatic PC in real-world settings in 2 European countries. A small proportion of patients received >1 line of systemic therapy for metastatic disease, which is likely due to

Accepted for publication March 12, 2015.

http://dx.doi.org/10.1016/j.clinthera.2015.03.016
0149-2918/$ - see front matter

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the aggressiveness of this disease and the lack of effective therapeutic options. (*Clin Ther*. 2015;37:1301–1316) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: chemotherapy, health resources, outcomes assessment, pancreatic adenocarcinoma, retrospective studies.

INTRODUCTION

Pancreatic cancer accounts for approximately 2.6% of all new cancer cases in both sexes in Europe.[1] In the United Kingdom, the total incidence of pancreatic cancer remained stable overall between 1975 and 1977 and 2008 and 2010, given a decrease in incidence in men and a similar increase in women during these periods.[2] In contrast, an increase in the incidence in both sexes was reported in Burgundy, France, between 1981 and 2005 for men (from 5.7 in 1981–1985 to 7.9 per 100,000 in 2001–2005) and women (from 2.6 in 1981–1985 to 4.6 per 100,000 in 2001–2005).[3] To our knowledge, the apparent disparity in changes in sex-specific incidence rates in the United Kingdom and France over time has not been documented in the literature. Although there is no guarantee that cancer incidence rates will change in parallel in all strata (eg, by age, sex, and region or country), underlying regional differences in risk factors demonstrated to affect incidence rates (eg, smoking and obesity) may play a part in these seemingly contradictory findings.[2]

In Europe, where pancreatic cancer is the fourth leading cause of cancer-related death and has an increasing mortality rate in both sexes, it is predicted that 82,300 deaths will occur in 2014 due to this disease.[4] Part of the reason for a high case-fatality rate in pancreatic cancer is that many patients do not experience symptoms until the disease is in an advanced stage, leading to delays in diagnosis and subsequent treatment initiation. In addition, despite substantial research efforts, until relatively recently, there has been little therapeutic advancement in the treatment of this disease in the adjuvant setting[5,6] or in advanced disease.[1,7,8]

Leucovorin, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX) and the gemcitabine plus nab-paclitaxel combination represent the most recent advancements for the first-line treatment of metastatic disease. Conroy et al,[8] of the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup, demonstrated that patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 receiving FOLFIRINOX achieved a median overall survival of 11.1 months compared with 6.8 months in patients who received gemcitabine (hazard ratio = 0.57; 95% CI, 0.45–0.73; $P < 0.001$). Patients who received FOLFIRINOX also experienced significantly increased toxicity relative to gemcitabine alone. Comparable results have been achieved in routine clinical practice in France, where the safety and efficacy of this regimen were evaluated.[9] In addition, real-world data from a large, integrated oncology network in the United States demonstrated an increase in the use of FOLFIRINOX[10] after the availability of data from the randomized study described by Conroy et al.[8] The overall survival data from a real-world setting presented by Cartwright et al[10] were significantly better for FOLFIRINOX than for gemcitabine alone ($P < 0.001$), although the magnitude of effect was not as large as that reported in the results of the clinical trial described by Conroy et al.[8] To achieve a more favorable benefit–risk profile for patients, efforts are ongoing to evaluate the safety and efficacy of modified FOLFIRINOX regimens. Nab-paclitaxel, in combination with gemcitabine, has been approved by the US Food and Drug Administration[11] and the European Medicines Agency (EMA)[12] for patients with a Karnofsky PS of 70 or higher based on results reported by Von Hoff et al.[7] Clinical trial results found that the median overall survival for the nab-paclitaxel combination was significantly better than for gemcitabine alone (median = 8.5 months [vs] 6.7 months; hazard ratio = 0.72; 95% CI, 0.62–0.83; $P < 0.001$), and toxicity was greater among patients treated with the combination.[7]

Although pancreatic cancer is a major cause of morbidity and mortality in economically developed nations, only limited data have been published describing real-world treatment patterns and health care resource use associated with the treatment of pancreatic cancer in any European country. As part of our objectives, we set out to characterize whether FOLFIRINOX use is increasing in select countries in Europe. Furthermore, to our knowledge, there are limited data on the frequency of complications in this population and the extent to which these aspects of the disease are associated with health care resource use. Therefore, we undertook a study to evaluate

outcomes, including health care resource use, among patients with metastatic pancreatic cancer treated in France and the United Kingdom.

MATERIALS AND METHODS

This was a retrospective medical research study that evaluated treatments and outcomes as documented in medical records for patients with metastatic pancreatic cancer who were diagnosed between January 1, 2009, and December 31, 2012, and who received cancer-directed therapies in France and the United Kingdom.

Data Source and Study Design

A purposive sampling design was used to ensure that information was obtained on a similar number of patients in each country; consequently, among the total 103 physicians recruited to participate, 53 were located in France and 50 were located in the United Kingdom. Physicians were required to be caring for a minimum of 6 patients with metastatic pancreatic adenocarcinoma on or after January 1, 2009, and to have been in clinical practice for 5 to 35 years. Each physician was instructed to select records of his or her own patients for abstraction using a quasi-random selection approach based on the first initial of each potential patient's surname. A customized data collection form was developed based on the study's specific objectives and was administered via a secure, online interface. Data were collected without identification of the patient or physician to the study sponsor and authors (data collection was facilitated by a global research firm, A Plus A Medical Market Research, Lyon, France). As a retrospective medical research study, country-specific ethical review board requirements were reviewed, and it was determined that this study was exempt in both France and the United Kingdom. Furthermore, the study was judged to be exempt from informed consent requirements by the RTI International Institutional Review Board.

Patient Sample Description

Eligible patients were aged at least 18 years and were diagnosed with metastatic pancreatic adenocarcinoma between January 1, 2009, and December 31, 2012. Patients could have been initially diagnosed with an earlier stage of pancreatic cancer and progressed to metastatic disease if the diagnosis of metastatic disease was made during the study period. Patients must have received at least 1 cancer-directed therapy for metastatic disease (ie, systemic chemotherapy, a targeted systemic therapy, radiation therapy, or surgery) during the study period. To ensure a distribution of diagnosis dates and to observe relevant changes in treatment patterns, soft quotas were imposed in the ratio of 1:2:2:2 for the year of diagnosis of metastatic disease for 2009, 2010, 2011, and 2012, respectively, such that for every 1 patient for whom data were collected in 2009, data for 2 patients were collected each year: 2010, 2011, and 2012. In addition, we required a minimum follow-up time in the medical record of at least 3 months after the diagnosis of metastatic pancreatic adenocarcinoma. Patients with pancreatic neuroendocrine tumor (carcinoid and other types), those diagnosed with another primary malignancy (other than nonmelanoma skin cancer) at any time during the follow-up period, as well as those enrolled in an interventional clinical trial related to pancreatic cancer for any period during their treatment were excluded from this study. Patients who participated in observational studies were eligible to participate.

Study Measures

Patient characteristics abstracted from the medical records were age, sex, ethnic origin (for the United Kingdom only; ethnicity was not collected in France due to local laws on data privacy), type of insurance, ECOG PS[13] at first diagnosis, location of primary pancreatic tumor (head, body, tail, and other), and presence of comorbidities. Treatments evaluated included systemic chemotherapy and/or targeted therapy, radiation therapy, and surgery with either curative intent or palliation, accounting for combinations and line of therapy. Supportive care measures and treatments for well-known complications of metastatic pancreatic cancer were also evaluated. National Comprehensive Cancer Network guidelines and the clinical experience of the study team were used to inform which treatments were evaluated as part of the study.[14,15]

A complication was defined as a disease, condition, or injury that developed during the treatment of pancreatic cancer and that could be reasonably attributed to the pancreatic cancer rather than its treatment. Measures of supportive care were evaluated and defined as the management of pain and other distressing symptoms to reduce suffering and support quality

of life. The frequencies of Grade 3 or 4 adverse events, as documented in product labeling in addition to reasons for discontinuation of chemotherapy and/or targeted therapy, were also explored.

Health care use measures that were assessed included hospitalizations, additional outpatient office visits unrelated to systemic treatment administration, emergency department admissions, and visits to pain management clinics. End-of-life care was evaluated based on reported enrollment in long-term-care facilities and hospice care.

Participating physician characteristics were collected, including the number of years in practice, specialty, average number of metastatic pancreatic cancer patients treated in a year, and geographic region of practice.

Statistical Analyses

Descriptive analyses were performed to display means, SDs, medians, and ranges for continuous variables and frequency distributions for categorical variables. All analyses were conducted for the entire study population and separately by country. Furthermore, we assessed FOLFIRINOX and gemcitabine use as first-line therapy for metastatic disease, stratified by ECOG PS score in each country, and the top 3 most frequent first-line regimens used by year of diagnosis. All analyses were conducted using SAS version 9.3 software (SAS Institute Inc, Cary, North Carolina).

RESULTS

Physician Characteristics

Table I presents characteristics of participating physicians. The physicians had an average of 12 years of practice experience and all were oncology specialists. Participating physicians reported that between January 1, 2009, and December 31, 2012, they treated an average of 113 (France) and 135 (United Kingdom) patients with pancreatic adenocarcinoma (of any stage). The geographic distribution of physicians across the various regions in France and the United Kingdom were based on soft quotas, which were imposed to ensure that data would be contributed by physicians practicing in as many regions of each country as possible. To achieve this representation, fewer physicians participated from larger metropolitan cities such as Paris, France, relative to the size of the population.

Patient Characteristics and Disease History

Four hundred patients were included in the study (200 patients in each country). Of these, 327 patients presented initially with metastatic disease and the remaining 73 had been diagnosed at earlier stages and progressed to metastatic disease. Stage at initial diagnosis was unknown for 1 patient in the United Kingdom and was assumed to be metastatic disease in the analysis. Table II presents patients' demographic and other characteristics. The majority of patients

Table I. Physician characteristics.

Characteristic	France (n = 53)	United Kingdom (n = 50)	Total (N = 153)
Patients with pancreatic adenocarcinoma (any stage) treated on or after January 1, 2009			
Mean (SD)	113 (111.80)	135 (117.29)	124 (114.46)
Years in practice			
Mean (SD)	13 (5.16)	11 (4.46)	12 (4.86)
Median	12	11	11
Range (minimum, maximum)	(5, 30)	(5, 27)	(5, 30)
France	< ———— n (%) ———— >		
Telephone code 01 (Paris area)	14 (26.42)	–	–
Telephone code 02 (northwest)	5 (9.43)	–	–
Telephone code 03 (north and northeast)	11 (20.75)	–	–
Telephone code 04 (southeast)	13 (24.53)	–	–
Telephone code 05 (southwest)	10 (18.87)	–	–
United Kingdom			
North	–	6 (12.00)	–
Midlands and east	–	10 (20.00)	–
Greater London and southeast	–	17 (34.00)	–
Southwest	–	9 (18.00)	–
Scotland, Wales, and Northern Ireland	–	8 (16.00)	–

Table II. Patient characteristics.

Characteristic	France (n = 200)	United Kingdom (n = 200)	Total (N = 400)
Age at metastatic disease diagnosis, y			
Mean (SD)	63.8 (8.42)	59.9 (9.37)	61.8 (9.1)
Median	63.6	60.3	62.2
Range (minimum, maximum)	(40.5, 86.8)	(28.6, 80.7)	(28.6, 86.8)
Age distribution, y	< ——— n (%) ——— >		
18–44	14 (7.00)	3 (1.50)	17 (4.25)
45–54	47 (23.50)	25 (12.50)	72 (18.00)
55–64	72 (36.00)	87 (43.50)	159 (39.75)
65–74	59 (29.50)	68 (34.00)	127 (31.75)
75+	8 (4.00)	17 (8.50)	25 (6.25)
Sex			
Male	131 (65.50)	122 (61.00)	253 (63.25)
Female	69 (34.50)	78 (39.00)	147 (36.75)
Ethnic origin*			
White/Caucasian	–	174 (87.00)	–
African/black	–	16 (8.00)	–
Asian or Pacific Islander	–	9 (4.50)	–
Other	–	1 (0.50)	–
Don't know	–	–	–
Supplemental private insurance			
Yes	91 (45.50)	18 (9.00)	109 (27.25)
No	33 (16.50)	164 (82.00)	197 (49.25)
Don't know	76 (38.00)	18 (9.00)	94 (23.50)
ECOG PS			
Mean (SD)	1.2 (0.8)	1.2 (0.7)	1.2 (0.7)
Distribution of ECOG PS†			
0	31 (15.50)	26 (13.00)	57 (14.25)
1	105 (52.50)	116 (58.00)	221 (55.25)
2	57 (28.50)	49 (24.50)	106 (26.50)
3	6 (3.00)	7 (3.50)	13 (3.25)
4	1 (0.50)	1 (0.50)	2 (0.50)
Don't know	–	1 (0.50)	1 (0.25)
Location of the primary pancreatic tumor			
Head	95 (47.50)	114 (57.00)	209 (52.25)
Body	63 (31.50)	64 (32.00)	127 (31.75)
Tail	33 (16.50)	17 (8.50)	50 (12.50)
Other	3 (1.50)	–	3 (0.75)
Don't know	6 (3.00)	5 (2.50)	11 (2.75)

ECOG = Eastern Cooperative Oncology Group; PS = performance status.
*Ethnic origin not asked in France.
†Source: Reference 13.

were men (63.3%), and the median age at the time of metastatic disease diagnosis was 62.2 years, with more than 70% of patients between ages 55 and 74 years. More than two thirds of patients had an ECOG PS score of 0 or 1 when metastatic disease was diagnosed, with a mean ECOG PS score of 1.2 for patients in both countries.

Figure 1 presents comorbidities recorded in at least 5% of patients at the time of metastatic disease diagnosis. Hypertension and diabetes mellitus were the most commonly reported comorbidities. More than 40% of patients had a smoking history (ie, were either current or former smokers).

Treatment Patterns

First-Line Therapy for Metastatic Disease

Nearly all patients (97.3%) received chemotherapy to treat metastatic disease: 9.3% received radiation therapy and 7.8% received a targeted therapy (categories not mutually exclusive). Among the 389 patients who received chemotherapy, only 37 had received prior treatment for earlier-stage disease (adjuvant chemotherapy or

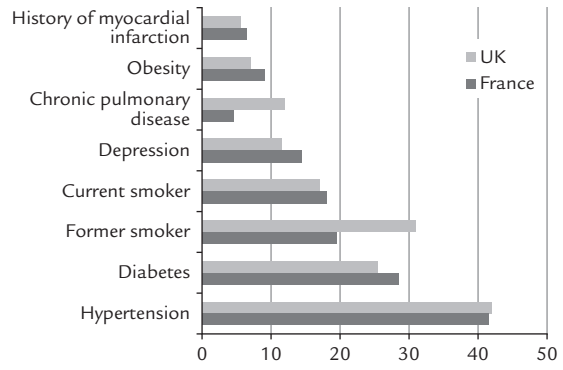

Figure 1. Comorbidities recorded in at least 5% of patients at the time of metastatic disease diagnosis. UK = United Kingdom.

chemotherapy for locally advanced disease). As illustrated in Table III, overall, the most commonly administered regimens used as first-line therapy for metastatic disease were gemcitabine alone (46.0%), FOLFIRINOX (20.1%), gemcitabine plus capecitabine (10.8%), and gemcitabine plus oxaliplatin (9.5%). In France, the most commonly administered regimens were gemcitabine alone (46.5%), FOLFIRINOX (28.3%), and gemcitabine plus oxaliplatin (14.7%). In the United Kingdom, the most commonly administered regimens were gemcitabine alone (45.6%), gemcitabine plus capecitabine (20.9%), and FOLFIRINOX (11.5%). Given ongoing efforts to evaluate the efficacy and safety of modified FOLFIRINOX regimens, we sought to gather information regarding use of such regimens in our study.[16–18] In both countries, we found that a small proportion (<2%) of patients received a modified FOLFIRINOX regimen, which was characterized as receiving less than the starting dose for 1 of the drugs in the regimen, as recommended by Conroy et al[8] (results not shown). This finding is not surprising, given more recent publications for the modified doses relative to the end of our data-collection period (ie, December 31, 2012).

We further analyzed the use of gemcitabine alone and FOLFIRINOX, either of which was administered to nearly two thirds of patients in the study. Figure 2 depicts the proportions of patients receiving these regimens as the first-line therapy for metastatic disease, stratified by ECOG PS score. In both countries, a disproportionate number of patients with an ECOG PS score of 0 were treated with FOLFIRINOX, and a greater proportion of patients with an ECOG PS score of 2 received gemcitabine alone.

Table III. First chemotherapy and targeted therapy for metastatic pancreatic adenocarcinoma.

Type of Chemotherapy/Biological Therapy Administered	France (n = 198)		United Kingdom (n = 191)		Total (N = 389)	
	n	%	n	%	n	%
Gemcitabine	92	46.46	87	45.55	179	46.02
Gemcitabine + erlotinib	3	1.52	4	2.09	7	1.80
Gemcitabine + oxaliplatin	29	14.65	8	4.19	37	9.51
Gemcitabine + cisplatin	3	1.52	13	6.81	16	4.11
Gemcitabine + capecitabine	2	1.01	40	20.94	42	10.80
FOLFIRINOX (includes leucovorin + fluorouracil + irinotecan + oxaliplatin)	56	28.28	22	11.52	78	20.05
Single-agent fluoropyrimidine*	1	0.51	7	3.67	8	2.05
Fluoropyrimidine + oxaliplatin†	11	5.56	4	2.09	15	3.85
Other/NA‡	1	0.51	6	3.13	7	1.80

NA = not available.
*Includes either fluorouracil (bolus or continuous infusion) + leucovorin or capecitabine alone.
†Includes either fluorouracil (bolus or continuous infusion) + oxaliplatin or capecitabine + oxaliplatin.
‡Includes cisplatin, "other regimen," and "not available."

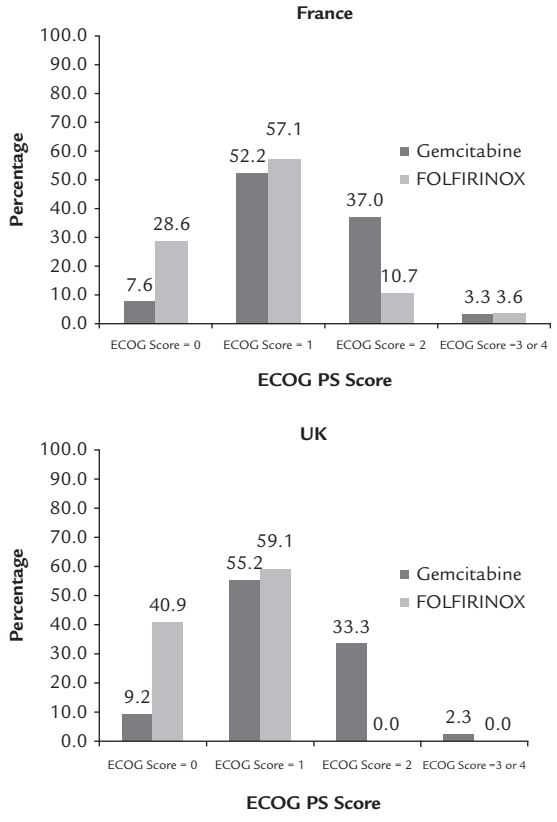

Figure 2. Proportions of patients receiving these regimens as the first-line therapy for metastatic disease, stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) score. UK = United Kingdom.

Figure 3 presents a time-trend analysis of the 3 most frequently administered first-line chemotherapy regimens for metastatic disease. In both countries, a progressive increase in the use of FOLFIRINOX over the 4 study years is apparent.

Reasons for treatment discontinuation among patients receiving each of the 3 most commonly administered first-line therapies for metastatic disease were assessed. The most common reason for discontinuation of any of the therapies was disease progression. For example, for gemcitabine alone, 63.0% of patients in France and 43.7% in the United Kingdom discontinued for this reason. The proportion of patients who discontinued due to intolerance or toxicity varied somewhat by treatment regimen and by country. Among patients receiving gemcitabine, 8.7% discontinued due to intolerance or toxicity in France and 10.3% did so in the United Kingdom. For those receiving gemcitabine and oxaliplatin or gemcitabine and capecitabine, 10.3% and 2.8% of patients in France and the United Kingdom, respectively, discontinued for this reason. Among those receiving FOLFIRINOX, 17.9% discontinued for intolerance or toxicity in France and 27.3% did so in the United Kingdom. Overall, treatment was ongoing at the time of data reporting for approximately 19% of patients receiving FOLFIRINOX as first-line therapy for metastatic disease. This proportion was greater for patients receiving FOLFIRINOX compared with patients receiving other treatments due to the increased use of FOLFIRINOX during the later years that patients were eligible for the study.

Second- and Third-Line Therapies for Metastatic Disease

In France, 40.4% of patients (n = 80) received second-line systemic therapy for metastatic disease, and 15.2% of patients (n = 29) did so in the United Kingdom. In France, the most commonly reported therapies included gemcitabine (28.8%); combination therapy with continuous-infusion 5-FU, oxaliplatin, and leucovorin (17.5%); and capecitabine (10.0%). In the United Kingdom, the most commonly reported therapies included capecitabine (27.6%); combination therapy with continuous-infusion 5-FU, oxaliplatin, and leucovorin (24.1%); and gemcitabine (10.3%).

Sixteen patients in France (20.0%) and 1 patient in the United Kingdom (3.4%) received third-line systemic therapy for metastatic disease. In France, the most commonly reported therapies included combination therapy with continuous-infusion 5-FU, irinotecan, and leucovorin (31.3%); capecitabine (25.0%); and gemcitabine (25.0%). The reporting physician did not know the specific regimen received by the 1 patient in the United Kingdom.

Adverse Events and Complications

The evaluation of adverse events was restricted to those documented as Grade 3 or 4 in the patient's medical record. Table IV presents the number and percentage of patients who experienced Grade 3 or 4 adverse events among those who received each of the 3 most commonly administered first-line therapies for metastatic disease.

In each country, there was variation in the proportion of patients experiencing Grade 3 or 4 adverse events across the top-3 most commonly administered first-line therapies for metastatic disease. Overall, the most

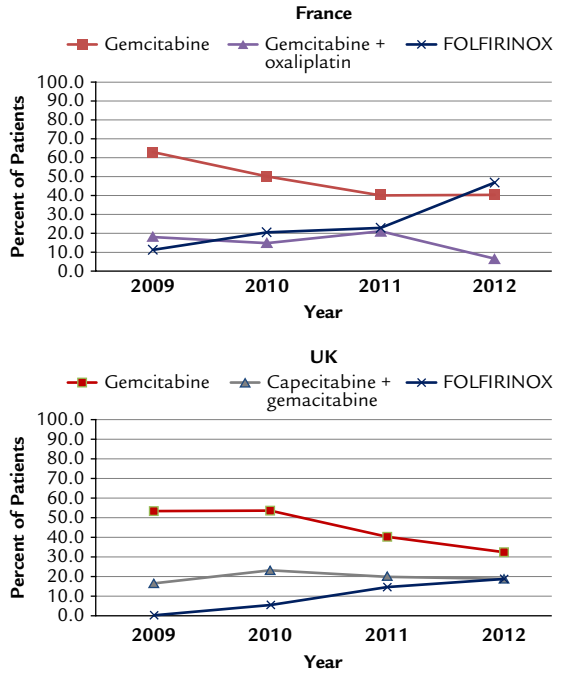

Figure 3. A time-trend analysis of the 3 most frequently administered first-line chemotherapy regimens for metastatic disease. In both countries, a progressive increase in the use of a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) over the 4 study years is apparent. Note: In 2009 only, gemcitabine + cisplatin was among the three most frequently administered first chemotherapy regimens for metastatic disease in the UK, but it is not shown in this figure. Although FOLFIRINOX was not among the three most frequently administered first chemotherapy regimens for metastatic disease in the UK in 2009, it was included in the group beginning in 2010 and is shown in this figure for all years.

common adverse events recorded were neutropenic fever, thrombocytopenia, and gastrointestinal events.

Overall, 52.5% of patients experienced at least one complication of metastatic pancreatic cancer (not presented in tabular form). The most commonly experienced complications were cachexia (24.8%), biliary obstruction (18.8%), malnutrition (17.0%), depression (13.5 %), and intractable ascites (12.0%). In France, 46.5% of patients experienced complications, with the most common being cachexia (21.5%), depression (17.5%), malnutrition (17.0%), biliary obstruction (16.0%), and intractable ascites (12.0%). In the United Kingdom, 58.5% of patients experienced a complication, with the most common being cachexia (28.0%), biliary obstruction (21.5%), malnutrition (17.0%), intractable ascites (12.0%), and depression (9.5%).

Supportive Care

The majority of patients (92.0%) received at least one specific type of therapy for supportive care (Table V). Sixty-seven percent received pharmacologic or procedural therapy for pain control, 50.0% received antiemetics, 25.8% were administered antibiotics, and 26.0% required blood transfusions. Hematopoietic growth factors were administered to 26.5% of patients in France but to only 3.0% in the United Kingdom. Twenty-six percent of patients in France and 9.5% in the United Kingdom received therapy for distress management, defined as the identification and treatment of psychosocial problems in patients with cancer.[19]

HEALTH CARE RESOURCE USE

Table VI presents a summary of health care resource use. As expected, most patients had at least 1 office visit (defined as visit unrelated to the administration of chemotherapy): 66.5% in France and 86.5% in the United Kingdom. Among patients with at least 1 office visit, the median number of office visits was 6 in both countries. More than half (54.0%) had at least 1 inpatient hospitalization, and among this group, 41.7% had 1, 33.3% had 2, and 25.0% had 3 or more inpatient hospitalizations. Among those with at least 1 inpatient hospitalization, the median length of stay overall was 8 days (10 days in France and 6 days in the United Kingdom). Forty-five percent of patients in France and 28.5% of patient in the United Kingdom had at least 1 emergency department visit, and approximately one quarter of the patients in both countries had a pain management clinic visit. During the study observation period, 26.5% (n = 53) of patients in France and 42.5% (n = 85) in the United Kingdom received end-of-life care, as defined by enrollment in either hospice care or a long-term-care facility.

DISCUSSION

Our study was a retrospective evaluation of medical records of patients with metastatic pancreatic

Table IV. Grade 3 to 4 adverse events reported for the 3 most commonly administered first therapy regimens following metastatic disease diagnosis.

	France						United Kingdom					
	Gemcitabine (n = 92)		FOLFIRINOX (n = 56)		Gemcitabine + Oxaliplatin (n = 29)		Gemcitabine (n = 87)		Gemcitabine + Capecitabine (n = 40)		FOLFIRINOX (n = 22)	
Grade 3 or 4 Adverse Event*	n	%	n	%	n	%	n	%	n	%	n	%
Any	6	6.52	11	19.64	2	6.90	6	6.90	6	15.00	8	36.36
Neutropenia	2	2.17	2	3.57	–	–	–	–	1	2.50	3	13.64
Neutropenic fever	–	–	5	8.93	–	–	2	2.30	1	2.50	4	18.18
Thrombocytopenia	3	3.26	5	8.93	–	–	3	3.45	–	–	1	4.55
Bleeding	–	–	1	1.79	–	–	–	–	–	–	–	–
Anemia	3	3.26	3	5.36	1	3.45	–	–	1	2.50	–	–
Eye toxicity	–	–	–	–	–	–	–	–	–	–	1	4.55
Palmar-plantar (hand-foot) syndrome	–	–	3	5.36	–	–	–	–	4	10.00	–	–
Asthenia	3	3.26	4	7.14	1	3.45	–	–	1	2.50	–	–
Fatigue, lethargy, general deterioration	2	2.17	2	3.57	1	3.45	3	3.45	1	2.50	–	–
Pain (abdominal, general, arthralgia, or myalgia)	–	–	1	1.79	–	–	–	–	–	–	–	–
Paresthesia/sensory neuropathy	–	–	5	8.93	2	6.90	–	–	–	–	1	4.55
Edema	1	1.09	–	–	–	–	–	–	–	–	–	–
Infection	1	1.09	–	–	–	–	–	–	–	–	–	–
Gastrointestinal events (diarrhea, nausea/vomiting, stomatitis)	1	1.09	4	7.14	–	–	–	–	2	5.00	3	13.64
Abnormal liver blood tests (alkaline phosphatase elevated, ALT (SGPT) elevated, AST (SGOT) elevated, bilirubin elevated)	–	–	1	1.79	–	–	–	–	–	–	–	–
Other	–	–	–	–	–	–	–	–	1	2.50	–	–

ALT = alanine aminotransferase; AST = aspartate aminotransferase; FOLFIRINOX = a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvate transaminase.
*Not mutually exclusive.

Table V. Supportive care.

Supportive Care*	France (n = 200) n	%	United Kingdom (n = 200) n	%	Total (N = 400) n	%
Pain control	134	67.00	134	67.00	268	67.00
Opiate analgesic	129	64.50	127	63.50	256	64.00
Other analgesic	40	20.00	63	31.50	103	25.75
Radiotherapy	9	4.50	11	5.50	20	5.00
Percutaneous celiac plexus blockade	2	1.00	5	2.50	7	1.75
Splanchnic nerve block	2	1.00	2	1.00	4	1.00
Psychological intervention	65	32.50	4	2.00	69	17.25
Sedation for refractory pain	9	4.50	1	0.50	10	2.50
Epidural infusions	–	–	1	0.50	1	0.25
Other	–	–	1	0.50	1	0.25
Distress management	52	26.00	19	9.50	71	17.75
Antiemetic	113	56.50	87	43.50	200	50.00
Antibiotic	54	27.00	49	24.50	103	25.75
Antibacterial	9	4.50	14	7.00	23	5.75
Antifungal	18	9.00	6	3.00	24	6.00
Antiviral	1	0.50	–	–	1	0.25
Transfusion	59	29.50	45	22.50	104	26.00
Palliative surgery	2	1.00	–	–	2	0.50
Bypass of intestinal obstruction	2	1.00	–	–	2	0.50
Embolization	2	1.00	2	1.00	4	1.00
Endoscopic stent placement	38	19.00	29	14.50	67	16.75
Percutaneous biliary drainage with stent placement	11	5.50	6	3.00	17	4.25
Percutaneous biliary drainage without stent placement	–	–	1	0.50	1	0.25
Growth factors	53	26.50	6	3.00	59	14.75
GCSF (eg, filgrastim, pegfilgrastim)	43	21.50	6	3.00	49	12.25
GM-CSF (eg, molgramostim, sargramostim)	2	1.00	–	–	2	0.50
Erythropoiesis stimulating agent (eg, erythropoietin, epoetin alpha, epoetin beta, darbepoetin alpha, methoxy polyethylene glycol-epoetin beta)	37	18.50	–	–	37	9.25
Other	2	1.00	3	1.50	5	1.25
No supportive care	10	5.00	12	6.00	22	5.50
Don't know	–	–	9	4.50	9	2.25

GCSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor.
*Supportive care focuses on management of pain and other distressing symptoms to reduce suffering and support quality of life.

adenocarcinoma who received cancer-directed therapy in France and the United Kingdom. The primary objective was to describe patterns of care in both countries rather than to compare the treatment patterns and outcomes between the 2 countries. Consistent with this objective, and with limited ability to adjust for potentially confounding factors due to the nature of the study, no formal statistical tests

Table VI. Health care resource use.

Health Care Use	France (n = 200)	United Kingdom (n = 200)	Total Cohort (N = 400)
Office visit			
n (%)	133 (66.50)	173 (86.50)	306 (76.50)
Mean (SD)	8.1 (7.3)	8.8 (7.1)	8.5 (7.1)
Median	6	6	6
Range (minimum, maximum)	(1, 35)	(1, 35)	(1, 35)
Emergency department visit			
n (%)	90 (45.00)	57 (28.50)	147 (36.75)
Mean (SD)	2.1 (1.5)	2.1 (2.0)	2.1 (1.7)
Median	2	1	2
Range (minimum, maximum)	(1, 9)	(1, 9)	(1, 9)
Pain management clinic visit			
n (%)	51 (25.50)	50 (25.00)	101 (25.25)
Mean (SD)	2.2 (1.6)	3.2 (2.1)	2.7 (1.9)
Median	2	3	2
Range (minimum, maximum)	(1, 8)	(1, 12)	(1, 12)
Inpatient stay*			
n (%)	115 (57.50)	101 (50.50)	216 (54.00)
Mean (SD)	2.2 (1.8)	2.0 (1.5)	2.1 (1.7)
Median	2	2	2
Range (minimum, maximum)	(1, 14)	(1, 12)	(1, 14)
Distribution of inpatient stays (n, %)			
1	42 (36.52)	48 (47.52)	90 (41.67)
2	41 (35.65)	31 (30.69)	72 (33.33)
≥2	32 (27.83)	22 (21.78)	54 (25.00)
Time to first hospitalization since diagnosis of metastatic disease, mo			
Mean (SD)	5.6 (7.3)	5.3 (6.4)	5.4 (6.9)
Median	2.7	3.0	2.9
Range (minimum, maximum)	(0, 35.3)	(0, 36.8)	(0, 36.8)
Length of stay (among those with at least 1 stay), d			
Mean (SD)	15.3 (20.0)	7.7 (6.3)	11.7 (15.7)
Median	10.0	6.0	8.0
Range (minimum, maximum)	(1, 112)	(1, 52)	(1, 112)
Long-term-care facility transfer (n,%)	21 (10.50)	7 (3.50)	28 (7.00)
Time to transfer to long-term-care facility since diagnosis of metastatic disease, mo			
Mean (SD)	10.9 (11.9)	17. 4 (22.0)	11.9 (13.2)
Median	8.2	5.1	7.9
Range (minimum, maximum)	(0, 43.2)	(4.1, 42.8)	(0, 43.2)
Hospice transfer (n,%)	39 (19.50)	81 (40.50)	120 (30.00)

(continued)

Table VI. (continued).

Health Care Use	France (n = 200)	United Kingdom (n = 200)	Total Cohort (N = 400)
Time to transfer to hospice setting since diagnosis of metastatic disease, mo			
Mean (SD)	12.3 (9.1)	10.9 (8.4)	11.4 (9.0)
Median	10.3	9	9.3
Range (minimum, maximum)	(0.3, 39.1)	(1.1, 44.0)	(0.3, 44.0)

*Inpatient stay is an overnight or day admission, excluding emergency department visits.

comparing results between countries are reported; nevertheless, several apparent variations in practice by country were noted.

Although there are still relatively few therapeutic options for patients with metastatic pancreatic cancer, FOLFIRINOX and gemcitabine plus nab-paclitaxel provide new and meaningful alternatives to gemcitabine alone for patients who have good PS and normal bilirubin levels. According to the European Society for Medical Oncology–European Society of Digestive Oncology guidelines,[20] in addition to FOLFIRINOX now being an option for patients, gemcitabine remains a valid alternative for first-line treatment of metastatic disease. Gemcitabine-based combinations with cytotoxic agents (ie, 5-FU, capecitabine, irinotecan, cisplatin, and oxaliplatin) also are available; however, supporting Phase 3 data have not confirmed a major survival advantage. The guidelines note limited evidence supporting gemcitabine in combination with either biologic agents or erlotinib in first-line settings. Although the combination of gemcitabine with erlotinib has been approved by the US Food and Drug Administration and the EMA, the lack of clinically meaningful efficacy in the majority of patients may limit the role of this regimen to use in the subgroup most likely to benefit. The most recent guidelines were published before the availability of Phase 3 data supporting the gemcitabine plus nab-paclitaxel combination.[7] Therefore, this regimen, although EMA-approved,[12] was not listed as an alternative at the time this article was written. For those whose disease progresses and are in need of a second-line therapy, the combination of oxaliplatin and 5-FU can be administered to patients who received gemcitabine in the first-line setting; for patients who received FOLFIRINOX in the first-line setting, single-agent gemcitabine is recommended.[20]

To our knowledge, our study is the first to report an increase in FOLFIRINOX use in select European countries since publication of the Conroy et al[8] clinical trial results in 2011. Although we found gemcitabine alone to be used most commonly in both countries to treat patients in first-line metastatic disease, FOLFIRINOX was used approximately twice as frequently in France as in the United Kingdom, which is perhaps a reflection of the fact that the original trial data for the regimen were generated in France. In both countries, the majority of patients receiving FOLFIRINOX had better ECOG PS scores than those treated with gemcitabine alone, and they also experienced greater treatment-related toxicities and discontinuation due to intolerance or toxicity. Furthermore, a greater proportion of patients used hematopoietic growth factors in France, which is perhaps due in part to greater FOLFIRINOX use and the need to manage side effects of this treatment or potentially due to reimbursement considerations. These results suggest that the lower observed rates of Grade 3 or 4 neutropenia and neutropenic fever associated with FOLFIRINOX use in France than in the United Kingdom may have been due to the increased use of granulocyte colony stimulating factors in France.

We found that only a small proportion of patients received more than one line of systemic therapy for metastatic disease, which reinforces the aggressiveness

of this disease and the lack of therapeutic options in this space. Sufficient palliation is especially relevant for these patients given the unique nature of the disease, including secondary complications; end of life is often marked by severe symptoms and poor quality of life.[21] Multidisciplinary management of symptoms due to biliary obstruction, gastric outlet obstruction, and cancer-related pain are of primary importance.[19] To our knowledge, no detailed studies of the real-world frequency of complications of pancreatic cancer in any European country have been published to date. More than half of the patients in our study experienced disease complications during the period of metastatic disease, and a greater proportion would be expected to experience these with longer follow-up times. As expected with this disease, obstruction (biliary or duodenal), cachexia, and malnutrition were the most frequently observed complications in both France and the United Kingdom. In addition, a supplementary analysis of the study data presented here suggested that there was an association between the presence of complications and select measures of health care resource use. In both countries, patients who experienced complications were more likely to be hospitalized than those who did not; in France, patients with complications were more likely to have an office and emergency department visit than those who did not have a complication. Further research is warranted to further confirm these associations, as well as to quantify the specific costs associated with treating complications in this population, because they are likely to be significant.

One of the objectives of our study was to estimate the frequency of Grade 3 or 4 adverse events in a real-world setting. The frequency of Grade 3 or 4 adverse events in our study was less than would be expected for patients participating in clinical trials, owing to the retrospective nature of the data collection. However, in a relative sense, and consistent with results presented by Conroy et al,[8] our study demonstrated that patients who received FOLFIRINOX experienced Grade 3 or 4 adverse events with greater frequency than patients receiving gemcitabine as first-line therapy for metastatic disease. Overall, the top-3 Grade 3 or 4 adverse events reported for patients receiving FOLFIRINOX included neutropenic fever followed by thrombocytopenia and paresthesia/sensory neuropathy. For gemcitabine, the most common included thrombocytopenia followed by fatigue/lethargy, then asthenia and anemia that occurred in equal numbers of patients.

It is our belief that patients in our study are likely to be generally representative of the population of patients who receive cancer-directed therapy for metastatic pancreatic adenocarcinoma in France and the United Kingdom, given the geographic representativeness of the population, concurrent comorbidities, and presence of disease complications. In addition, our observed patterns of treatment are consistent with what might be expected after the availability of data characterizing the overall survival benefit of FOLFIRINOX. Patients in this study were younger on average than in the general population of patients with metastatic pancreatic cancer, possibly owing to the requirement that all patients had to have received cancer-directed therapy for metastatic disease in addition to having a minimum of 3 months of medical record data available for review. For example, 47% of all incident cases of pancreatic cancer in the United Kingdom between 2009 and 2011 were among patients older than 75 years,[22] whereas in our study only 8.5% of patients with pancreatic cancer (any stage) in the United Kingdom were older than age 75 years at diagnosis. Population-based data on PS are not available for patients receiving chemotherapy for metastatic pancreatic cancer in France and the United Kingdom; however, the distribution of PS scores that we observed were comparable to patients enrolled in recently published clinical trials of metastatic pancreatic cancer treatment.[23,24]

To our knowledge, our study is the first retrospective analysis in any European country to report information on health care resource and patterns of systemic therapy use across multiple lines of therapy for patients with metastatic pancreatic cancer. Furthermore, limited data have been published to date in the United States on these objectives. Studies including the time period after presentation (June 2010) and publication (May 2011) of the Phase 3 FOLFIRINOX results are even further limited. Our study includes follow-up through December 2012, Cartwright et al[10] through November 2013, and DaCosta Byfield et al[25] through December 2010.

Consistent with our findings, Cartwright et al,[10] previously demonstrated an increase in FOLFIRINOX use and decrease in gemcitabine use in patients with good PS treated in a network of US private oncology practices. Dacosta Byfield et al[25] reported gemcitabine as the most

common systemic therapy received among patients with metastatic pancreatic cancer in a large, US-managed health care organization; however, follow-up extended just 6 months postpresentation of FOLFIRINOX Phase 3 results. Rates of office visits were noted as a significant driver of resource use relative to the control population, in addition to outpatient, inpatient, and emergency department visits with inpatient costs identified as the single largest cost driver. O'Neill et al[26] evaluated direct medical costs of patients older than age 65 years with locoregional or distant pancreatic cancer in the US Surveillance, Epidemiology, and End Results–Medicare database and found inpatient hospitalizations accounting for the largest proportion of costs for patients with distant disease. No details on systemic therapy treatment patterns were reported.[26] Lastly, Neiderhuber et al[27] published findings from the US National Cancer Data Base outlining practice patterns in patients with pancreatic cancer from 1985–1986 to 1991. The authors found that 66.1% of patients with Stage IV disease did not receive any systemic treatment. No details on chemotherapy regimens were reported for the 33.9% who were treated.

Our study is subject to several limitations inherent to many retrospective medical record review studies. In particular, patients selected for study inclusion represented a convenience sample, in that the records were obtained from physicians who were willing to participate in the study. In addition, we imposed soft quotas for geographic distribution, not only to gain a better sense of the range of practice throughout each country, but also to avoid the results being affected too strongly by practice in densely populated urban areas. As a consequence of these design decisions, as well as an unknown extent to which physicians might self-select for participating in a study such as this, our findings may be limited when generalizing to the overall pancreatic cancer population in the countries we studied. Furthermore, owing to the observational nature of this study and the limited control of potential confounding, the results presented here are descriptive and do not purport to show causal relationships. Caution should be exercised in comparing results between the 2 countries studied, which differ with regard to the organization of medical care, country-specific considerations regarding patient access to care and medicines, and other cultural factors.

The data we analyzed were entered directly by the treating physicians based on medical records available at the time of data entry, and therefore are potentially subject to data entry errors and other limitations of retrospective data capture. Although we used automated data checks to maximize internal data consistency, responses were not validated against the patients' medical records by an independent reviewer. Physicians were, however, asked to provide additional clarifying details if any conflicting responses were found within the data collection form. In addition, to increase the likelihood that physicians responded fully and accurately, the data collection form was designed to limit physicians' time burden. Therefore, the information collected was not exhaustive, and there could be additional measures that would be useful in understanding variations in treatment and outcomes that were not captured. Furthermore, physicians reported data based on information available in the patients' medical records to which they had access. Although major events such as inpatient hospitalizations are likely to have been recorded, it is possible that patients could have received health care services in other care settings that were not reported back to the treating physician and, therefore, were not part of their medical record and not captured in this study. In France, many patients are seen for consultation in hospital outpatient settings as opposed to a physician's office. We did not collect information specific to hospital outpatient settings, which also may help to explain the lower observed rate of office visits for France compared with the United Kingdom. Finally, 19% of patients in our study were still receiving FOLFIRINOX at the time of data collection. Therefore, the opportunity to observe any safety or tolerability considerations for those patients and/or failure of therapy due to disease progression was reduced and should be taken into account when reviewing the results of this study.

CONCLUSIONS

Despite these limitations, our study captures detailed and generally representative clinical and treatment data for patients with metastatic pancreatic cancer in real-world settings in 2 large European countries. Future research efforts are warranted to evaluate patterns of cancer-directed and supportive care treatment, frequency of complications, and health care resource use in countries other than France and the United Kingdom. Continuing assessments of future changes in treatment patterns as a result of recent regulatory decisions in support of gemcitabine plus

nab-paclitaxel, as well as modified FOLFIRINOX regimens that might be used in an effort to minimize toxicity, will add important information to the body of knowledge in the area of pancreatic cancer treatment. Furthermore, a more comprehensive assessment of the distribution of costs for this patient population would be informative.

ACKNOWLEDGMENTS

The authors thank Debanjali Mitra (RTI Health Solutions at the time of the study) for her contributions to the original study design, Sean Candrilli (RTI Health Solutions) for engaging in helpful discussions of the study design and results, Ravi Goyal (RTI Health Solutions) for his assistance with analyses, and Valérie Derrien (A Plus A Medical Market Research) for assisting with data collection. Final decisions regarding manuscript content were made jointly by the authors. E. Smyth, B. Bapat, and J. Kaye were the primary developers of the study design, and T. André provided input on data collection elements. B. Bapat had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors assisted in interpreting the study findings and drafting the manuscript text, all authors provided critical input to the content of the manuscript, and all were responsible for approving the manuscript and its contents.

CONFLICTS OF INTEREST

J. Kaye is a full-time employee of RTI Health Solutions, an independent, nonprofit research organization that received funding from Eli Lilly and Company to conduct this study. B. Bapat was an employee of RTI Health Solutions at the time that this study was conducted; she is now an employee of Evidera. D. Ball and E. Smyth are employees of Eli Lilly and Company. The manuscript underwent scientific quality and legal review by Eli Lilly and Company before submission. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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