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Epidemiology and natural history of central venous access device use and infusion pump function in the NO16966 trial

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Background: Central venous access devices in fluoropyrimidine therapy are associated with complications; however, reliable data are lacking regarding their natural history, associated complications and infusion pump performance in patients with metastatic colorectal cancer.

Methods: We assessed device placement, use during treatment, associated clinical outcomes and infusion pump performance in the NO16966 trial.

Results: Device replacement was more common with FOLFOX-4 (5-fluorouracil (5-FU) + oxaliplatin) than XELOX (capecitabine + oxaliplatin) (14.1% vs 5.1%). Baseline device-associated events and post-baseline removal-/placement-related events occurred more frequently with FOLFOX-4 than XELOX (11.5% vs 2.4% and 8.5% vs 2.1%). Pump malfunctions, primarily infusion accelerations in 16% of patients, occurred within 1.6–4.3% of cycles. Fluoropyrimidine-associated grade 3/4 toxicity was increased in FOLFOX-4-treated patients experiencing a malfunction compared with those who did not (97 out of 155 vs 452 out of 825 patients), predominantly with increased grade 3/4 neutropenia (53.5% vs 39.8%). Febrile neutropenia rates were comparable between patient cohorts \pm malfunction. Efficacy outcomes were similar in patient cohorts \pm malfunction.

Conclusions: Central venous access device removal or replacement was common and more frequent in patients receiving FOLFOX-4. Pump malfunctions were also common and were associated with increased rates of grade 3/4 haematological adverse events. Oral fluoropyrimidine-based regimens may be preferable to infusional 5-FU based on these findings.

Fluoropyrimidines form the foundation of the vast majority of chemotherapy regimens used in the treatment of metastatic colorectal cancer (mCRC), and they can take the form of intravenous 5-fluorouracil (5-FU; by continuous or bolus infusion) or oral formulations (capecitabine). Fluoropyrimidine-based

regimens include XELOX (oral capecitabine plus infusional oxaliplatin), FOLFOX (infusional leucovorin (LV), 5-FU and oxaliplatin) and FOLFIRI (infusional LV, 5-FU and irinotecan), each of which has a well-established role in the management of patients with mCRC. These regimens are now included in the key

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evidence-based practice guidelines in Europe and the United States (Van Cutsem *et al*, 2010; NCCN, 2013).

The preferred 5-FU administration schedule for the FOLFOX or FOLFIRI regimens is intravenous infusions of either 22 or 46 h duration. Patients receiving these regimens usually require placement of a central venous access device (CVAD), as treatment involves repeated and prolonged infusions. Catheter insertion requires skilled personnel, and it is usually performed under local anaesthesia, taking ~30–50 min, on average, to complete (Gann and Sardi, 2003; Shen-Gunther *et al*, 2003). Central venous access device placements are often associated with complications such as infections and venous thrombosis, resulting in antibiotic use, hospitalisation and CVAD replacements (Debourdeau *et al*, 2009; Beckers *et al*, 2010). A number of other complications have been observed, including insertion-related problems (McGee and Gould, 2003) and catheter sheath formation (Xiang *et al*, 1998). Previous studies have reported CVAD-associated complications in 8–15% of patients with CRC (Martoni *et al*, 2006; Inaba *et al*, 2007; Kawamura *et al*, 2008). In a randomised phase II study of patients with advanced CRC treated with XELOX or FOLFOX (utilising protracted infusion of 5-FU and oxaliplatin), venous line complications occurred in 15% of FOLFOX-treated patients, which resulted in suspension or cessation of treatment (Martoni *et al*, 2006). The INT-0153 study compared the clinical efficacy of continuous infusion 5-FU (CIFU) plus levamisole *vs* bolus 5-FU/LV plus levamisole in the adjuvant treatment of patients with stage III and high-risk stage II colon cancer, and found that nearly twice as many patients discontinued CIFU/levamisole than those who discontinued bolus 5-FU/LV/levamisole (106 out of 460 *vs* 64 out of 459, respectively), despite significantly higher rates of grade 4 toxicities in the bolus arm (5% *vs* 39%). The main adverse events observed were haematological and gastrointestinal in nature. Early treatment discontinuation in the CIFU arm was more often associated with non-life-threatening adverse events, such as hand-foot syndrome, or events associated with the delivery and administration of CIFU, such as pump therapy logistics, pump malfunctions, CVAD-associated thrombosis and catheter-related neck pain (Poplin *et al*, 2005).

There is, presently, a paucity of data on the natural history of CVADs and CVAD-associated complications from large studies of patients with mCRC. Moreover, data regarding the performance and reliability of infusional pumps have not been prospectively reported in the scientific literature. Herein, we report the largest prospective evaluation of CVAD placement and use during treatment, and of CVAD-associated clinical outcomes. Data were obtained from the NO16966 trial, which was a phase III, randomised investigation into the comparative efficacy of XELOX and FOLFOX-4 in the front-line treatment of patients with mCRC. When used, CVADs were placed in patients receiving XELOX as a result of the oxaliplatin component of the regimen.

PATIENTS AND METHODS

Study design. The design of the NO16966 study and the patient population have been described previously (Cassidy *et al*, 2008). Based on the results of the pivotal trial evaluating bevacizumab in mCRC, the trial design was amended after patient accrual had begun (Saltz *et al*, 2007). The amended trial used a 2 × 2 factorial design and randomised patients to either FOLFOX-4 or XELOX in combination with bevacizumab or placebo (Cassidy *et al*, 2008). The primary endpoint was progression-free survival. During the study, data were prospectively collected regarding CVAD placements (but not the specific type of CVAD) or CVAD removals and/or replacements, and adverse events associated with CVAD insertion, removal and replacement (graded according to the

National Cancer Institute Common Terminology Criteria, version 3.0 (National Cancer Institute, 2006); available for initial placements only). Central venous access device placement was at the discretion of the investigator. Data were prospectively collected on the presence of an infusion pump malfunction during a treatment cycle, as well as start and stop times associated with individual infusions of 5-FU. Adherence to oral capecitabine was assessed by pill counts at the time of patient clinic visits.

NO16966 was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients participating in the study. Approval of the protocol was obtained from an independent ethics committee or the institutional review board of each site.

Patients. The entire NO16966 trial population, including patients treated with bevacizumab or placebo, was used for this evaluation. The safety population includes all randomised patients who received at least one dose of any component of the study regimens. Patients were recruited between July 2003 and February 2005.

Statistical analyses. Analyses were derived from the safety population and included patients with available CVAD data. Patients were grouped into cohorts consisting of the total safety population or subsets, dependent on the specific analyses performed: time to first CVAD placement (in patients with a first placement after treatment start); time from first placement to first replacement (in patients with a first removal); and time from first placement to second replacement (in patients with a second removal).

Incidence rates for each cohort were compared between the XELOX and FOLFOX-4 regimens using the Pearson's χ^2 -test. Median times to each endpoint (\pm s.e.) were estimated using the Kaplan–Meier method, and the distributions were compared using the log-rank test. As the patient cohorts selected could have been subsets of the total safety population, results of statistical tests are provided for descriptive purposes only.

Central venous access device-associated complications and adverse events, along with incidence rates, were summarised in terms of those reported after CVAD placement on the baseline case report form (CRF), and those reported during treatment after CVAD removal/replacement on a treatment cycle-specific CRF. Progression-free survival and overall survival among patients treated with FOLFOX-4 who experienced a pump malfunction during treatment were compared with those who did not using the Kaplan–Meier method. The total number of patients experiencing ≥ 1 grade 3/4 adverse events of relevance to fluoropyrimidine therapy were pooled and compared using the χ^2 -test. Only the highest grade reported per adverse event and patient was included for statistical analyses. Pump malfunction data were recorded for 5-FU infusions only, and therefore relate only to patients treated with FOLFOX-4.

Multivariate logistic regression analyses explored the potential independent association between study treatment (FOLFOX-4 *vs* XELOX) and the risk of CVAD-related adverse events post-implantation/insertion and with respect to the FOLFOX-4 patients alone, the association of pump malfunctions and risk of grade 3/4 adverse events of special interest for fluoropyrimidines/neutropenia.

Cox proportional hazard regression models were performed for progression-free survival and overall survival, and logistic regression analyses were performed for overall response rate.

The additional covariates used in the multivariate logistic and the Cox regression analyses included age (<65 *vs* ≥ 65 years), gender, baseline ECOG performance status (0 *vs* 1/2), number of metastatic sites at baseline (<2 *vs* ≥ 2 organs) and infusion duration (<22 *vs* ≥ 22 h). The hypothesis testing of all covariates was two-sided at $\alpha = 0.025$.

RESULTS

Patient characteristics. The patient baseline demographics for the NO16966 trial has been described previously (Cassidy *et al*, 2008). Patient demographics and disease characteristics of the cohorts used to analyse CVAD-related complications and pump malfunctions were generally comparable both to the overall population of the study and to each other (Supplementary Tables 1 and 2). The disposition of patients and availability of the derived data regarding CVAD placement are outlined in Figure 1.

CVAD placement. Initial CVAD placement data were available for 1341 out of 1998 patients (67%, Table 1). Central venous access devices were placed in 1194 patients (60%) on/before the treatment start date, with 147 (7%) having a CVAD placed after treatment start.

While CVADs were placed on/before the treatment start date in 797 patients receiving FOLFOX-4 and 397 patients receiving

XELOX, placements were performed after treatment start in 91 and 56 patients receiving FOLFOX-4 and XELOX, respectively.

For patients with a first CVAD placement after treatment start, the time to first CVAD placement was shorter in patients receiving FOLFOX-4 compared with those receiving XELOX. The median time to first placement was 13.0 days after treatment start (95% confidence interval (CI): 10–15 days) for patients treated with FOLFOX-4, and 81.0 days after treatment start (95% CI: 60–109 days) for patients treated with XELOX (log-rank test $P < 0.0001$; Figure 2 and Supplementary Table 3).

CVAD removal/replacement. A higher proportion of patients treated with FOLFOX-4 required a CVAD replacement after removal of their first CVAD than those treated with XELOX (125 out of 888 (14.1%) vs 23 out of 453 (5.1%) patients, respectively). Kaplan–Meier survival analyses estimated the median times to replacement to be similar in the analytic cohorts (Figure 3 and Supplementary Table 3). A similar result was observed for the subpopulation of patients with a first replacement

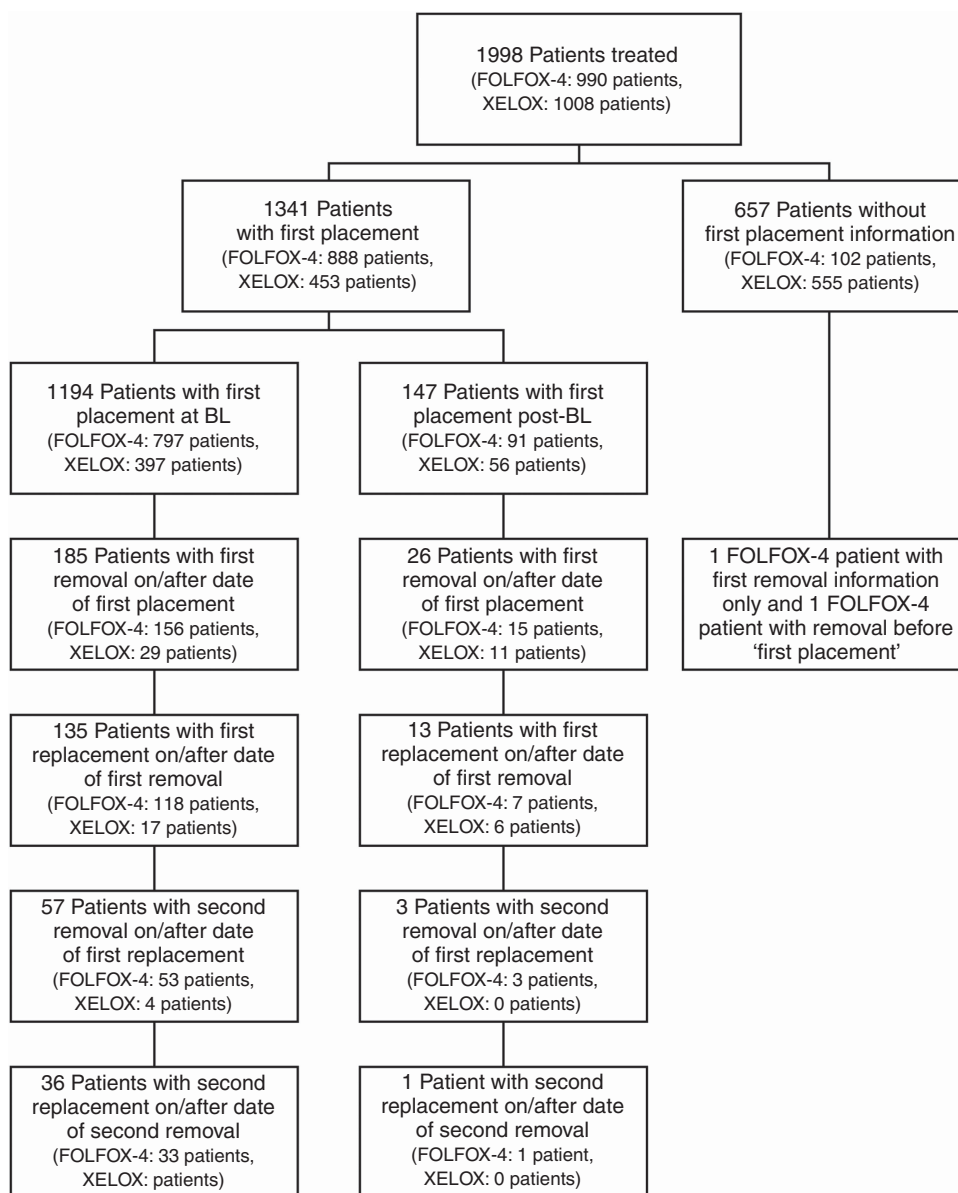


Figure 1. Distribution of patient data. Abbreviations: BL = baseline (placement on/before the start of treatment); Post-BL = post-baseline (placement after the start of treatment).

Table 1. CVAD placement data for patients treated in the NO16966 study (patients in the safety population who had placement data)

Patients, n (%)	FOLFOX-4, n = 888 ^a		XELOX, n = 453 ^a	
	First placement on/before treatment start, n = 797	First placement after treatment start, n = 91	First placement on/before treatment start, n = 397	First placement after treatment start, n = 56
First removal on/after date of first placement ^b	156 (19.6)	15 (16.5)	29 (7.3)	11 (19.6)
First replacement on/after date of first removal ^c	118 (14.8)	7 (7.7)	17 (4.3)	6 (10.7)
Second removal on/after date of first replacement ^d	53 (6.6)	3 (3.3)	4 (1.0)	0 (0)
Second replacement on/after date of second removal ^e	33 (4.1)	1 (1.1)	3 (0.8)	0 (0)

Abbreviations: CVAD = central venous access device; FOLFOX-4 = 5-fluorouracil + oxaliplatin; XELOX = capecitabine + oxaliplatin.

^aPatients with first placement data.

^bRegardless of whether the first placement was on/before or after the treatment start date.

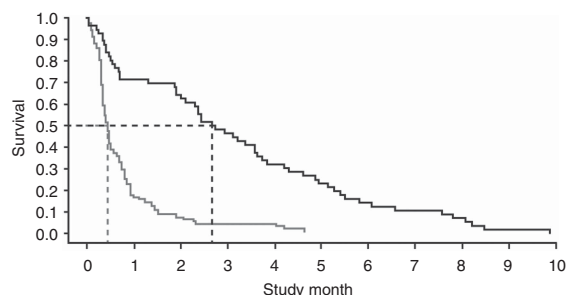
^cPatients with a first removal.

^dPatients with a first replacement.

^ePatients with a second removal.

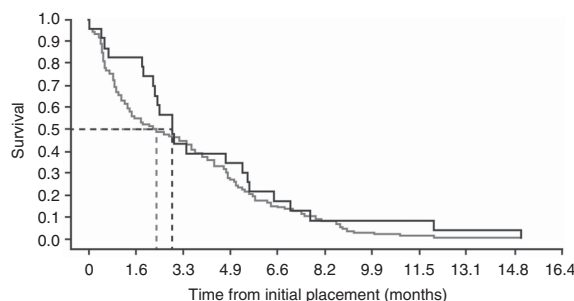
	Median, days (95% CI)	Log-rank test P
FOLFOX-4 ± bevacizumab/placebo	13 (10–15)	< 0.0001
XELOX ± bevacizumab/placebo	81 (60–109)	

	Median, days (95% CI)	Log-rank test P
FOLFOX-4 ± bevacizumab/placebo	70 (43–111)	< 0.0001
XELOX ± bevacizumab/placebo	89 (70–163)	



Number at risk	0	1	2	3	4	5	6	7	8	9	10
FOLFOX-4 ± bevacizumab/placebo	91	15	6	4	4	0	0	0	0	0	0
XELOX ± bevacizumab/placebo	56	40	36	26	18	13	8	6	4	1	0

Figure 2. Kaplan–Meier curve of time to first CVAD placement among patients with first CVAD placements after treatment start, treated with FOLFOX-4 ± bevacizumab/placebo or XELOX ± bevacizumab/placebo (patients in the safety population who had placement data).



Number at risk	0	1.6	3.3	4.9	6.6	8.2	9.9	11.5	13.1	14.8	16.4
FOLFOX-4 ± bevacizumab/placebo	125	69	56	35	18	11	4	2	1	1	0
XELOX ± bevacizumab/placebo	23	19	10	8	4	2	2	2	1	1	0

Figure 3. Kaplan–Meier curve of time from first CVAD placement to first CVAD replacement among patients with first replacement (after first removal), treated with FOLFOX-4 ± bevacizumab/placebo or XELOX ± bevacizumab/placebo (patients in the safety population who had placement data).

after a first removal treated with chemotherapy alone: no significant differences were seen regardless of chemotherapy regimen or use of bevacizumab. Second replacements were uncommon and occurred mainly in patients treated with chemotherapy alone (data not shown).

CVAD-associated complications and adverse events. Adverse events associated with CVAD placement and use were relatively uncommon, and the majority of events were associated with placement. More than 80% of patients with CVAD placements had their first CVAD-related adverse event within 120 days after initial placement (Figure 4). Central venous access device-associated adverse events after initial placement occurred in 138 out of 1998 patients with a baseline placement (6.9%). Catheter/insertion site events were the most frequent events, occurring in 129 out of 1998 patients (6.5%), and were associated with the catheter site in 154

out of 169 (91.1%) of all cases. Common adverse events in this category included pain, haematoma and haemorrhage. Central venous access device-associated adverse events occurred more frequently at baseline placement with FOLFOX-4 compared with XELOX (11.5% vs 2.4%; Table 2). Adverse events associated with CVAD removal or replacement were also more frequent in patients receiving FOLFOX-4 than in those receiving XELOX (8.5% vs 2.1%, respectively; Table 3). The most common adverse events were equally distributed between CVAD site infections and other local complications. These events included central line/site infection, catheter site cellulitis, catheter thrombosis and catheter-related complications that were not otherwise specified. The CVAD-associated adverse event rates for FOLFOX-4 or XELOX plus bevacizumab were similar to those for chemotherapy alone (data not shown). Multivariate logistic regression analyses confirmed that treatment was independently associated with the

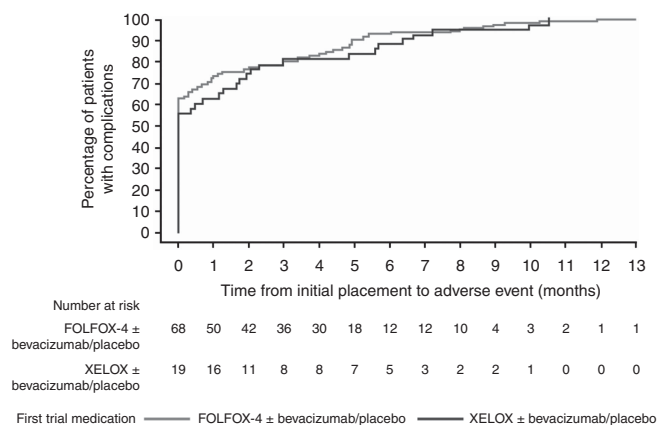


Figure 4. Cumulative incidence of CVAD-related complications (patients in the safety population who had placement data).

Table 2. Adverse events reported after CVAD placement on the baseline CRF page in >0.1% of patients treated with FOLFOX-4 or XELOX (patients in the safety population who had placement data)

Adverse event, n (%)	FOLFOX-4, n = 990	XELOX, n = 1008
Total patients with ≥1 adverse events	114 (11.5)	24 (2.4)
General disorders and administration site conditions	106 (10.7)	23 (2.3)
Catheter site pain	59 (6.0)	14 (1.4)
Catheter site haematoma	34 (3.4)	5 (0.5)
Catheter site haemorrhage	21 (2.1)	2 (0.2)
Catheter site erythema	3 (0.3)	1 (0.1)
Catheter site swelling	2 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	5 (0.5)	1 (0.1)
Pneumothorax	2 (0.2)	1 (0.1)
Injury, poisoning and procedural complications	2 (0.2)	0 (0)
Procedural nausea	2 (0.2)	0 (0)
Nervous system disorders	2 (0.2)	0 (0)
Dizziness	2 (0.2)	0 (0)

Abbreviations: CRF = case report form; CVAD = central venous access device; FOLFOX-4 = 5-fluorouracil + oxaliplatin; XELOX = capecitabine + oxaliplatin.

risk of CVAD-associated complications (odds ratio (OR) 0.23, 97.5% CI: 0.13–0.40, $P < 0.0001$), including general disorders and administration site conditions, for example, catheter thrombosis, catheter-related complications, catheter site pain/inflammation/discharge and pyrexia (OR 0.17, 97.5% CI: 0.07–0.42; $P < 0.0001$).

Pump malfunctions. The study protocol allowed for the use of disposable, single-use pumps or for reusable, programmable pumps for the 5-FU infusion according to investigator’s choice and site preference. The pump type was recorded; however, more detailed information on the manufacturer or model was not collected. Disposable and reusable pumps were used equally across treatment cycles. Pump malfunctions during 5-FU infusion occurred in 16% of patients treated with FOLFOX-4. The malfunction rate was consistent across cycles (1.3–4.9%) and over time (Figure 5). Disposable, single-use pumps malfunctioned more frequently than reusable, programmable pumps.

Among the group of patients experiencing a pump malfunction, the most common issue was related to accelerated delivery of 5-FU,

Table 3. Adverse events reported after CVAD replacement or removal on a treatment cycle CRF page in >0.1% of patients treated with FOLFOX-4 or XELOX (patients in the safety population who had placement data)

Adverse event, n (%)	FOLFOX-4, n = 990	XELOX, n = 1008
Total patients with ≥1 adverse events	84 (8.5)	21 (2.1)
Infections and infestations	42 (4.2)	8 (0.8)
Central line infection	29 (2.9)	4 (0.4)
Infection	5 (0.5)	0 (0)
Catheter site infection	2 (0.2)	1 (0.1)
Catheter site cellulitis	2 (0.2)	0 (0)
Septic shock	2 (0.2)	0 (0)
General disorders and administration site conditions	40 (4.0)	7 (0.7)
Catheter thrombosis	17 (1.7)	3 (0.3)
Catheter-related complication	11 (1.1)	3 (0.3)
Pyrexia	5 (0.5)	0 (0)
Catheter site pain	3 (0.3)	0 (0)
Vascular disorders	3 (0.3)	4 (0.4)
Thrombophlebitis	2 (0.2)	0 (0)
Thrombosis	0 (0)	2 (0.2)

Abbreviations: CRF = case report form; CVAD = central venous access device; FOLFOX-4 = 5-fluorouracil + oxaliplatin; XELOX = capecitabine + oxaliplatin.

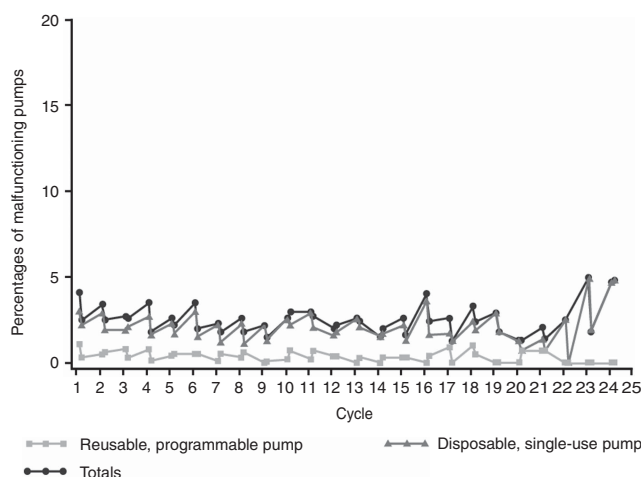


Figure 5. Percentages of pump malfunctions by pump type (safety populations for the FOLFOX-4, FOLFOX-4 + placebo and FOLFOX + bevacizumab groups).

with 61% of patients who experienced a pump malfunction having an infusion duration of <22 h vs 11% of patients without a pump malfunction (Table 4). The majority of patients not experiencing a malfunction (88%) had an infusion duration of 22–24 h, vs 31.8% in patients experiencing a pump malfunction.

The rates of grade 3/4 adverse events specifically related to fluoropyrimidine treatment in patients with FOLFOX-4 who experienced a pump malfunction compared with those who did not are shown in Table 5. Overall, there was a trend towards increased adverse events in patients who experienced a malfunction (97 out of 155 vs 452 out of 825 patients; χ^2 -test; $P = 0.0729$). The incidence of grade 3/4 neutropenia was significantly higher in patients experiencing a malfunction (83 out of 155 (53.5%) vs 328 out of 825 (39.8%) patients, respectively; $P = 0.0009$). Data were

Table 4. Treatment infusion duration for infusions with and without a pump malfunction (safety populations for the FOLFOX-4, FOLFOX-4 + placebo and FOLFOX + bevacizumab groups)

Duration	Malfunction, n = 559 infusions	No malfunction, n = 21 497 infusions
< 12 h, n (%)	22 (3.9)	58 (0.3)
12–14 h, n (%)	1 (0.2)	20 (0.1)
14–16 h, n (%)	4 (0.7)	16 (0.1)
16–18 h, n (%)	35 (6.3)	114 (0.5)
18–20 h, n (%)	96 (17.2)	427 (2.0)
20–22 h, n (%)	183 (32.7)	1800 (8.4)
22–24 h, n (%)	178 (31.8)	18851 (87.7)
24–26 h, n (%)	27 (4.8)	148 (0.7)
> 26 h, n (%)	13 (2.3)	63 (0.3)

Abbreviation: FOLFOX-4 = 5-fluorouracil + oxaliplatin.

Table 5. Grade 3/4 adverse events specifically related to fluoropyrimidine treatment across all cycles of patients treated with FOLFOX-4, based on the presence of a pump malfunction (patients in the safety population who had placement data)

Adverse events, n (%)	Malfunction, n = 155	No malfunction, n = 825
Total patients with ≥ 1 adverse events ^a	107 (69.0)	496 (60.1)
Gastrointestinal disorders ^a	25 (16.1)	157 (19.0)
Diarrhoea ^b	15 (9.7)	103 (12.5)
Nausea ^b	7 (4.5)	38 (4.6)
Vomiting ^b	7 (4.5)	39 (4.7)
Stomatitis (all) ^b	3 (1.9)	20 (2.4)
Blood and lymphatic system disorders ^a	91 (58.7)	361 (43.8)
Neutropenia ^b	83 (53.5)	328 (39.8)
Febrile neutropenia ^b	12 (7.7)	33 (4.0)
Granulocytopenia ^b	1 (0.6)	4 (0.5)
Skin and subcutaneous tissue disorders ^a	2 (1.3)	12 (1.5)
Hand-foot syndrome ^b	2 (1.3)	12 (1.5)
Infections and infestations ^a	0 (0)	6 (0.7)
Neutropenic sepsis ^b	0 (0)	5 (0.6)
Neutropenic infection ^b	0 (0)	1 (0.1)

Abbreviation: FOLFOX-4 = 5-fluorouracil + oxaliplatin.

^aPatients who experienced different adverse events at grade 3 and 4 were counted under the most severe intensity for each adverse event.

^bPatients were counted once under the most severe intensity.

not, however, available to establish whether the episodes of neutropenia occurred during treatment cycles where there was a pump malfunction. Rates of neutropenic sepsis were comparable between the two cohorts as were rates of gastrointestinal side effects. Multivariate logistic analyses, restricted to FOLFOX-4-treated patients (as only they were exposed to a pump), showed that pump malfunction was associated with an increased risk of grade 3/4 neutropenia (OR 1.57, 97.5% CI: 1.03–2.38; $P = 0.00165$) and a numerical trend for increased risk of grade 3/4 adverse events of special interest for fluoropyrimidines such as neutropenia and gastrointestinal effects (OR 1.25, 97.5% CI: 0.82–1.92; $P = 0.2361$).

Clinical efficacy outcomes were similar between patients who experienced a pump malfunction and those who did not; the objective response rate (56.1% vs 48.1%), progression-free survival

(median 284 days vs 252 days) and overall survival (median 683 days vs 583 days) parameters were comparable between groups. There was no evidence to suggest a detrimental effect of pump malfunction on efficacy outcomes, as assessed by multivariate Cox proportional hazards analyses of progression-free survival and overall survival, and multivariate logistic regression analyses of overall response rate.

Capecitabine compliance. Patients treated with oral capecitabine showed high levels of adherence, as assessed by pill counts at the end of each treatment cycle. The median adherence ratio (pills taken vs planned; 1.00 indicated perfect adherence) was 1.00 (perfect adherence) across analytical cohorts: XELOX = 1.00 (range 0.70–4.67), XELOX plus placebo = 1.00 (0.30–3.00) and XELOX plus bevacizumab = 1.00 (0.71–13.94).

DISCUSSION

The NO16966 trial is the largest patient population from a randomised phase III clinical study to provide data regarding the use of CVADs. Based on this study, it is clear that CVAD-associated complications, the requirement for CVAD replacement and the occurrence of pump malfunctions during treatment were common. Of note, patients treated with XELOX \pm bevacizumab/placebo required fewer subsequent replacements and experienced fewer CVAD-associated adverse events than those treated with FOLFOX-4 \pm bevacizumab/placebo. As such, differences in CVAD-associated complication rates between patients treated with FOLFOX-4 plus bevacizumab or XELOX plus bevacizumab appear to result from the continued repeated use of infusional 5-FU associated with the FOLFOX-4 regimen.

Thrombosis and infections are well-known complications of CVADs. However, in the NO16966 study, we observed lower or comparable rates of thrombosis compared with 1–18% in several other studies involving CVADs (where patients did not receive prophylaxis against thrombosis) (Verso *et al*, 2005; Karthaus *et al*, 2006; Fagnani *et al*, 2007; Ng *et al*, 2007; Araújo *et al*, 2008; Surov *et al*, 2008; Biffi *et al*, 2009; Starling *et al*, 2009; Beckers *et al*, 2010; Cavanna *et al*, 2010; Barbetakis *et al*, 2011; Kriegl *et al*, 2011; Saber *et al*, 2011). We also observed lower or comparable rates of infection than the 2.4–58.3% previously reported rates (Karthaus *et al*, 2006; Fagnani *et al*, 2007; Ng *et al*, 2007; Beckers *et al*, 2010; Cavanna *et al*, 2010; Barbetakis *et al*, 2011), although even lower infection rates of 0.4–2.5% have also been reported in some studies (Araújo *et al*, 2008; Biffi *et al*, 2009). Consistent with our findings, adverse events have been reported to occur relatively early following CVAD placement (Fagnani *et al*, 2007; Inaba *et al*, 2007; Ng *et al*, 2007; Cavanna *et al*, 2010; Saber *et al*, 2011). In the INT-0153 study (Poplin *et al*, 2005), catheter-related complications and pump issues (logistics and malfunctions) may have adversely impacted the delivery of CIFU, and the authors speculated that this may, in part, explain why CIFU did not improve clinical outcomes when compared with bolus 5-FU.

Pump malfunctions during FOLFOX-4 treatment were relatively common in NO16966 and occurred in a relatively high proportion of patients (16%), with malfunctions reported in 1.3–4.9% of patients across treatment cycles. The majority of malfunctions were observed for disposable pumps; however, programmable pump malfunctions constituted ~20% of the total malfunctioning pumps. Shorter infusion times were associated with malfunctions in approximately two-thirds of infusions. Fluoropyrimidine-induced cytotoxicity is known to be both dose- and schedule-dependent (The Meta-Analysis Group In Cancer, 1998; Lamont and Schilsky, 1999). These pharmacological properties raised questions regarding the potential association of altered drug delivery by pump malfunctions and risk for

adverse events as well as efficacy outcomes. Increased rates of grade 3/4 adverse events specifically related to fluoropyrimidines (predominantly neutropenia) were observed in patients who experienced a pump malfunction. Nevertheless, clinical efficacy outcomes appeared to be comparable regardless of malfunction.

The strength of the present analysis comes from the fact that the NO16966 trial included the largest patient population, to date, that provided data on the use of CVADs in mCRC. However, one of the main limitations of this analysis relates to the fact that information on the specific types of catheters used was not collected. Presumably, the catheter type/insertion for both regimens was based on local standards of care, and as a result, the specific type of catheter may have impacted on the subsequent incidence of adverse events. However, it should be noted that the overall incidence and pattern of onset of adverse events were comparable to those previously reported in the literature. Another potential limitation of our analysis was that CVAD-associated adverse events were only reported during the study treatment period. These events were only recorded during placement and/or removal/replacement of CVADs using the specific CRF, and events were tracked only during the study treatment period. All other events were collected together regardless of whether they were caused by a CVAD, underlying cancer clinical state, study treatment regimens or other reasons. The other potential reasons for CVAD-associated adverse events were tracked using general adverse event CRFs throughout the study treatment period and for an additional 4 weeks after discontinuation of study treatment. Of note, the rate of hand-foot syndrome was similar in both arms.

Treatment with the oral fluoropyrimidine, capecitabine, effectively avoids many of the resource issues associated with CVADs. A medical resource utilisation companion study to the NO16966 trial showed that the number of drug administration visits and CVADs placed was reduced with XELOX vs FOLFOX-4, despite the addition of intravenous oxaliplatin and bevacizumab (Scheithauer *et al*, 2007). A separate United States cost minimisation analysis of NO16966 reported that the total estimated direct costs for XELOX without bevacizumab were \$1300 less than for FOLFOX-4 without bevacizumab, and \$3100 less for XELOX with bevacizumab than FOLFOX-4 with bevacizumab. The estimated indirect costs for XELOX were \$1500–\$1700 less than for FOLFOX (Garrison *et al*, 2007). Similarly, a cost minimisation analysis of XELOX vs FOLFOX-6 showed that XELOX is associated with significantly reduced mean disease management costs compared with FOLFOX-6 (€12918 vs €17226; $P < 0.001$). Patients treated with XELOX also spend less time at the hospital than patients treated with FOLFOX-6 (Conroy *et al*, 2010; Perrocheau *et al*, 2010). A review of 4973 patients in the Thomson Healthcare MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases showed that capecitabine-based therapy was associated with fewer complications than 5-FU-based therapy (Chu *et al*, 2009). As a result, the mean predicted monthly cost of complications associated with 5-FU plus oxaliplatin was higher than that of those associated with XELOX (difference = \$1165, 95% CI: \$892–\$1595). Notably, no difference in total costs were observed when drug acquisition, administration and complication costs were combined (Chu *et al*, 2009).

In summary, this study provides additional insights regarding the frequency and nature of CVAD-associated complications that occur during the front-line treatment of patients with mCRC. Our analysis shows that regimens based on an oral fluoropyrimidine (e.g., XELOX) are preferable to infusional 5-FU (e.g., FOLFOX-4) for the treatment of mCRC in the front-line setting with regard to CVAD-associated complications, the need for CVAD replacement, pump malfunctions and CVAD-associated adverse events, all of which adversely impact upon patient well being. These findings also have potentially important implications with respect to adjuvant chemotherapy. The majority (80%) of CVAD-associated

adverse events occurred within 120 days of treatment initiation, which is well within the usual 6-month duration of adjuvant chemotherapy. Adjuvant therapy is given with curative intent, but in reality, many patients are already cured by surgery and others relapse despite adjuvant therapy. Only a relatively small proportion of patients, therefore, directly benefit from adjuvant treatment. For this reason, any risk of potentially serious complications should be minimised. Thus, in this setting, oral fluoropyrimidine-based chemotherapy with either the XELOX regimen or capecitabine monotherapy may be a preferred treatment option when compared with FOLFOX-4 or other infusional 5-FU regimens.

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REFERENCES

- Araújo C, Silva JP, Antunes P, Fernandes JM, Dias C, Pereira H, Dias T, Fougo JL (2008) A comparative study between two central veins for the introduction of totally implantable venous access devices in 1201 cancer patients. *Eur J Surg Oncol* **34**(2): 222–226.
- Barbetakis N, Asteriou C, Kleontas A, Tsilikas C (2011) Totally implantable central venous access ports. Analysis of 700 cases. *J Surg Oncol* **104**(6): 654–656.
- Beckers MM, Ruven HJ, Seldenrijk CA, Prins MH, Biesma DH (2010) Risk of thrombosis and infections of central venous catheters and totally implanted access ports in patients treated for cancer. *Thromb Res* **125**(4): 318–321.
- Biffi R, Orsi F, Pozzi S, Pace U, Bonomo G, Monfardini L, Della Vigna P, Rotmensz N, Radice D, Zampino MG, Fazio N, de Braud F, Andreoni B, Goldhirsch A (2009) Best choice of central venous insertion site for the prevention of catheter-related complications in adult patients who need cancer therapy: a randomized trial. *Ann Oncol* **20**(5): 935–940.
- Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figuer A, Wong R, Koski S, Lichinitser M, Yang T-S, Rivera F, Couture F, Sirzén F, Saltz L (2008) Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* **26**(12): 2006–2012.
- Cavanna L, Civardi G, Vallisa D, Di Nunzio C, Cappucciati L, Bertè R, Cordani MR, Lazzaro A, Cremona G, Biasini C, Muroli M, Mordenti P, Gorgni S, Zaffignani E, Ambroggi M, Bidin L, Palladino MA, Rodinò C, Tibaldi L (2010) Ultrasound-guided central venous catheterization in cancer patients improves the success rate of cannulation and reduces mechanical complications: a prospective observational study of 1,978 consecutive catheterizations. *World J Surg Oncol* **8**: 91.
- Chu E, Schulman KL, Zelt S, Song X (2009) Costs associated with complications are lower with capecitabine than with 5-fluorouracil in patients with colorectal cancer. *Cancer* **115**(7): 1412–1423.
- Conroy T, Hebbar M, Bennouna J, Ducreux M, Ychou M, Llèdo G, Adenis A, Faroux R, Rebischung C, Kockler L, Douillard JY (2010) Quality-of-life findings from a randomised phase-III study of XELOX vs FOLFOX-6 in metastatic colorectal cancer. *Br J Cancer* **102**(1): 59–67.
- Debourdeau P, Kassab Chahmi D, Le Gal G, Kriegl I, Desruennes E, Douard M-C, Elalamy I, Meyer G, Mismetti P, Pavic M, Scrobhaci ML, Lévesque H, Renaudin JM, Farge D (2009) 2008 SOR guidelines for the prevention and treatment of thrombosis associated with central venous catheters in patients with cancer: report from the working group. *Ann Oncol* **20**(9): 1459–1471.
- Fagnani D, Franchi R, Porta C, Pugliese P, Borgonovo K, Bertolini A, Duro M, Ardizzoia A, Filipazzi V, Isa L, Vergani C, Milani M, Cimminiello C. POLONORD Group (2007) Thrombosis-related complications and mortality in cancer patients with central venous devices: an observational study on the effect of antithrombotic prophylaxis. *Ann Oncol* **18**(3): 551–555.
- Gann Jr M, Sardi A (2003) Improved results using ultrasound guidance for central venous access. *Am Surg* **69**(12): 1104–1107.

- Garrison L, Cassidy J, Saleh M, Lee F, Mena R, Fuloria J, Chang V, Ervin T, Stella P, Saltz L (2007) Cost comparison of XELOX compared to FOLFOX4 with or without bevacizumab (bev) in metastatic colorectal cancer. *J Clin Oncol* **25**(18S): Abstract 4074.
- Inaba Y, Yamaura H, Sato Y, Najima M, Shimamoto H, Nishiofuku H, Ura T, Muro K (2007) Central venous access port-related complications in outpatient chemotherapy for colorectal cancer. *Jpn J Clin Oncol* **37**(12): 951–954.
- Karthauss M, Kretzschmar A, Kröning H, Biakhov M, Irwin D, Marschner N, Slabber C, Fountzilias G, Garin A, Abecasis NG, Baronius W, Steger GG, Südhoff T, Giorgetti C, Reichardt P (2006) Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. *Ann Oncol* **17**(2): 289–296.
- Kawamura J, Nagayama S, Nomura A, Itami A, Okabe H, Sato S, Watanabe G, Sakai Y (2008) Long-term outcomes of peripheral arm ports implanted in patients with colorectal cancer. *Int J Clin Oncol* **13**(4): 349–354.
- Kriegel I, Cottu PH, Fourchotte V, Sanchez S, Fromantin I, Kirov K, Guillaume A, Pelloquin A, Esteve M, Salmon RJ (2011) Wound healing and catheter thrombosis after implantable venous access device placement in 266 breast cancers treated with bevacizumab therapy. *Anticancer Drugs* **22**(10): 1020–1023.
- Lamont EB, Schilsky RL (1999) The oral fluoropyrimidines in cancer chemotherapy. *Clin Cancer Res* **5**(9): 2289–2296.
- Martoni AA, Pinto C, Di Fabio F, Lelli G, Rojas Llimpe FL, Gentile AL, Mutri V, Ballardini P, Giaquinta S, Piana E (2006) Capecitabine plus oxaliplatin (xelox) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (pvifox) as first-line treatment in advanced colorectal cancer: a GOAM phase II randomised study (FOCA trial). *Eur J Cancer* **42**(18): 3161–3168.
- McGee DC, Gould MK (2003) Preventing complications of central venous catheterization. *N Engl J Med* **348**(12): 1123–1133.
- National Cancer Institute (2006) Common Terminology Criteria for Adverse Events v3.0 (CTCAE).
- NCCN (2013) NCCN Clinical Practice Guidelines in Oncology. *Colon Cancer*. Version 1.2014, p MS-23.
- Ng F, Mastorouides H, Paul E, Davies N, Tibballs J, Hochhauser D, Mayer A, Begent R, Meyer T (2007) A comparison of Hickman line- and Port-a-Cath-associated complications in patients with solid tumours undergoing chemotherapy. *Clin Oncol (R Coll Radiol)* **19**(7): 551–556.
- Perrocheau G, Bennouna J, Ducreux M, Hebbar M, Ychou M, Lledo G, Conroy T, Dominguez S, Faroux R, Florentin V, Douillard JY (2010) Cost-minimisation analysis in first-line treatment of metastatic colorectal cancer in France: XELOX versus FOLFOX-6. *Oncology* **79**(3–4): 174–180.
- Poplin EA, Benedetti JK, Estes NC, Haller DG, Mayer RJ, Goldberg RM, Weiss GR, Rivkin SE, Macdonald JS (2005) Phase III Southwest Oncology Group 9415/Intergroup 0153 randomized trial of fluorouracil, leucovorin, and levamisole versus fluorouracil continuous infusion and levamisole for adjuvant treatment of stage III and high-risk stage II colon cancer. *J Clin Oncol* **23**(9): 1819–1825.
- Saber W, Moua T, Williams EC, Verso M, Agnelli G, Couban S, Young A, De Cicco M, Biffi R, van Rooden CJ, Huisman MV, Fagnani D, Cimminiello C, Moia M, Magagnoli M, Povoski SP, Malak SF, Lee AY (2011) Risk factors for catheter-related thrombosis (CRT) in cancer patients: a patient-level data (IPD) meta-analysis of clinical trials and prospective studies. *J Thromb Haemost* **9**(2): 312–319.
- Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figuer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J (2007) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. *J Clin Oncol* **26**(12): 2013–2019.
- Scheithauer W, Cassidy J, Figuer A, Wong R, Koski S, Lichinitser M, Yang T, Clarke S, Díaz-Rubio E, Garrison LP (2007) A comparison of medical resource use for 4 chemotherapy regimens as first-line treatment for metastatic colorectal cancer (MCRC): XELOX vs. FOLFOX4 ± bevacizumab (A). *J Clin Oncol* **25**(18S): Abstract 4098.
- Shen-Gunther J, Mannel RS, Walker JL, Gold MA, Johnson GA (2003) Outpatient implantation of a central venous access system in gynecologic oncology patients. *J Reprod Med* **48**(11): 875–881.
- Starling N, Rao S, Cunningham D, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR (2009) Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. *J Clin Oncol* **27**(23): 3789–3793.
- Surov A, Jordan K, Buerke M, Arnold D, John E, Spielmann RP, Behrmann C (2008) Port catheter insufficiency: incidence and clinical-radiological correlations. *Onkologie* **31**(8–9): 455–461.
- The Meta-Analysis Group In Cancer (1998) Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. *J Clin Oncol* **16**: 3537–3541.
- Van Cutsem E, Nordlinger B, Cervantes A (2010) Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Ann Oncol* **21**(Suppl 5): v93–v97.
- Verso M, Agnelli G, Bertoglio S, Di Somma FC, Paoletti F, Ageno W, Bazzan M, Parise P, Quintavalla R, Naglieri E, Santoro A, Imberti D, Sorarù M, Mosca S (2005) Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. *J Clin Oncol* **23**(18): 4057–4062.
- Xiang DZ, Verbeken EK, Van Lommel AT, Stas M, De Wever I (1998) Composition and formation of the sleeve enveloping a central venous catheter. *J Vasc Surg* **28**(2): 260–271.

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