Bevacizumab in Addition to Palliative Chemotherapy for Patients With Peritoneal Carcinomatosis of Colorectal Origin: A Nationwide Population-Based Study

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Abstract

Data on the use and effect of bevacizumab, in addition to palliative chemotherapy, are currently lacking for patients with colorectal cancer presenting with peritoneal carcinomatosis (PC). The present study involved 1235 patients with colorectal PC receiving only palliative systemic therapy. Bevacizumab was prescribed to 436 patients (35%) and was associated with an improved median overall survival (11 months).

Background: Most patients with colorectal cancer (CRC) presenting with peritoneal carcinomatosis (PC) rely on palliative systemic treatment options. However, data on the use and effect of systemic treatment strategies, including targeted agents for the palliative treatment of colorectal PC, are lacking. We conducted a nationwide population-based study with data from the period in which the targeted agent bevacizumab was introduced in the Netherlands. **Patients and Methods:** The present study included all patients diagnosed from 2007 to 2014 with synchronous PC from CRC treated with only palliative systemic therapy. We assessed the use of bevacizumab, the standard choice of targeted treatment, in addition to first-line chemotherapy. Multivariable logistic regression analyses were performed to calculate the predictors for the additional prescription of bevacizumab. Survival estimates were calculated, and multivariable Cox analyses were performed to estimate the hazard ratios (HRs) of death stratified by the treatment received. **Results:** A total of 1235 patients received palliative chemotherapy, of whom 436 also received bevacizumab (35%). Patients aged $\geq$ 75 years and patients with PC from colonic tumors were less likely to receive chemotherapy plus bevacizumab. The addition of bevacizumab to palliative chemotherapy was associated with an improved overall median survival of 7.5 versus 11 months in both patients with isolated PC and those with concomitant extraperitoneal metastases. The improvement remained after adjustment for patient and tumor characteristics (HR, 0.7; 95% confidence interval, 0.64-0.83). **Conclusion:** The results of the present nationwide population-based study support the rationale for bevacizumab in addition to palliative chemotherapy for patients with PC of CRC and underline the need for ongoing efforts to precisely determine the role of targeted therapy in the treatment of PC.

Clinical Colorectal Cancer, Vol. 15, No. 2, e41-6 © 2015 Elsevier Inc. All rights reserved.
Keywords: Colorectal cancer, Palliative systemic therapy, Peritoneal metastases, Synchronous, Targeted therapy

Introduction

At the initial diagnosis, almost one fourth of all patients with colorectal cancer (CRC) will present with disseminated disease, with the liver and peritoneum the most frequently affected sites.[1,2] However, in the past 2 decades, substantial progress has occurred in the systemic treatment of metastatic CRC. The development of chemotherapeutic regimens combining 5-fluorouracil and oxaliplatin or irinotecan and the introduction of targeted agents such as

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Submitted: Jul 21, 2015; Revised: Nov 27, 2015; Accepted: Dec 9, 2015; Epub: Dec 17, 2015

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http://dx.doi.org/10.1016/j.clcc.2015.12.006

bevacizumab has improved the prognosis of patients with stage IV CRC remarkably, defining the backbone of current systemic therapy.[3-8]

Nevertheless, very little is known about the efficacy of these systemic regimens, including targeted therapy, in the subset of patients with CRC and peritoneal carcinomatosis (PC), a frequently encountered metastatic site with an invariably fatal prognosis.[9,10] Despite the development of potentially curative locoregional treatment modalities for a selected group of patients with PC, most of these patients remain dependent on palliative systemic treatment options. Therefore, the aim of the present nationwide population-based study was to provide data on the usage and effect of targeted therapy in addition to chemotherapy for the palliative treatment of patients with synchronous PC of colorectal origin.

Patients and Methods

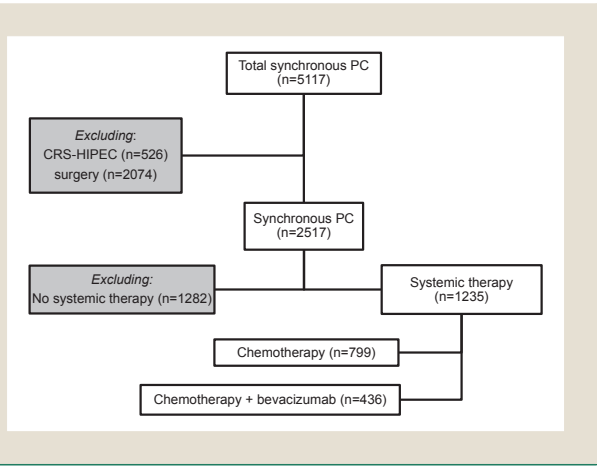
Patient Data

The Netherlands Cancer Registry (NCR) collects data for all patients with newly diagnosed cancer in the Netherlands, covering the entire Dutch population of approximately 16 million inhabitants. The NCR comprises 9 administrational regions, each covering 7 to 20 hospitals. These regions form a network of health care professionals and institutions for cancer care and palliative care in the Netherlands. Pathologists enter histopathologic and cytopathologic reports of all diagnosed cancers in the nationwide Dutch Pathology Network, which subsequently submits the data to the NCR. Specially trained registry staff collect the data on patient and tumor characteristics from the medical records using the registration and coding manual of the NCR. In this registration system, the classification of the primary tumor is determined by the TNM classification.[11] In the case of missing pathologic data, the clinical TNM stage is used. Synchronous metastases were defined as metastases diagnosed within 3 months after the initial CRC diagnosis and were registered according to the International Classification of Disease for Oncology.[12] Data on the location of distant metastases were available and complete for approximately 95% of all patients with metastasized disease since 2007 and from 2008 on were nearly complete for all the patients.

The data for all patients diagnosed from 2007 to 2014 with synchronous PC from CRC were extracted from the nationwide database (n = 5117). The present study focused on patients receiving only systemic therapy with palliative intent. Thus, patients treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) were excluded (CRS-HIPEC, n = 526). Moreover, patients undergoing primary surgery (local tumor resection, metastasectomy, debulking, n = 2074) or palliative treatment without systemic therapy (n = 1282) were also excluded from the present study, for a study population of 1235 patients with PC receiving only palliative systemic therapy (Figure 1).

In accordance with the Dutch national treatment guidelines, oxaliplatin-containing chemotherapy (eg, capecitabine/oxaliplatin [CAPOX] or folinic acid, 5-fluorouracil, oxaliplatin [FOLFOX]) has been recommended as the standard combination treatment for patients with stage IV CRC since 2001. In contrast, historically, patients received standard first-line monotherapy with a fluoropyrimidine (5-fluorouracil or capecitabine).[13]

Figure 1 An Overview of the Patients Diagnosed With Synchronous Peritoneal Carcinomatosis (PC) From Colorectal Cancer (CRC) From 2007 to 2014 in the Netherlands



Abbreviation: CRS-HIPEC = cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Both systemic chemotherapy and targeted therapy were registered (yes vs. no) ≤ 6 to 9 months after the initial diagnosis in the NCR. In the present study, bevacizumab was the standard targeted therapy in addition to first-line chemotherapy.[14,15]

Statistical Analysis

The number of patients with colorectal PC treated with palliative chemotherapy and the proportion of patients also receiving bevacizumab were calculated. The variation in the prescription of bevacizumab among the 9 administrative regions of the NCR was assessed and tested using a χ^2 test. The factors associated with the probability of receiving bevacizumab in addition to palliative chemotherapy were investigated by multivariable logistic regression analysis adjusted for age, gender, year of diagnosis, primary tumor localization, histologic subtype, differentiation grade, T and N stage, and radiotherapy. In addition, survival estimates of the patients with PC stratified by treatment received (palliative chemotherapy with or without bevacizumab) were calculated using the Kaplan-Meier method, and the proportions were compared using the log-rank test. Survival was defined as the time from the diagnosis of CRC until death, and patients lost to follow-up or still alive January 1, 2015 were censored. The median survival is presented with the 95% confidence intervals (CIs). Multivariable Cox proportional hazards regression analyses were also performed to investigate the independent prognostic effect of the addition of bevacizumab in patients with PC. Adjustments were made for the relevant patient and tumor characteristics. Survival analyses were performed in both the total study population of patients with PC and after stratification for the presence of concomitant extraperitoneal metastases. SAS/STAT statistical software (SAS system, version 9.3; SAS Institute, Cary, NC) was used for all analyses.

Results

A total of 1235 patients with synchronous PC from CRC treated with palliative systemic therapy were enrolled in the present study. Of the 1235 patients, 712 were men (58%) and 523 were women

(42%), with a median age of 65 years (minimum, 21 years; maximum, 91 years). Concomitant metastases were present in 851 patients (69%). Most of the concomitant metastases were located in the liver (77%). Pulmonary metastases and lymph node metastases were present in 188 patients (22%) and 159 patients (19%), respectively. Liver metastases were the only site of extraperitoneal disease in 433 patients (50%).

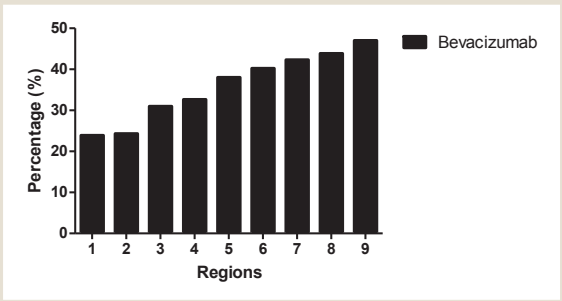
Palliative Systemic Treatment

All 1235 patients with PC received palliative chemotherapy. Bevacizumab was added to palliative chemotherapy for 436 patients (35%), with an interregional variation of 24% to 47% ($P < .0001$; Figure 2). The patients receiving palliative chemotherapy plus bevacizumab were younger than the patients receiving chemotherapy without this antivascular agent ($P < .0001$; Table 1). This was confirmed by the multivariable logistic regression analysis, which revealed that the likelihood of receiving bevacizumab in addition to palliative chemotherapy was influenced by patient age (Table 2). Elderly patients (aged $\geq$ 75 years) were less likely to receive bevacizumab than were patients aged 60 to 75 years (odds ratio [OR], 0.4; 95% CI, 0.29-0.61). Moreover, patients with primary signet ring cell carcinoma were less likely to receive additional bevacizumab than were patients with PC from adenocarcinoma (OR, 0.5; 95% CI, 0.32-0.89) or patients with colon cancer compared with those with rectal cancer (OR, 0.6; 95% CI, 0.46-0.93). Within colonic primary tumor localization, no differences were observed between right-sided and left-sided tumors (OR, 1.0; 95% CI, 0.72-1.52). Finally, it was observed that the likelihood of an additional bevacizumab prescription was lower for irradiated PC patients (OR, 0.5; 95% CI, 0.26-0.98).

Overall Survival

The addition of bevacizumab to palliative chemotherapy was associated with improved median overall survival, from 7.4 months (95% CI, 6.83-8.24 months) to 11.0 months (95% CI, 9.79-12.09 months; Figure 3). Similar results were observed after stratification for the presence of extraperitoneal metastases. The median survival improved from approximately 7.5 to 11 months with the additional prescription of targeted therapy in both patients with isolated PC ($P < .05$) and patients with concomitant extraperitoneal metastases ($P < .0001$). On multivariable Cox regression analysis with adjustment for relevant prognostic factors, the addition of bevacizumab to palliative chemotherapy was associated with a decreased risk of death (HR, 0.7; 95% CI, 0.64-0.83).

Figure 2 Prescription of Bevacizumab in Addition to Palliative Chemotherapy in the Netherlands, According to Region (n = 1235)



Discussion

In the present nationwide population-based study, we have demonstrated the use and potential effect of bevacizumab, in addition to palliative chemotherapy, in a selected group of patients with colorectal PC who did not meet the criteria for potentially curative treatment procedures.

In the past decade, remarkable progress has been achieved in the systemic treatment of metastatic CRC (mCRC).[13,14] In 2001, oxaliplatin was registered in the Netherlands and recommended as a first-line cytostatic agent in combination chemotherapy for stage IV CRC. In addition, bevacizumab was registered in 2005 for the first-line treatment of mCRC in the Netherlands. Bevacizumab targets the vascular endothelial growth factor (VEGF), which is the most important angiogenic factor. Metastasis formation and growth depends on the presence of sufficient oxygen, which is supplied by the formation of new blood vessels (angiogenesis). High levels of VEGF have been associated with metastases in CRC. Moreover, VEGF has been shown to play a role in peritoneal metastases and prognosis.[16,17] Blocking VEGF could reduce ascites formation and progression. For patients with peritoneal metastases, however, the effect of systemic regimens, including targeted therapy, remains uncertain. Radiographic imaging of peritoneal tumor deposits is difficult, limiting the available evidence on this topic. In addition, the hypothesis that PC should be regarded as locoregional, rather than the systemic spread of, disease caused a shift in clinical attention from systemic toward locoregional treatment modalities combining CRS and HIPEC. Various large case studies have demonstrated that this treatment can now be offered successfully, with 5-year survival rates of > 30%.[18-20] However, only selected patients with PC will be likely to benefit from this invasive treatment procedure.[20,21] Thus, most patients with colorectal PC will depend on palliative systemic treatment strategies.

To the best of our knowledge, this is the first nationwide population-based study describing the potential role of bevacizumab in the palliative treatment of colorectal PC. In view of the nationwide character of the present study, the number of patients with colorectal PC receiving this antivascular agent was substantial (n = 436). Bevacizumab was prescribed as a part of palliative systemic therapy to 35% of the patients with PC diagnosed and treated after 2007. Large interregional variations were observed in the prescription of this tumor targeting agent, reflecting the differences in policy toward the use of this novel tumor targeting therapy for the treatment of colorectal PC among the administrational regions in the Netherlands. Also, we observed that elderly patients were less likely to receive bevacizumab in addition to palliative chemotherapy. Older age has been described as one of the most important factors in refraining systemic chemotherapy, especially combination chemotherapy.[22-24] However, it has been shown that it is feasible to treat older patients with chemotherapy, even in the presence of widespread peritoneal disease combined with distant metastases.[25-27] In addition, several recent studies have suggested that age itself is not a contraindication to targeted therapy, because bevacizumab, the

Table 1 Clinicopathologic Patient Characteristics Stratified by Palliative Systemic Treatment (n = 1235)

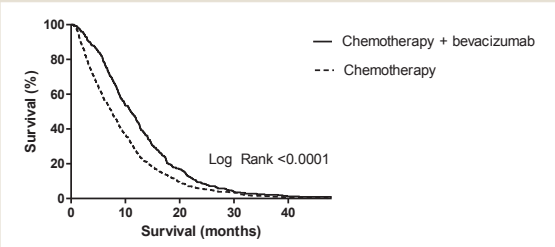
Characteristic	Chemotherapy + Bevacizumab (n = 436)	Chemotherapy Alone (n = 799)	*P* Value
Gender			.66
Male	255 (58)	457 (57)	
Female	181 (42)	342 (43)	
Age (years)			<.0001
<60	139 (32)	190 (24)	
60-75	246 (56)	413 (52)	
≥75	51 (12)	196 (24)	
Tumor localization			<.01
Rectum	86 (20)	115 (14)	
Colon	350 (80)	684 (86)	
Histologic subtype			.23
Adenocarcinoma	329 (75)	564 (71)	
Mucinous carcinoma	71 (16)	144 (18)	
Signet ring cell carcinoma	25 (6)	67 (8)	
Other	11 (3)	24 (3)	
Tumor grade			.73
Well/moderate	72 (17)	138 (15)	
Poor/undifferentiated	71 (15)	117 (16)	
Unknown	293 (68)	544 (70)	
Extent of metastases			.06
PC only	121 (28)	263 (33)	
PC other	315 (72)	536 (67)	
Radiotherapy	15 (3)	39 (5)	.24

Data presented as n (%).
Abbreviations: PC only = isolated peritoneal carcinomatosis; PC other = peritoneal carcinomatosis with concomitant extraperitoneal metastases.

standard recommended target agent in mCRC, is generally well-tolerated.[28-30] Finally, we observed that the prescription of bevacizumab was less likely for patients with colon cancer than for patients with rectal cancer. We cannot explain this difference. It might have been related to tumor or host factors for which we could not control in our analyses, such as the metastatic tumor load within organs or differences in comorbidity patterns.

In the present study, the addition of bevacizumab to palliative chemotherapy was associated with a significant increase in the median overall survival of 3.5 months (from 7.5 to 11 months), in both patients with isolated PC and patients with concomitant extraperitoneal metastases (mostly liver metastases). In patients with stage IV CRC, the addition of bevacizumab has been shown to improve median progression-free survival with approximately 4 months as first-line treatment.[7,31-33] However, most of these studies did not show an improvement in overall survival with the additional use of bevacizumab.[7,29,34] We hypothesized that in these studies, patients assigned to not receive bevacizumab as first-line treatment could have received bevacizumab in further treatment lines. However, patients with PC, such as described in our study, are unlikely to receive multiple lines of systemic treatment owing to the notorious prognosis of PC. Therefore, the gain in progression-free survival with bevacizumab can be translated into an overall survival benefit for these patients.

Figure 3 Overall Survival of Patients With Synchronous Peritoneal Carcinomatosis From Colorectal Origin According to Treatment Received (n = 1235)



Evidence on the potential role of targeting agents in the subset of patients with CRC presenting with PC is scarce and still debatable. Data have been derived from a few small studies that did not present stratified findings according to the presence of concomitant extraperitoneal metastases. In a study by Klaver et al[35] of 22 patients with PC, the median overall survival improved from 10.1 months to 18.2 months with the addition of targeted agents. In 2 other small studies, median survival rates of 15 and 23 months, respectively, were observed with addition of targeted therapy, mostly

Table 2 Multivariable Logistic Regression Analysis Modeling the Odds for Bevacizumab in Addition to Palliative Chemotherapy

Variable	Patients Receiving Bevacizumab (%)	OR	95% CI
Gender			
Male	36	Reference	
Female	35	1.0	0.80-1.32
Age (years)			
<60	42	1.2	0.94-1.63
60-75	37	Reference	
≥75	21	0.4	0.29-0.61[a]
Tumor localization			
Rectum	43	Reference	
Colon	34	0.6	0.46-0.93[a]
Histologic subtype			
Adenocarcinoma	37	Reference	
Mucinous carcinoma	33	0.9	0.62-1.22
Signet ring cell carcinoma	27	0.5	0.32-0.89[a]
Other	31	0.8	0.37-1.68
Tumor grade			
Well/moderate	34	Reference	
Poor/undifferentiated	38	1.2	0.77-1.85
Unknown	35	1.0	0.74-1.45
Extent of metastases			
PC only	32	Reference	
PC other	37	1.2	0.94-1.62
Radiotherapy			
No	36	Reference	
Yes	28	0.5	0.26-0.98[a]

Analysis was also adjusted for year of diagnosis and T and N stage.
Abbreviations: CI = confidence interval; OR = odds ratio; PC only = isolated peritoneal carcinomatosis; PC other = peritoneal carcinomatosis with concomitant extraperitoneal metastases.
[a]Statistically significant.

bevacizumab.[36,37] In contrast to these survival rates, the outcomes described in our nationwide study were dismal, probably reflecting differences in patient selection. In our study, patients eligible for CRS-HIPEC and surgical procedures were excluded, resulting in the selection of patients with PC with unfavorable prognostic characteristics. Moreover, the peritoneal tumor burden was expected to be extensive in our study population, because the patients were diagnosed in a nonoperative setting either clinically or from radiographic imaging, both inaccurate techniques for the early detection of PC. An extensive peritoneal tumor burden often coincides with physical complaints such as abdominal discomfort, nausea, loss of appetite, diarrhea, constipation, and unexplained weight loss or gain, all invariably associated with a poor outcome.

Owing to the nature of this population-based study, a potential selection bias was inevitable. No data on important prognostic factors such as comorbidity, socioeconomic status, functional status, or KRAS or BRAF mutational status were included in our database. Data on the differentiation grade were missing for 70% of the patients included in the present study, also probably owing to the nonoperative setting in which these patients were diagnosed. Finally, detailed information on the prescribed chemotherapeutic regimens was unavailable from the NCR.

Conclusion

The results of the present study support the rationale for the addition of bevacizumab to palliative treatment with the best available systemic chemotherapy schedules for patients with PC who do not meet the criteria for CRS and HIPEC or surgery. However, owing to the nonrandomized nature of our study, the results should be interpreted with caution.

Clinical Practice Points

- High-quality population-based data on the role of targeted therapy in the palliative treatment of PC from CRC are currently lacking; however, data on this topic are of utmost importance, because most patients with PC depend on the development of effective palliative treatment options.
- The present nationwide population-based study investigated the use and effect of the targeted agent bevacizumab with data from the period in which this antivascular agent was introduced in the Netherlands.
- The present study included 1235 patients diagnosed from 2007 to 2014 with synchronous PC from CRC treated only with palliative systemic therapy.

- Bevacizumab was prescribed in addition to palliative chemotherapy to 435 patients (35%) and was associated with a 3.5-month improvement in overall survival rates, in both patients with isolated PC and those with extraperitoneal metastases, even after adjustment for relevant prognostic factors.
- This finding, despite its limitations owing to the nonrandomized nature of our study, supports the rationale for bevacizumab in the palliative treatment of colorectal PC.
- Moreover, it underlines the need for ongoing efforts to further determine the role of targeted therapy in the treatment of colorectal PC.

Acknowledgments

The present study was supported by an unrestricted grant from Roche Pharmaceuticals, manufacturer of the targeted agent Avastin (bevacizumab). The funder did not have any involvement in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the report for publication, which was made independently by the authors. The authors thank the registration personnel of the Netherlands Cancer Registry for their dedicated data collection.

Disclosure

The authors have stated that they have no conflicts of interest.

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