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.

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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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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

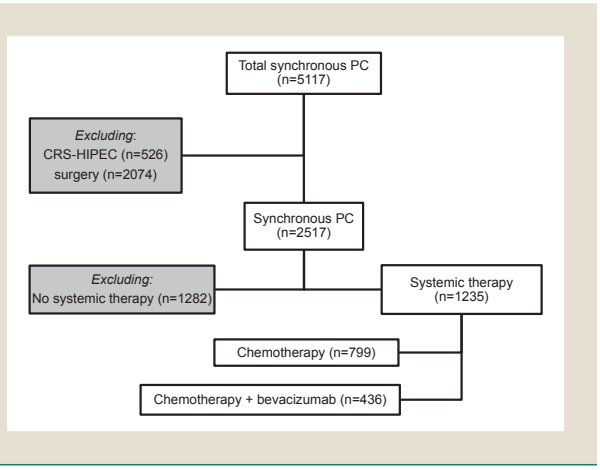
Patient Data

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