Journal of Geriatric Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Integrating geriatric assessment in the first line chemotherapy treatment in older patients with metastatic colorectal cancer: Results of a prospective observational cohort study (AVAPLUS)

Lore Decoster [a,*], Cindy Kenis [b], Benedicte Naessens [c], Ghislain Houbier [d], Marc De Man [e], Guy Lambrecht [f], Els Monsaert [g], Veerle Moons [h], Philippe Vergauwe [i], Hans Prenen [j], Eric Van Cutsem [j], Hans Wildiers [k]

[a] Department of Medical Oncology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Laarbeeklaan 101, 1090 Brussels, Belgium
[b] Department of General Medical Oncology and Geriatric Medicine, University Hospitals Leuven, 3000 Leuven, Belgium
[c] Department of Gastroenterology, AZ Nikolaas, Moerlandstraat 1, 9100 Sint-Niklaas, Belgium
[d] Department of Gastroenterology, CHC Liège, Rue de Hesbaye 75, 4000 Liège, Belgium
[e] Department of Gastroenterology, UZ Gent, De Pintelaan 185, 9000 Gent, Belgium
[f] Department of Gastroenterology, AZ Damiaan, Gouwelozestraat 100, 8400 Oostende, Belgium
[g] Department of Gastroenterology, AZ Maria Middelares, Buitenring Sint-Denijs 30, 9000 Gent, Belgium
[h] Department of Gastroenterology, Imelda Ziekenhuis, Imeldalaan 9, 2820 Bonheiden, Belgium
[i] Department of Gastroenterology, AZ Groeninge, President Kennedylaan 4, 8500 Kortrijk, Belgium
[j] Department of Gastroenterology, University Hospitals, Leuven, Herestraat 49, 3000 Leuven, Belgium
[k] Department of Medical Oncology, University Hospitals Leuven, Department of Oncology, KU Leuven, Herestraat 49, 3000 Leuven, Belgium

ARTICLE INFO

Article history:
Received 22 May 2017
Received in revised form 8 September 2017
Accepted 13 October 2017
Available online xxxx

Keywords:
Older patients
Metastatic colorectal cancer
Chemotherapy
Bevacizumab geriatric assessment

ABSTRACT

Objectives: This study aims to investigate the use of chemotherapy with or without bevacizumab in older patients with metastatic colorectal cancer (mCRC) in current daily practice and to identify predictive parameters for treatment-related outcomes.
Patients and Methods: This is a Belgian multi-centre, observational cohort study. Patients ≥ 70 years old with mCRC considered suitable for first-line chemotherapy were eligible for inclusion. At baseline geriatric screening and assessment was performed. Treatment choice was at the discretion of the investigator. Treatment duration, Progression Free Survival (PFS) and safety were recorded.
Results: Between August 2011 and July 2013, 252 patients with mCRC were included of which 50.8% were treated with bevacizumab. Median treatment duration was 5.5 months and median PFS was 8.9 months. Approximately 50% of patients experienced severe adverse events, most frequently diarrhea. In multivariate analysis, baseline Eastern Cooperative Oncology Group (ECOG)-performance status (PS) was predictive for treatment duration ($p = 0.0047$), PFS ($p < 0.0001$) and severe toxicity and baseline nutritional status for PFS ($p = 0.0007$). In patients with a good ECOG-PS, nutritional status was predictive for PFS.
Conclusions: In current daily practice in Belgium, half of older patients with colorectal cancer treated with chemotherapy also receive bevacizumab. Nearly half of older patients presented with severe toxicity during treatment. Baseline nutritional status is a predictive marker for PFS. Patients with a baseline ECOG-PS ≥ 2 have shorter PFS and higher risk of severe toxicity and should therefore be treated with caution.

1. Introduction

With approximately 6500 new diagnoses each year in Belgium, colorectal cancer (CRC) is the second most frequently diagnosed cancer [1]. An important proportion is older patients with 58% of all Belgian CRC patients aged ≥70 years and a mean age at diagnosis of 69.4 years for men and 71.1 years for women [2]. With the aging of the population, it is expected that the incidence of CRC in the older population will rise further.

Standard treatment of patients with metastatic CRC (mCRC) consists of combination chemotherapy with targeted agents such as bevacizumab or cetuximab [3]. However older patients with mCRC are underrepresented in most trials where the median age of patients is typically <65 years [4].

In randomized clinical trials in mCRC, bevacizumab demonstrated efficacy with different chemotherapy backbones [5–7]. In a pooled analysis of four randomized trials that assessed bevacizumab in with chemotherapy in mCRC, bevacizumab provided similar Progression

* Corresponding author at: Department of Medical Oncology, Oncologisch Centrum, UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.
E-mail address: lore.decoster@uzbrussel.be (L. Decoster).

https://doi.org/10.1016/j.jgo.2017.10.002
1879-4068/

Free Survival (PFS) and overall survival benefit in medically fit older patients as in younger patients, but an increased risk of thromboembolic events [8]. However, only 24% of patients in these randomized trials were 70 years or older and all were highly selected with good performance status (PS) and few comorbidities [8]. Therefore they are not representative for the older CRC population in daily clinical practice, which presents considerably more heterogeneity [9]. Patients with the same chronological age have different biological age based on their functional or cognitive status, comorbidities, and poly-pharmacy. This results in a risk for under-treatment in fit patients [10] or over-treatment with increased risk for treatment-related severe toxicity in frail patients. Geriatric assessment (GA) provides objective information on the overall health status, detects unknown geriatric problems, and guides the complex treatment decisions in older patients [11–13].

The aim of the present prospective observational cohort study was to complement the knowledge on first-line chemotherapy with or without bevacizumab in older patients with mCRC in current daily practice in Belgium and to evaluate the possible role of GA.

2. Materials and Methods

2.1. Trial Design

This observational study is a Belgian multi-centre, non-interventional, prospective cohort study.

Patients ≥ 70 years old with previously untreated mCRC and considered suitable to receive first-line chemotherapy with or without bevacizumab were eligible for inclusion. Patients who met the eligibility criteria were identified by the treating physician before the start of the chemotherapy and enrolled consecutively after written informed consent.

Chemotherapy schedule, dosing and treatment duration were at the discretion of the investigator and in accordance with labelling.

The study was approved by the local institutional review boards at every participating site.

2.2. Outcomes Assessments

The scheduling of patients visits, method, and frequency of clinical assessments were part of routine care and were not carried out at protocol pre-specified fixed intervals and were not independently assessed. The exception was Eastern Cooperative Oncology Group (ECOG) PS [14], geriatric screening and GA, which were performed in all patients at baseline, preferably before the start of the planned treatment or if impossible within four weeks of treatment initiation.

The geriatric screening included the G8 and the Flemish version of the Triage Risk Screening Tool (fTRST) [11].

The GA included nine items: living situation (not alone, alone), activities of daily living (ADL) (independent, dependent), instrumental activities of daily living (IADL) (independent, dependent), Mini-Mental State Examination (MMSE) (normal, abnormal cognition), 15-item Geriatric Depression Scale (GDS-15) (not at risk for depression, at risk), Mini Nutritional Assessment (MNA) (normal, abnormal nutritional status), Charlson Comorbidity Index (CCI) (absence, presence of comorbidities), falls history (fall during the last year) and Mobility-Tiredness Test (Mob-T) (normal, abnormal mobility-related fatigue) [15–22].

The total GA score was calculated based on the presence of deficiencies on the seven following criteria: living alone, ADL score > 6, IADL score < 5 in men and <8 in women, MMSE score < 24, GDS-15 score ≥ 5, MNA score < 24 and presence of at least one comorbidity on the CCI. The higher the total GA score, the more deficiencies observed. A geriatric profile is defined as the presence of ≥2 criteria.

Treatment duration was defined as the time interval between the first and the last, first-line mCRC treatment administration, which is the time to treatment failure for any reason.

PFS was defined as the time interval between initiation of first-line therapy and tumor progression evaluated in current practice or death from any cause, whichever comes first.

To evaluate toxicity, all adverse events (AEs) encountered during the study were to be reported and their intensity and relationship to chemotherapy or bevacizumab therapy was determined by the investigator. AEs of special interest for bevacizumab were recorded. Intensity of AEs was graded by the treating physician on a 3-point scale: mild: discomfort noticed but no disruption of normal daily activity; moderate: discomfort sufficient to reduce or affect daily activity; severe: inability to work or perform normal daily activity.

2.3. Statistical Analysis

The study being observational, no formal sample size calculation was performed. The safety population included all patients with at least one documented dose of chemotherapy, the reference population excluded patients with a major protocol deviation.

The primary endpoint was treatment duration. Secondary endpoints were PFS, toxicity, and GA results. PFS results were analysed on the reference population, all other results on the safety population.

The statistical methods were mainly descriptive. Continuous variables were presented using the number of observed values, mean, standard deviation (SD), median, minimum and maximum. Categorical variables were presented using numbers and percentages of patients.

Comparison of categorical data was performed using a Fisher exact test or a Chi square test when appropriate.

Treatment duration and PFS were described using Kaplan–Meier plots. For treatment duration, patients who were still under treatment at time of study withdrawal (because of consent withdrawal, lost to follow-up…) were censored on the last mCRC treatment date known. For PFS, patients who had neither progressed nor died at time of study end were censored on the date of study end.

To explore associations between treatment-related variables (treatment duration, PFS and severe toxicity) and the different geriatric screening and GA components, univariate and multivariate analyses were performed. In the univariate analyses, log-rank tests for treatment duration and PFS and Wilcoxon or Student t-tests for severe toxicity were used. Multivariate analyses used a stepwise approach. For the selection of covariates, the association between each covariate and the dependent variable was analysed in a univariate way using logistic regression models for severe toxicity, and Cox regression models for treatment duration and PFS. Covariates with a p-value < 0.075 were selected. The covariates selected in the previous step were introduced in the multivariate model (logistic regression model for severe toxicity and Cox regression model for treatment duration and PFS). Then a stepwise (for logistic regression model) or a backward (for Cox regression model) selection was used to retain only independently significant covariates at the threshold of 5%. Univariate and multivariate analyses were repeated considering only patients with an ECOG-PS value < 2 at baseline.

Data analyses were performed using SAS software version 9.4. All statistical tests were two-sided at the 5% significance level, and corresponding 95% CI were reported as appropriate.

3. Results

3.1. Patient Characteristics

Between August 2011 and July 2013, 34 Belgian centres screened a total of 254 patients (Fig. 1). Of these patients, 252 received at least one dose of chemotherapy and were included in the safety population. Of these 252 patients, 128 were treated with bevacizumab-containing chemotherapy and 124 patients received chemotherapy without bevacizumab. In this group of non-bevacizumab patients, eight patients were treated with cetuximab. Due to major protocol deviations, two patients were excluded from the reference population with PFS data; one

Please cite this article as: Decoster L, et al, Integrating geriatric assessment in the first line chemotherapy treatment in older patients with metastatic colorectal cancer: Results ..., J Geriatr Oncol (2017), https://doi.org/10.1016/j.jgo.2017.10.002