Critical Reviews in Oncology/Hematology 115 (2017) 59–66

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Treatment options for metastatic colorectal cancer in patients with liver dysfunction due to malignancy

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Contents

ARTICLE INFO

Article history:
Received 12 December 2016
Received in revised form 28 February 2017
Accepted 27 March 2017

Keywords:
Hepatic dysfunction
Chemotherapy
Hyperbilirubinaemia
Monoclonal antibodies
Targeted therapy

ABSTRACT

Background: The survival of colorectal cancer patients is frequently determined by the extent of metastatic invasion to the liver; in cases of major involvement, therapeutic strategies are limited because the liver is necessary for drug metabolism.
Material and methods: We have reviewed articles about the pharmacokinetic profiles of each drug used in colorectal cancer patients with hepatic dysfunction to determine which of these treatments are most feasible.
Results: Some drugs appear to be feasible options for patients with hepatic insufficiency. Agents such as 5-fluorouracil and oxaliplatin, as well as monoclonal antibodies such as bevacizumab, cetuximab, and panitumumab, can potentially be used in these cases. On the other hand, irinotecan and regorafenib cannot be recommended because of the risk of increased toxicity.

Abbreviations: 5-FU, 5-fluorouracil; CEA, carcinoembryonic antigen; CYP3A4, cytochrome 3A4; DPD, dihydropyrimidine dehydrogenase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; LV, leucovorin; LV/5-FU, leucovorin-base plus 5-fluorouracil; OS, overall survival; PD, progressive disease; PR, partial response; PFS, progression-free survival; SD, stable disease; UGT, uridine diphosphate glucuronosyltransferase; ULN, upper limit of normal; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; TAS 102, Trifluridine/tipiracil; T½, half-life time.

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http://dx.doi.org/10.1016/j.critrevonc.2017.03.029

Conclusion: Treatment of patients with colorectal cancer and liver dysfunction represents a major challenge because the prognosis is usually very poor and alteration of liver function is normally an exclusion criterion in clinical trials. In this review, we present evidence regarding the use of each drug in patients with colorectal cancer and hepatic impairment.

1. Introduction

Colorectal cancer is the second most commonly diagnosed cancer in the world. In 2012, 1.3 millon new cases of colorectal cancer were diagnosed worldwide, with 447,000 new cases in Europe alone (Van Cutsem et al., 2014; Ferlay et al., 2015). Colorectal cancer mortality has decreased by 39% in United States in the past two decades due to early detection of the disease as well as better access to colonoscopy and new treatments (Ait Ouakrim et al., 2015).

In Europe, chemotherapy regimens for patients with colorectal cancer commonly include 5-fluorouracil (5-FU), oxaliplatin, and irinotecan (Van Cutsem et al., 2016). New targeted therapies continue to be developed; the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have currently approved five targeted therapies: bevacizumab, aflibercept, cetuximab, panitumumab, and regorafenib.

Approximately 50% of patients with colorectal cancer will develop liver metastases during their lifetime; 20% will be synchronous and 30% metachronous (Roderburg et al., 2011). Fortunately, there has been tremendous progress in the treatment of patients with colorectal cancer that has metastasized to the liver, including novel targeted therapies, SIR-Spheres, chemoembolization, and hepatic arterial infusion chemotherapy.

Liver dysfunction due to malignancy is an uncommon cause of acute liver failure. The mechanism by which malignancy causes liver dysfunction is multifactorial and may include direct reduction of the volume of functional healthy liver or intrahepatic and extrahepatic biliary obstruction (Field et al., 2008). Furthermore, portal vein occlusion due to portal-vein thrombosis as a consequence of a hypercoagulable state or tumor thrombi may cause parenchymal infarction (Field et al., 2008; Khashab et al., 2007; Harrison et al., 1981). Humoral and immunological factors associated with cancer may also increase cholestasis and inflammatory damage in the liver (Field et al., 2008).

Serological tests of liver function evaluate synthetic function by serum albumin levels and prothrombin time, cellular injury by asparate aminotransferase and alanine aminotransferase concentrations, and cholestasis by alkaline phosphatase, gammaglutamyltransferase, and direct-reacting bilirubin levels. The serum concentration of bilirubin is a specific measure of potentially serious liver damage and an important indicator of liver functional loss (Field et al., 2008).

Prognosis is considered dismal if impaired liver function is secondary to metastasized colorectal cancer, with a median survival time of only a few weeks (Harrison et al., 1981). Management of such patients represents a serious challenge because there is little published guidance regarding the choice of therapy. It is further complicated by the increased risk of chemotherapy-related complications. Nevertheless, the literature contains a few examples of such therapies. In this review, we compare different chemotherapy and targeted therapy modalities that have been employed to treat patients with colorectal cancer and liver deficiency induced by metastasis and make recommendations based on our findings from the literature.

2. Material and methods

We reviewed articles regarding the pharmacokinetic profile of each drug that has been used in patients with colorectal cancer and hepatic dysfunction to determine which drugs are the most feasible and safe. We subsequently performed an electronic search of the Medline database covering the period from 1996 to 2016 using the MeSH headings "colorectal cancer," "liver dysfunction," and the names of all of the drugs used to treat metastatic colorectal cancer namely "FOLFOX", "5FU", "FOLFIRI", "Capecitabine", "Regorafenib", "TAS 102", "Cetuximab", " Bevacizumab", "Panitumumab", "Aflibercept". The search was limited to English-language publications and human subjects. We reviewed all pertinent titles and abstracts and further assessed papers that we judged appropriate for inclusion in this review. We discuss papers that describe use of the various drugs in patients with colorectal cancer and liver dysfunction.

3. Results

3.1. Chemotherapy

Chemotherapy is the cornerstone of metastatic colorectal cancer treatment. 5-FU is the standard chemotherapeutic agent for palliative therapy. It has a proven impact on survival time in patients with colorectal cancer, with response rates ranging from 10% to 50% depending on the regimen used (Simmonds, 2000; De Gramont et al., 1988; Piedbois et al., 1998). The addition of oxaliplatin or irinotecan to 5-FU regimens results in a significant increase in positive response, prolonged time to tumor progression, and survival (Saltz et al., 2000; de Gramont et al., 2000). Although there are pharmacokinetic studies for monotherapy anticancer drugs, there is a lack of data regarding drug combinations.

3.1.1. 5-fluorouracil

First-line systemic chemotherapy for metastatic colorectal cancer commonly includes 5-FU and leucovorin base (LV/5-FU). The main effect of the pyrimidine analogue 5-FU is irreversible inhibition of thymidylate synthase. Eighty percent of 5-FU is catabolized by dihydropyrimidine dehydrogenase (DPD) in the liver, where it is abundantly expressed. DPD is the rate-limiting enzyme in 5-FU catabolism and converts 5-FU to dihydrofluorouracil (Longley et al., 2003; Fleming et al., 2003). There appears to be no correlation between bilirubin levels and 5-FU clearance. We did not find any pharmacokinetic data regarding administration of 5-FU bolus in patients with liver dysfunction. However, Fleming et al. investigated infusional administration of LV/5-FU in patients with liver dysfunction, including those with bilirubin levels >5 mg/dL (Fleming et al., 2003). It seems that it can be safely used without additional toxicity in patients with hyperbilirubinemia (Fleming et al., 2003).

3.1.2. Capecitabine

Capecitabine is an oral prodrug that is metabolized to 5-FU. It is equivalent in effectiveness to 5-FU in patients with metastatic colorectal cancer (Eklund et al., 2005; Hwang et al., 2006; Petrelli et al., 2012; Loree et al., 2014; Ducreux et al., 2011; Cassidy et al., 2011a;