Critical Reviews in Oncology/Hematology 115 (2017) 1–12

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

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

Second-line chemotherapy for advanced pancreatic cancer: Which is the best option?

Giuseppe Aprile[a,b,*], Francesca V. Negri[c], Francesco Giuliani[d], Elisa De Carlo[a], Davide Melisi[e], Francesca Simionato[e], Nicola Silvestris[d], Oronzo Brunetti[d], Francesco Leone[f], Donatella Marino[f], Daniele Santini[g], Emanuela Dell'Aquila[g], Tea Zeppola[g], Marco Puzzoni[h], Mario Scartozzi[h]

[a] Department of Oncology, University and General Hospital, Udine, Italy
[b] Department of Oncology, San Bortolo General Hospital, ULSS8 Berica, East District, Vicenza, Italy
[c] Medical Oncology, University Hospital, Parma, Italy
[d] Medical Oncology Unit, National Cancer Institute IRCCS "Giovanni Paolo II", Bari, Italy
[e] Medical Oncology, University of Verona, Italy
[f] Medical Oncology, Candiolo Cancer Institute, FPO, IRCCS, University of Torino (TO), Italy
[g] Department of Medical Oncology, University Campus Bio-Medico, Roma, Italy
[h] Department of Oncology, University Hospital, Cagliari, Italy

Contents

ARTICLE INFO

Article history:
Received 8 August 2016
Received in revised form 28 February 2017
Accepted 21 March 2017

Keywords:
Advanced pancreatic adenocarcinoma
Second-line treatment
Clinical trials
Nanoliposomal irinotecan

ABSTRACT

Despite recent biological insight and therapeutic advances, the prognosis of advanced pancreatic cancer still remains poor. For more than 15 years, gemcitabine monotherapy has been the cornerstone of first-line treatment. Recently, prospective randomized trials have shown that novel upfront combination regimens tested in prospective randomized trials have resulted in improved patients' outcome increasing the proportion of putative candidate to second-line therapy. There is no definite standard of care after disease progression. A novel formulation in which irinotecan is encapsulated into liposomal-based nanoparticles may increase the efficacy of the drug without incrementing its toxicity. NAPOLI-1 was the first randomized trial to compare nanoliposomal irinotecan and fluorouracil-leucovorin (5-FU/LV) to 5-FU/LV alone after a gemcitabine-based chemotherapy. This review focuses on the current data for the management of second-line treatment for metastatic

* Corresponding author at: Department of Oncology, San Bortolo General Hospital, ULSS8 Berica - East District, 37, Viale Rodolfi, 36100 Vicenza, Italy. Tel.: +39 3470048600; fax: +39 0444 757341.
E-mail address: giuseppe.aprile@aulss8.veneto.it (G. Aprile).

http://dx.doi.org/10.1016/j.critrevonc.2017.03.025

pancreatic adenocarcinoma, presents the most interesting ongoing clinical trials and illustrates the biologically-driven future options beyond disease progression.

1. Introduction

In an era characterized by dramatic improvements in cancer therapy, exocrine pancreatic tumor remains a malignancy with a dismal prognosis (Ryan et al., 2014). The reasons include limited knowledge of underpinning molecular biology, late disease stage at diagnosis and early diffuse dissemination, poor performance status of advanced patients (mainly due to anorexia, nausea/vomiting, weight loss and pain), and lack of effective therapies. For over two decades, gemcitabine (GEM) has been the standard treatment for locally advanced and metastatic disease, based on the results of a randomized phase III trial in which it was compared with bolus 5-Fluorouracil (5-FU) demonstrating an advantage in clinical benefit (CB), a not validated end-point, and a modest improvement in overall survival (OS) (Burris et al., 1997). After treatment failure with gemcitabine, many studies have explored the possibility to treat patients who retained a good performance status, who are about 40% of those who have received a first-line therapy (Nagrial et al., 2015). Unfortunately, only two of these studies were randomized: the first one compared glufosfamide with best supportive care (BSC) while the second one (CONKO-003), due to the lack of acceptance of BSC as control arm, used FU plus leucovorin (FA) as reference arm. In the first trial, 303 patients were randomly assigned to glufosfamide and BSC or BSC alone. Median survival was slightly increased in the experimental arm (105 days vs 84 days, HR 0.85, 95%CI 0.66–1.08, P = 0.19) but the gain was not statistically significant. Moreover, six patients treated with the experimental drug had severe renal impairment (Ciuleanu et al., 2009). The survival of patients treated with BSC was overall poor. Besides, the CONKO-003 demonstrated the superiority of a combination of oxaliplatin (OHP) plus FA-FU (OFF) over FA-FU alone (Oettle et al., 2014). Based on the results of CONKO-003 current guidelines recommend OHP and FU as the preferred option for second-line therapy. In the last years, two key randomized phase III trials changed the approach to the front-line treatment of advanced pancreatic cancer. In the Prodige/Accord trial the triple drugs combination of OHP, Irinotecan (CPT-11), Folinic acid (FA) and FU obtained a significant improvement in response rate (RR), progression-free (PFS) and OS when compared to standard GEM in patients with good performance status and age less than 70 years (Conroy et al., 2011). This study was the first to demonstrate that GEM is not always necessary as first-line therapy and that its use might not be required as first-line approach. In the second trial (Von Hoff et al., 2013), the addition of nab-paclitaxel to GEM resulted in better RR, PFS and OS than GEM alone demonstrating that a GEM-based combination is more efficacious than the single drug. Besides enriching the therapeutic armamentarium, the results of these two trials offer the possibility to treat distinctively patients with different clinical features and open the way to the possibility of using therapeutic sequences in patients with good performance status. In this light the recent publication of the results of NAPOLI trial (Wang-Gillam et al., 2016a), a phase III randomized study showing the superiority of nanoliposomial irinotecan when compared to FU-FA in metastatic pancreatic cancer patients who progressed after a first-line GEM-based therapy, represents a new and welcome treatment option. Take together the data of all these studies indicate that unlike the past many more options are now available and that one of the challenge is to identify the best candidate for the optimal sequence of therapy. In this review, we will analyze the data of first and second-line therapy and the expanded actual scenario in the treatment of advanced pancreatic cancer with a look to the near future based on the ongoing clinical trials.

2. Clinical background: why this is a relevant question and what we should know

Invariably, despite promising results from recent studies with FOLFIRINOX and gemcitabine/nab-paclitaxel, patients with advanced pancreatic cancer will progress. Nevertheless, about half of these remain in good clinical condition and thus may receive one or more subsequent lines of chemotherapy (Walker and Ko, 2014). In a retrospective series of metastatic pancreatic cancer patients, 45% and 21% of them received 2 or more lines of treatment after failure of gemcitabine, respectively (Bachet et al., 2009). Recently, Nagrial et al. reported the results of a systematic review of 24 first-line studies performed between 1998 and 2012 and comprising 52 treatment arms (Nagrial et al., 2015). The use of second line therapy was noted in 17% of all studies. The prescription of a second-line therapy ranged from 16% to 68% with a pooled mean of 43%. Interestingly, the rate of utilization significantly increased from studies published pre-2007 (35%) to post-2007 (48%). Furthermore, all these studies were conducted in the pre-FOLFIRINOX and gemcitabine/nab-paclitaxel era; as such, they mostly included patients who received a gemcitabine-based first-line regimen. With respect to these data, the rate of the use of subsequent anticancer therapy was 47% and 38% in the combination arms of PRODIGE (Conroy et al., 2011) and MPACT (Von Hoff et al., 2013) trials, respectively.

Most of these clinical trials included patients with good or excellent performance status (ECOG PS 0 or 1) while, in the real world setting, this group of patients is the minority with subjects ineligible for clinical trials due to age and/or performance status, presenting a very poor median survival (Ueda et al., 2013). A key point of all these studies is the selection of the patient subgroup that could benefit from either second-line chemotherapy or BSC, according to the ASCO indication not to use cancer-directed therapies for patients with solid tumors and low performance status (Schnipper et al., 2012). Among the clinical and laboratory factors, the most important are the patient's performance status, specific hematological and laboratory values (including serum albumin), and the response obtained to first-line therapy (Erdogan et al., 2013; Kim et al., 2012).

With the aim to increase the percentage of patients eligible for a second-line chemotherapy, palliative and supportive care plays a key role in pancreatic cancer patients' management. In fact, improvement of both HRQoL and OS are mutually correlated in various malignancies, including pancreatic cancer (Bonnetain et al., 2010). So, interventions aimed to improve clinical situations directly attributable to the disease (i.e., biliary and gastric outlet obstructions, tumor-associated pain, depression, thromboembolic events, malnutrition and pancreatic insufficiency) are an innovative and interesting complementary approach for these patients (Torgerson and Wiebe, 2013). In particular, several data support the benefit of an adapted physical activity in pancreatic cancer patients. In fact, as an apparent paradox, rest may be deleterious for these patients, probably due to a reduction of the circulating levels of