European Journal of Cancer (2013) 49, 593–603

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: A meta-analysis of randomised trials

Domenico Ciliberto [a,e], Cirino Botta [a,e], Pierpaolo Correale [b], Marco Rossi [a], Michele Caraglia [c], Pierfrancesco Tassone [a,d], Pierosandro Tagliaferri [a,*]

[a] *Medical Oncology Unit, Campus Salvatore Venuta, Department of Experimental and Clinical Medicine, "Magna Graecia" University and "Tommaso Campanella" Cancer Center, Catanzaro, Italy*
[b] *Medical Oncology, Department of Oncology, Siena University, Siena, Italy*
[c] *Department of Biochemistry and Biophysics, Second University of Naples, Naples, Italy*
[d] *Temple University's College of Science & Technology, Philadelphia, PA, USA*

Available online 16 September 2012

KEYWORDS
Meta-analysis
Advanced pancreatic cancer
Gemcitabine
Combination therapy

Abstract ***Background:*** Pancreatic cancer is the fourth leading cause of cancer-related death worldwide. Gemcitabine is the mainstay treatment for advanced disease. However, almost all up-to-date trials, that evaluated the benefit of gemcitabine-combination schedules, failed to demonstrate an improvement in overall survival (OS). In this study, we performed a systematic review and a meta-analysis of randomised clinical trials (RCTs) to investigate the efficacy and safety of gemcitabine-based combination regimens as compared to gemcitabine alone in the management of pancreatic cancer.

Methods: Clinical trials were collected by searching different databases (PubMed, Embase and the Central Registry of Controlled Trials of the Cochrane Library) and abstracts from major cancer meetings. We considered period ranging from January 1997 to January 2012. Primary end-point was OS, secondary end-points were response rate (RR), disease control rate (DCR) and safety. Hazard ratios (HRs) of OS, odds-ratios (ORs) of RR, DCR and risk ratios of grade 3–4 toxicity rates (TRs), were extracted as presented in retrieved studies and used for statistical analysis. Meta-analytic estimates were derived using random-effects model.

Findings: Thirty-four trials for a total of 10,660 patients were selected and included in the final analysis. The analysis showed that combination chemotherapy confers benefit in terms of OS (HR: 0.93; 95% confidence interval (CI): 0.89–0.97; $p = 0.001$). ORs for both RR and DCR demonstrated a significant advantage for combination therapy (OR for RR: 0.60, 95%CI: 0.47–0.76, $p < 0.001$; OR for DCR: 0.79; 95%CI: 0.66–0.93; $p = 0.006$). Toxicities were more

* *Corresponding author:* Address: Medical Oncology, Magna Græcia University and Tommaso Campanella Cancer Center, Campus "Salvatore Venuta", Germaneto Catanzaro 88100, Italy. Tel.: +39 09613694324; fax: +39 09613697341.
E-mail address: tagliaferri@unicz.it (P. Tagliaferri).
[e] These authors equally contributed to this work.

0959-8049/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejca.2012.08.019

frequent with the combination treatment and significance in terms of risk ratio was reached for diarrhoea (0.53, 95%CI: 0.36–0.79), nausea (0.74, 95%CI: 0.56–0.96), neutropenia (0.71, 95%CI: 0.59–0.85) and thrombocytopenia (0.57, 95%CI: 0.43–0.75).

Interpretation: The combination chemotherapy as compared to gemcitabine alone significantly improves OS in advanced pancreatic cancer (APC). However, this advantage is marginal whereas the treatment-related toxicity is increased, suggesting the use of gemcitabine-based combination regimens only in selected patient populations. New prospective trials, based on translational approaches and innovative validated biomarkers, are eagerly awaited on this topic.

© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

Advanced pancreatic cancer (APC) is a major health problem in industrialised countries and represents the fourth cause of cancer-related death worldwide.[1,2] Unfortunately, the 5-year life expectancy for APC patients is still poor with anecdotal long-term survivors.[3]

The treatment of APC is based on a multidisciplinary approach that includes surgery, radiotherapy and chemotherapy, although the impact of therapy is merely palliative.[4] Several clinical–pathological factors may influence patients' prognosis; among them, the unresectable disease at diagnosis (stage III–IV according to TNM – Tumour, Nodes, Metastasis - cancer staging system) is the variable that mostly influences the final outcome.[5,6] Currently, single agent gemcitabine is the mainstay of treatment for APC with potential benefits in terms of quality of life and overall survival (OS).[7] However, the median survival of these patients is 5–6 months with a 1-year survival rate of about 15–20%.[8] In the past years different trials investigated the efficacy of combination chemotherapy or targeted therapy but none of them reported results strong enough to change the practice of gemcitabine monotherapy.[9,10] In 2007–2008 Sultana et al. and Heinemann et al., in two independent meta-analyses, described a small, though significant, advantage in OS for combination chemotherapy arm versus gemcitabine alone, showing comparable results in term of hazard ratios (HRs) (0.91; 95%CI 0.85–0.97).[11,12] Heinemann et al. reported a subgroup analysis that demonstrated the superiority of combination chemotherapy schedules, including platinum and fluoropyrimidines respectively. Indeed, even if an improvement in terms of response rate (RR) and progression free survival (PFS) was found in many of these trials, only one of them reported a significant increase in OS: Moore et al. described a minimal 2-weeks increase in OS for the erlotinib–gemcitabine combination-therapy compared with gemcitabine alone.[13]

Based on these data, while the treatment with gemcitabine alone is considered current clinical practice worldwide, the role of gemcitabine-based combination therapy in the treatment of APC still remains to be elucidated.[14,15] To this end, we evaluated the impact of gemcitabine-based combination therapy as compared to gemcitabine alone on survival, antitumour activity and safety, in overall and subgroup evaluations, in the attempt to present the most complete analysis of currently available evidence.

2. Methods

2.1. Searching

We retrieved the most widely recognised bibliographic sources (PubMed, Embase and the Central Registry of Controlled Trials of the Cochrane Library) and meeting abstract databases (ASCO and ESMO) and selected studies presented between January 1997, at the time of gemcitabine treatment introduction, and January 2012. Prospective studies only were allowed in this analysis in order to reduce or minimise the risk of selection or information bias.[16–18] The search was performed by using the following key-words: pancreatic, tumour, cancer, advanced, metastatic, chemotherapy, gemcitabine, prospective and randomised in different combinations: e.g. 'advanced pancreatic cancer, gemcitabine chemotherapy'. The 'related articles' function and references retrieved from articles were used to perform the search of all related studies, abstracts and citations. For this search only papers written in English language were considered.

2.2. Selection

In the studies included in the present review, patients must have been enrolled according to the following characteristics:

2.3. Inclusion criteria

The studies had to report diagnosis of locally APC or metastatic disease and common demographic characteristics of trial population (age, sex and performance status). No major comorbidities or second tumours (except for non-melanoma skin cancers and local cervix tumour) were allowed. In the control arm patients received a gemcitabine monotherapy regimen, while in the experimental arm they were treated with a gemcitabine

Download English Version:

https://daneshyari.com/en/article/8444991

Download Persian Version:

https://daneshyari.com/article/8444991

Daneshyari.com