Critical Reviews in Oncology/Hematology 116 (2017) 68–81

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

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

Review

Third-line systemic treatment versus best supportive care for advanced/metastatic gastric cancer: A systematic review and meta-analysis

Wing-lok Chan[a,*], Kwok-keung Yuen[a], Steven Wai-kwan Siu[a], Ka-on Lam[b], Dora Lai-wan Kwong[b]

[a] Department of Clinical Oncology, Queen Mary Hospital, Hong Kong, Hong Kong
[b] Department of Clinical Oncology, University of Hong Kong, Hong Kong, Hong Kong

Contents

ARTICLE INFO

Article history:
Received 18 July 2016
Received in revised form 18 April 2017
Accepted 3 May 2017

Keywords:
Gastric cancer
Metastatic

ABSTRACT

This review evaluated the efficacy, toxicities and quality of life of third-line systemic treatment (TLT) versus best supportive care (BSC) in metastatic gastric cancer patients after failing two lines of systemic treatment.

Six studies were included, involving 890 participants (TLT: 587, BSC: 303, Asian: 679, 76.3%), median 53–61 years old, ECOG 0–1 with no major co-morbidities. Compared with BSC, TLT improved overall survival (HR 0.63; 95% CI 0.46–0.87, corresponding to an improvement in medial OS from 3.20 to 4.80 months), progression-free survival (HR 0.29; 95% CI 0.18–0.45), objective response rate (RR 5.28; 95%

* Corresponding author at: Department of Clinical Oncology, 1/F Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, Hong Kong.
E-mail address: cwl088@ha.org.hk (W.-l. Chan).

http://dx.doi.org/10.1016/j.critrevonc.2017.05.002

Chemotherapy
Targeted therapy
Palliative care

CI 1.00–27.83) and disease control rate (RR 4.51; 95% CI 2.64–7.71). The efficacy results favoring TLT should be interpreted with caution for the substantial heterogeneities, wide confidence intervals and selection bias. More toxicities occurred in the TLT arms.
This review highlighted the paucity of QOL data. Future studies should focus more on QOL-related outcomes. PROSPERO registration: 2015 CRD42015017873.

1. Introduction

Gastric cancer is the fifth most common cancer and remains the world's third leading cause of cancer mortality (Torre et al., 2015). Despite the improvement in multi-modality management approach, the recurrence rate is still high. About 40–80% patients suffer from disease relapse (Gallo and Cha, 2006; Gunderson, 2002). Moreover, more than half of the patients at diagnosis are already too advanced and not operable.

In the last decade, first-line then second-line palliative chemotherapy with or without targeted agent has become a standard treatment in patients with advanced/metastatic gastric cancer. A Cochrane review and meta-analysis performed by Wagner demonstrated a significant survival benefit in favor of chemotherapy compared with best supportive care (BSC) (Hazard ratio (HR) 0.37; 95% confidence interval (CI) 0.24–0.55, $P < 0.0001$) (Wagner et al., 2010). This could be interpreted as an improvement in median survival from 4.3 months with BSC to 11 months with chemotherapy. Combination chemotherapy is superior to monotherapy (HR 0.83, 95% CI 0.74–0.93, $P = 0.001$). Large proportions of patients are either non-responders or have progression after first-line chemotherapy, and proceed for second-line treatment. Several systematic reviews and meta-analyses had confirmed that second-line chemotherapy improved survival compared with BSC (Kim et al., 2013; Lacovelli et al., 2014; Liepa et al., 2015). According to Lacovelli's study, the risk of death was decreased by 18% (HR = 0.82; 95% CI 0.79–0.85; posterior probability HR ≥ 1: <0.00001) with active therapies and the effect was even greater in patients with good performance status (ECOG = 0) (Lacovelli et al., 2014).

With the development of new chemotherapies or targeted agents which are seemingly more effective and have less toxicity, many patients can still maintain a good general condition after failing second-line therapies. According to previous studies, around 20–90% patients continued on active third-line or further lines treatment (Kang et al., 2012; Hironaka et al., 2013; Wilke et al., 2014). This gives patients another chance to control the malignancy, maintain quality of life (QOL), relieve symptoms and even improve survival.

Taxanes and irinotecan are the possible options in third-line setting as most of the metastatic gastric cancer patients had used 5FU/platinum based chemotherapy. Previous studies on taxane-based chemotherapy or irinotecan-based chemotherapy (either monotherapy or combination with 5FU) showed an overall response rate of 10–25% with progression-free survival (PFS) 2.1–3.3 months and overall survival (OS) 5.6–10.9 months (Kang et al., 2013; Kim et al., 2007; Lee et al., 2008, 2012, 2013; Moon et al., 2010; Park et al., 2005; Shimoyama et al., 2009; Tarazona et al., 2016). A phase III RCT from Korea also demonstrated a trend of better survival (HR 0.81, 95% CI 0.45–1.46) with third-line chemotherapy using single agent irinotecan or docetaxel (Kang et al., 2012).

Recent phase I to III studies with agents targeting on different molecular pathways including Her-2/EGFR/VEGFR/cMET/ATM/FGFR/IGFR/mTOR/PD-L1 are on-going internationally and some were published. These targeted agents were studied as monotherapy or in combination with chemotherapy, as first-line, second-line or further lines of treatment. Their results are conflicting and worth a deeper look to avoid publication bias of the positive studies.

1.1. Why it is important to do this review

Metastatic gastric cancer patients usually have poor prognosis with short life expectancy. Various anti-cancer agents have been used for third-line and beyond, but the data are not conclusive. Since active treatment can cause toxicities, the benefits must be balanced with the side effects. There is a lack of international standard for patients after second-line treatment. Hence a systematic review to evaluate the efficacy and toxicity of third-line treatment including both chemotherapy and targeted agents is performed.

2. Materials and methods

The methodology of this systematic review has been registered in PROSPERO in March 2015 (registration: CRD42015017873).

2.1. Study criteria

Phase II and III prospective randomized controlled trials (RCTs) that compared third-line or further lines of systemic treatment with BSC/placebo.

Inclusion criteria:

- Studies involving only patients with pathologically confirmed adenocarcinoma of stomach.
- Studies with at least one third-line or further lines treatment group.
- Studies with best supportive care group/placebo.

Exclusion criteria:

Studies with only treatment groups but no BSC/placebo group.
Trials with radiotherapy or intraperitoneal chemotherapy were outside the scope of our research and were excluded.

2.2. Search methods

Studies were identified by searching electronic databases including the Cochrane Register of Controlled Trials (CENTRAL, Issue 7, 2016), MEDLINE Ovid (1996 to July week 2, 2016), EMBASE Ovid (1996 to 21 July, 2016) and CINAHL (1996 to July week 2, 2016). The search strings used are reported in Appendix 1. Handsearching for published abstracts from conference proceedings was performed: The American Society for Clinical Oncology 2000 to 2016, The European Council of Clinical Oncology 2000 to 2015 (published in the European Journal of Cancer), and The European Society