ISPOR 2021

11st November
Copenhagen,
Denmark

Meta-analysis and Cost-Effectiveness Analysis of Oxaliplatin-based Chemotherapy Versus Irinotecan-based Chemotherapy for the First-line Treatment of Metastatic Advanced Colorectal Cancer in China

Xiao Zhang[1], Wen Su[2], Ziyi Lin[3], Yifei Jian[3], Jianwei Xuan[3]

[1]China Pharmaceutical University, Nanjing, China 211198, [2] Shanghai Centennial Scientific, Shanghai, China 200032,[3] Sun Yat-sen University, Guangzhou, China 510006

INTRODUCTION

- Colorectal cancer (CRC) is one of the most common human malignancies and a leading cause of cancer-related death worldwide[1]. In China, about 376,000 new cases were diagnosed and nearly 191,000 patients died of colorectal cancer in 2015[2].
- Nearly 25 % of patients already have metastatic disease at the moment of diagnosis[3]. The 5-year survival rate of metastatic colorectal cancer (mCRC) is only 14.2%, significantly lower than non-mCRC[4].
- Over the past 10 years, various combinations of chemotherapy were investigated for the treatment of mCRC[5]. 5-fluorouracil (5-FU) is one of the most extensively used drugs in the treatment of mCRC[6–8]. Meanwhile, two other cytotoxic drugs (irinotecan and oxaliplatin) had their efficacy confirmed in the treatment of mCRC, thus becoming part of treatment protocols[6, 9–11].
- There has been many randomized clinical trials (RCT) analyzed the efficacy of different chemotherapy regimens consisting on drugs such as 5-FU, capecitabine, irinotecan and oxaliplatin.

OBJECTIVE

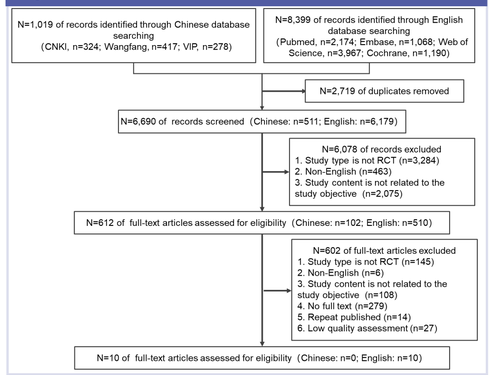
To evaluate efficacy, safety and the long-term cost-effectiveness of oxaliplatin-based chemotherapy versus irinotecan-based chemotherapy for the first-line treatment of mCRC in China.

METHODS

- **Systematic review and meta-analysis:**
  - The following electronic databases were searched: Pubmed, Embase, Web of science, Cochrane library; CNKI, Wanfang, VIP.
  - The Cochrane Collaboration's tool was used to assess risk of bias of included studies.
  - RCT comparing oxaliplatin-based chemotherapy with irinotecan-based chemotherapy among mCRC patients were considered. A total of 10 clinical trials were identified[12-21]. The PRISMA flow chart is illustrated in Figure 1.
  - The meta-analysis was conducted using RevMan 5.3. The continuous outcomes were measured by the mean difference (MD), dichotomous outcomes were measured by risk ratio (RR).
- **Cost-effectiveness analysis:**

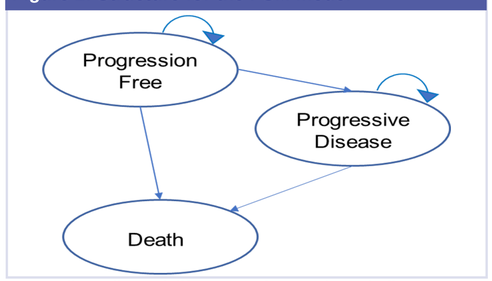
  Model overview
  - A partitioned survival model (PSM) was used to determine long-term health outcomes and economic consequences of interventions in the 1st-line treatment of mCRC. Partitioned survival is a typical approach in modeling metastatic cancers, and has been used in many HTA submissions. The model schematic in Figure2 illustrates the three mutually exclusive health states: progression-free (PF), progressive disease (PD) and death.

Figure 1: The PRISMA flow chart



  - The proportion of patients in the PF state at each cycle is based on the progression-free survival (PFS) curve; the proportion of patients in the death state at each cycle is based on the complement of overall survival (OS) curve (1 – OS), and the proportion of state at each cycle was calculated as the difference between the proportion of patients surviving and the proportion of patients remaining in the PD state (OS - PFS).

Figure 2: Structure for the PSM model



  - Quality-adjusted life-years (QALYs) and direct costs expressed in 2019 CNY from China payer's perspective were calculated.
  - Both costs and clinical benefits were discounted at an annual rate of 5.0%.

  Model inputs
  - The PFS and OS curves were based on the RCT[12,13] and meta-analysis results.
  - Due to the lack of the patient-level, an exponential distribution was assumed for the PFS and OS fit in oxaliplatin-based (Ox-based) chemotherapy group.
  - Besides, the proportional hazard was assumed in order to estimate the PFS and OS curves of irinotecan-based (Iri-based) chemotherapy group with the HR generated from the meta-analysis.
  - Adverse event (AE) risks associated with Ox-based group were obtained from clinical trials and meta-analysis.
  - PFS/PD treatment cost, AEs cost and palliative end-of-life care cost were included in the model. Costs and utilities of different health states were extracted from published literatures [22-27].

RESULTS

- **Systematic review and meta-analysis**
  - A total of 3,667 mCRC patients that compared Ox-based chemotherapy (n=1,579) with Iri-based chemotherapy (n=1,861) were included. The forest plots of PFS and OS are presented in Figures 3-4. Results of AE are presented in Table 1.
  - Patients who received the Ox-based chemotherapy had higher OS (HR=0.81, 95 % CI: 0.68 to 0.98; P= 0.03), and higher PFS (HR=0.84, 95 % CI: 0.67 to 1.04; P=0.10).
  - Ox-based chemotherapy has a lower risk of diarrhea (RR=0.53, 95 % CI: 0.42 to 0.56; P< 0.0001), a higher risk of neurological events (RR= 20.21; 95 % CI: 7.47 to 54.69; P< 0.0001) and a higher risk of thrombocytopenia (RR=3.36; 95 % CI: 1.46 to 7.73; P=0.004).

Figure 3. Forest plot of PFS

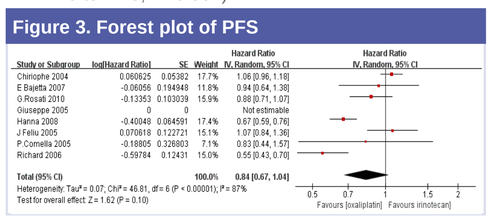
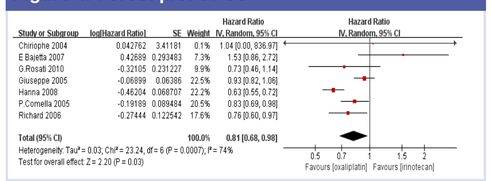


Figure 4. Forest plot of OS



- **Cost-effectiveness analysis**
  - Base-case analysis results are presented in Table 2.

Table 1: Meta-analysis results of AEs

	RR	95%CI	P value
Leukopenia	0.68	0.36-1.29	0.24
Nausea/vomiting	0.85	0.47-1.52	0.58
Febrile neutropenia	0.64	0.22-1.84	0.41
Diarrhea	0.53	0.43-0.56	< 0.0001
Cutaneous	0.72	0.14-3.63	0.69
Fatigue	1.29	0.63-2.62	0.49
Anemia	1.3	0.63-2.68	0.48
Neurological	20.21	7.47-54.69	< 0.0001
Thrombocytopenia	3.36	1.46-7.73	0.004
Neutropenia	1.13	0.80-1.59	0.5
Paresthesias	7.38	3.73-14.57	< 0.0001
Dehydration	0.51	0.28-0.92	0.03

  - Because of the longer survival, the total cost in the oxaliplatin-based chemotherapy group was also higher than irinotecan-based chemotherapy. The ICER was ¥123,454 /QALY, below commonly cited willingness-to-pay threshold of ¥212,676/QALY (three times GDP per capita in China).
  - Probabilistic sensitivity analysis indicated that oxaliplatin-based chemotherapy was cost-effective in 73.7% of the simulations. The incremental cost-effectiveness plane is presented in Figure 5. The resulting cost-effectiveness acceptability curve is presented in Figure 6.

Table 2: Cost-effectiveness analysis results

	Ox-based chemotherapy	Iri-based chemotherapy
Total cost (RMB)	¥295,483	¥267,382
Total QALYs	1.398	1.170
Incremental cost	¥28,101	
Incremental QALYs	0.228	
ICER	¥123,454	

Figure 5: Cost-effectiveness Plane

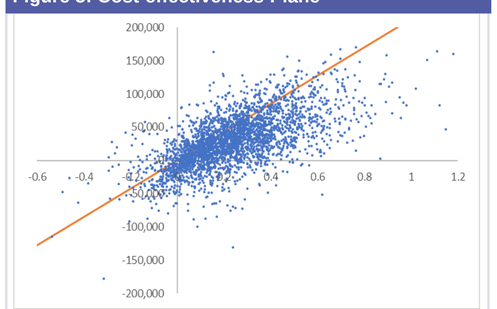
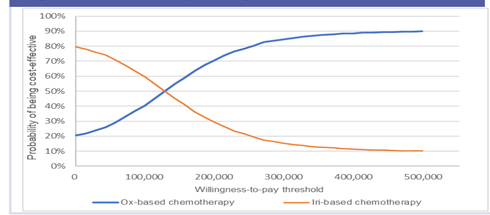


Figure 6: CE acceptability curve



DISCUSSION

- Lack of patient level data should be noted as a limitation, the study just used one parametric models based on median PFS, OS to extrapolate the survival curves.
- Cost differences were not adjusted for different 2nd-line treatment therapies. We instead used an average best supportive care cost for both arms from published literature.
- Although the Ox-base chemotherapy group survival curves were derived from clinical trials, the patients included in these trials are not Chinese patients. The difference in the level of medical care in different countries maybe the impact factor for the patients survival.

CONCLUSIONS

Oxaliplatin-based chemotherapy improved health outcomes compared to irinotecan-based chemotherapy and was projected to be more cost-effective for the first-line treatment of mCRC patients in China.

REFERENCES

1. Afnan Al-Menhali, et al. J Med Food. 2015 Jan;18(1):54-9.
2. Wanqing Chen, et al.CA CANCER J CLIN 2016.
3. Lim HJ, et al. J Oncol Pract 2009; 5(4):153-8
4. https://seer.cancer.gov/statfacts/html/colorect.html. Accessed Oct 30th 2019.
5. Jackson NA, et al. Cancer. 2009;115(12):2617–29.
6. Colucci G, et al. J Clin Oncol. 2005;23(22):4866–75.
7. Schmoll HJ, et al. J Clin Oncol. 2007;25(1):102–9.
8. Fuchs CS, et al. J Clin Oncol. 2007;25(30):4779–86.
9. Gramont A, et al. J Clin Oncol Off J Am Soc Clin Oncol. 2000;18(16):2938–47.
10. Douillard JY, et al. Lancet (London, England). 2000;355(9209):1041–7.
11. Saltz LB, et al. N Engl J Med. 2000;343(13):905–14.
12. Hanna K Sanoff, et al.J Clin Oncol. 2008 Dec 10;26(35):5721-7.
13. Rosati G,, et al. Ann Oncol. 2010 Apr;21(4):781-786.
14. Tournigand C, et al. J Clin Oncol. 2004 Jan 15;22(2):229-37.
15. Giuseppe Colucci, et al. J Clin Oncol. 2005 Aug 1;23(22):4866-75.
16. P. Comella, etal. Ann Oncol. 2005 Jun;16(6):878-86.
17. J Feliu, et al. Br J Cancer. 2005 Nov 28;93(11):1230-5.
18. Kalofonos HP, et al. Ann Oncol. 2005 Jun;16(6):869-77.
19. Richard M Goldberg, et al. J Clin Oncol. 2006 Jul 20;24(21):3347-53.
20. Bajetta E, et al. Br J Cancer. 2007 Feb 12;96(3):439-44.
21. Goldberg RM, et al. J Clin Oncol. 2004 Jan 1;22(1):23-30.
22. Li J, et al. Lancet Oncol. 2015;16:619–629.
23. https://db.yaozh.com/?=yaozh. Accessed Oct 30th 2020.
24. Marc Peeters, et al, et al. J Clin Oncol. 2010 Nov 1;28(31):4706-13.
25. Cui J, et al. Expert Rev Pharm Outcomes Res. 2021 Aug;21(4):691-697
26. Qin S, et al. Cost Eff Resour Alloc. 2018 Aug 4;16:29.
27. Wu B, et al. BMC Cancer. 2014 Dec 19;14:984.

SOURCE OF FUNDING: This study was sponsored by Sanofi China.