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Meta-Analysis and Cost-Minimization Analysis of Oxaliplatin-based Chemotherapy Versus Irinotecan-based Chemotherapy with Targeted Molecular Agents in the 1st-line Treatment of Metastatic Colorectal Cancer In China

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INTRODUCTION

- Colorectal cancer (CRC) is one of the most common malignancies 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, and 50% of all CRC patients will develop metastases over time as the disease progresses[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]. Several studies analyzed the efficacy of bevacizumab combined with different chemotherapy regimens consisting on drugs such as 5-FU, capecitabine, irinotecan and oxaliplatin[6].

OBJECTIVE

To evaluate the efficacy, safety and long-term cost-effectiveness of Oxaliplatin-based chemotherapy plus targeted molecular agents (Ox-based regimens) versus Irinotecan-based chemotherapy plus targeted molecular agents (Iri-based regimens) as the first-line treatment of mCRC from Chinese healthcare system perspective.

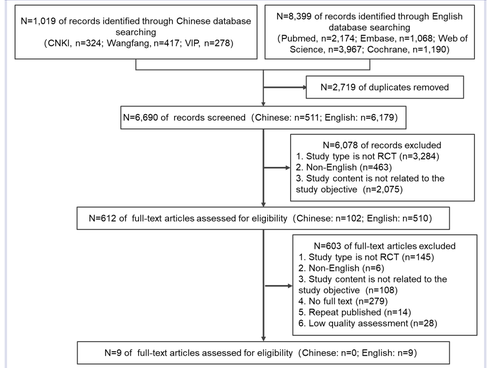
METHODS

- **Systematic review and meta-analysis:**
  - The following electronic databases were searched
    - Databases in English: Pubmed, Embase, Web of science, Cochrane library, ClinicalTrials.gov
    - Databases in Mandarin: CNKI, Wanfang, CQVIP, and chictr.org.cn.
  - The Cochrane Collaboration's tool was used to assess risk of bias of included studies.
  - RCT comparing Ox-based regimens with Iri-based regimens among mCRC patients were considered. A total of 10 articles from 9 clinical trials were identified[7-16]. 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-minimization analysis :**

Model overview

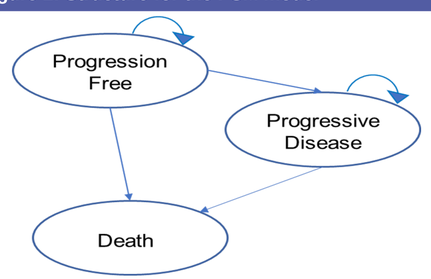
- A partitioned survival model (PSM) was used to determine long-term health outcomes and economic consequences of interventions in the 1st-line treatment of mCRC. Partitioned survival is a typical approach in modeling metastatic cancers, and has been used in many HTA submissions. The model schematic 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



- In order to reflect the chronic nature of mCRC, a lifetime (50 years) horizon was used.
- 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.
- Lognormal, loglogistic and ggamma distributions model were assumed for the PFS and OS fit in Ox-based regimens group.
- Besides, the proportional hazard was assumed in order to estimate the PFS and OS curves of Iri-based regimens 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.

RESULTS

- **Systematic review and meta-analysis**
  - A total of 2,282 mCRC patients that compared Ox-based regimens (n=1,120) with Iri-based regimens (n=1,162) were included. The forest plots of PFS and OS are presented in Figures 3-4. Results of AE are presented in Table 1.
  - The results demonstrated that patients in the two groups had similar OS (HR=1.02; 95 % CI: 0.91 to 1.15, P=0.72) and PFS (HR=1.07; 95 % CI: 0.98 to 1.17; P=0.16).
  - Ox-based regimens has a lower risk of febrile neutropenia (RR=0.31; 95 % CI: 0.11 to 0.87; P=0.03) and leukopenia (RR=0.44; 95 % CI: 0.23 to 0.85; P=0.01), while it had higher rates of neurological events (RR=27.74; 95 % CI: 7.88 to 97.57; P<0.001) and thrombocytopenia (RR=7.88; 95 % CI: 2.39 to 26.02; P<0.001).

Figure 3. Forest plot of PFS

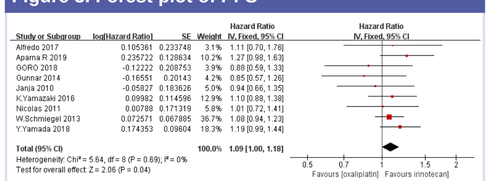


Figure 4. Forest plot of OS

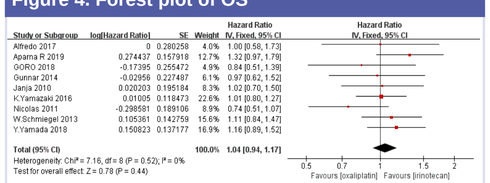


Table 1: Meta-analysis results of AEs

	RR	95%CI	P value
Leukopenia	0.37	0.22-0.63	0.0002
Nausea/vomiting	0.49	0.13-1.86	0.29
Febrile neutropenia	0.21	0.08-0.56	0.002
Diarrhea	0.78	0.54-1.13	0.19
Cutaneous	1.03	0.43-2.44	0.95
Fatigue	1.07	0.64-1.80	0.79
Anemia	0.46	0.23-0.93	0.03
Neurological	40.81	13-128	＜0.0001
Thrombocytopenia	5.52	2.14-14.22	0.0004
Neutropenia	0.76	0.47-1.23	0.26
Paresthesias	0.37	0.22-0.63	0.0002
Dehydration	0.49	0.13-1.86	0.29

- **Cost-minimization analysis :**
  - Given the similar PFS and OS in Meta-analysis results, a cost-minimization analysis method was used to calculate and compare the life-time direct medical costs of Ox-based regimens and Iri-based regimens.
  - The survival curves in two groups are presented in Figure 5-6. Base-case analysis results are presented in Table 2.

Figure 5. Base-case survival curves for Ox-based regimens

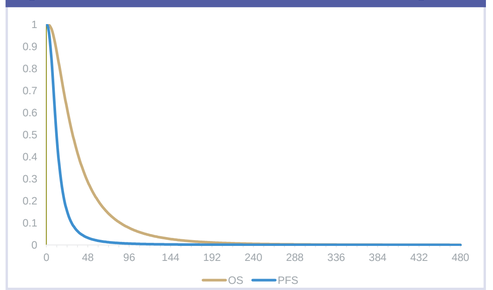
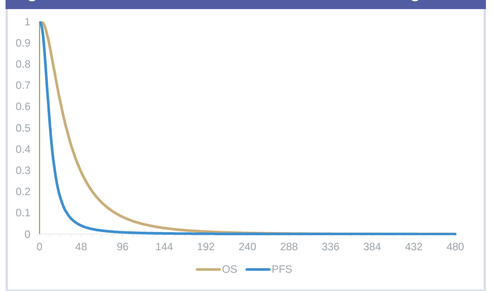


Figure 6. Base-case survival curves for Iri-based regimens



- The cost-minimization analysis showed that Ox-based regimens saved ¥39,355 per patient in direct medical costs in a lifetime horizon compared with Iri-based regimens.

Table 2: Cost-effectiveness analysis results

	Ox-based chemotherapy	Iri-based chemotherapy
Total cost (RMB)	¥658,116	¥697,472
Incremental cost	- ¥39,355	

DISCUSSION

- Although the meta-analysis results shows two regimens have similar efficacy (P>0.05), the patients included in the meta trials are not Chinese patients. The difference in the level of medical care in different countries maybe the impact factor for the patients survival.
- 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.

CONCLUSIONS

The two regimens have similar efficacy and safety profiles. Ox-based regimens are of better economic value with lower overall costs compared with Iri-based regimens for the 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. Welch S, et al. BMC Cancer. 2016 Aug 24;16(1):677.
7. Gunnar Folprecht, et al. Lancet Oncol. 2010 Jan;11(1):38-47.
8. Ocvirk J, et al. World J Gastroenterol. 2010 Jul 7;16(25):3133-43.
9. Nicolas Moosmann, et al. J Clin Oncol. 2011 Mar 10;29(8):1050-8.
10. Schmiegel W, et al. Ann Oncol. 2013 Jun;24(6):1580-7.
11. G Folprecht, et al. Ann Oncol. 2014 May;25(5):1018-25.
12. K Yamazaki, et al. Ann Oncol. 2016 Aug;27(8):1539-46.
13. Carrato A, et al. Eur J Cancer. 2017 Aug;81:191-202.
14. Goro Nakayama, et al. Oncologist. 2018 Aug;23(8):919-927.
15. Yamada Y, et al. Ann Oncol. 2018 Mar 1;29(3):624-631.
16. Aparna R Parikh, et al. Clin Cancer Res. 2019 May 15;25(10):2988-2995.
17. Li J, et al. Lancet Oncol. 2015;16:619–629.
18. https://db.yaozh.com/?=yaozh. Accessed Oct 30th 2020.
19. Marc Peeters, et al, et al. J Clin Oncol. 2010 Nov 1;28(31):4706-13.
20. Cui J, et al. Expert Rev Pharm Outcomes Res. 2021 Aug;21(4):691-697
21. Qin S, et al. Cost Eff Resour Alloc. 2018 Aug 4;16:29.
22. Wu B, et al. BMC Cancer. 2014 Dec 19;14:984.

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