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Research Article

Myeloid Toxicity Profile is Related to Treatment Outcome in Trials of Second-Line Chemotherapy of Patients with Metastatic Colorectal Cancer

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Abstract

Objectives: Although for targeted therapies some toxicities have been shown to predict drug activity, this is unclear for cytotoxic chemotherapy. However, various studies have documented that neutropenia is related to the activity of chemotherapy in patients with metastatic colorectal cancer (mCRC). The aim of the study is to evaluate whether a difference in toxicity rate between treatment arms corresponds to a different progression-free survival (PFS).

Methods: A systematic review and a selection of the randomized phase III trials of second-line chemotherapy of patients with mCRC were performed. All the studies that reported bone marrow (neutropenia, anemia, thrombocytopenia) and gastrointestinal (diarrhea, stomatitis, vomiting) toxicities were included. For each trial, the relationship between the difference in the frequency rates of each of the toxicities between study arms with the difference in PFS was evaluated by Pearson's test (rho), in order to detect a possible correlation between toxicity and outcome.

Results: Thirteen studies were selected. The difference in neutropenia rates between the study arms correlated with the difference in PFS (rho = 0.817; p-value 0.004; 10 studies). In particular, the correlation was significant for mild neutropenia (rho = 0.764; p-value 0.004; 12 studies). Similar data were detectable for thrombocytopenia and anemia, but not for diarrhea and vomiting.

Conclusion: Differently than gastrointestinal side effects, a mild to moderate bone marrow toxicity is associated to the activity of second-line cytotoxic chemotherapy in patients with mCRC, and therefore it could reflect not only the direct toxicity of the drugs but also some chemotherapy-related response mechanisms.

Keywords: Colorectal cancer, second-line chemotherapy, neutropenia, thrombocytopenia, diarrhea, vomiting

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Colorectal carcinoma (CRC) is the third common malignancy worldwide and the second in terms of cancer-related deaths.[1] Both in patients who present with metastases at diagnosis and in those with relapse after curative resection of the primary tumor, the therapy of choice for metastatic colorectal cancer (mCRC) still remains predominantly cytotoxic chemotherapy.[2]

Cytotoxic antineoplastic drugs used in mCRC have various limiting toxicities, but the most frequent are myeloid toxicities (MY-tox) or gastrointestinal toxicities (GI-tox). In the presence of a linear relationship of drug dose with toxicity and activity, it would be expected that an increase in toxicity rates corresponds to an increase in chemotherapy activity. However, it has never been reported, while chemother-

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apy-related serious adverse events (SAEs) in mCRC have been associated to enzymatic deficit or pharmacogenomic profiles. In addition, the toxicity profile of some drugs, such as fluorouracil, varies greatly depending on the schedule, and in any case, it does not appear that the same patients reporting more toxicity also report correspondingly a more pronounced drug activity.[3]

On the other hand, various studies have documented an increased chemotherapy activity in patients with mCRC reporting early chemotherapy-induced neutropenia.[4] It is unclear whether this relationship is a direct drug dose-to-target effect in the individual patient, or is partly mediated by secondary activities on the myeloid series. Furthermore, the prognosis of patients reporting SAEs is usually worse, however when chemotherapy activity improved in patients with MY-tox, the benefit was independent from the severity of the MY-tox.[5,6]

The aim of the study is to evaluate whether different MY-tox or GI-tox rates between treatment arms correspond to different PFS in randomized trials of second-line chemotherapy of patients with mCRC.

Methods

Study Selection

The literature search was run with the aim to find randomized clinical trials of second-line chemotherapy of patients with metastatic colorectal cancer that reported any rate of bone marrow (neutropenia, anemia, thrombocytopenia) and gastrointestinal (diarrhea, stomatitis, vomiting) toxicities, mild or severe, and as outcome measure the progression-free survival. We decided to limit the analysis to only three adverse events for myeloid series and three for gastrointestinal tract, preferring vomiting to nausea due to less subjective evaluation criteria. The research was done by the following criteria: "(colon or colorectal) and (metastatic or advanced) and (carcinoma or adenocarcinoma or cancer or tumor) and chemotherapy and (refractory or second-line) and (toxicity or safety)". The research was done in the PubMed and EMBASE databases, within the time limit from 2001 to 2020, and restricting to randomized controlled trials, evaluating all full-lenght articles in English. Systematic reviews and reference lists of the selected articles were cross-checked to find other similar studies. If more articles reported the results of the same study, the most recent or most complete paper was kept. After the exclusion of duplicates, the authors examined the articles by the titles. Among the ones whose titles were relevant, authors evaluated the abstracts, and identified the full-length original studies, including only phase III trials of second-line chemotherapy.

Statistical Analysis

Two arms per trial were selected for the analysis. The differences in the results of these two arms (Δ, delta) were calculated for PFS, and for the rates of myeloid toxicities (anemia, neutropenia, thrombocytopenia) and gastrointestinal toxicities (diarrhea, vomiting, stomatitis). The Pearson ρ correlation coefficient (r) was used as a measure of correlation between the difference in each toxicity (delta tox) and the difference in PFS (delta PFS).

A two-sided p-value <0.05 was considered significant. The analyses were conducted using the statistical computing language R (version 3.6.0 for Linux).

Results

With the specified search criteria PubMed returned 1049 articles and EMBASE 826. After the selection process, the eligible articles were 13, referring to 13 randomized phase III studies and 14 study cohorts.[7-19] Each step of the systematic review has been summarized in the PRISMA flow of Figure 1 and in Table suppl 1.

The characteristics of the studies are listed in Table 1. One study reported two comparison between the two arms, referred to two different molecularly selected populations.[14] Of the 14 comparisons across the 13 selected studies, which included 28 arms and 9687 patients (4848 vs. 4839), with a median of 315 patients per arm (range 95-650), eight had OS as endpoint, two PFS, two ORR, and one OS/PFS as co-primary.

The toxicity rates for each arm are resumed for both MY-tox (Table 2) and GI-tox (Table 3), and delta of their rates have been calculated.

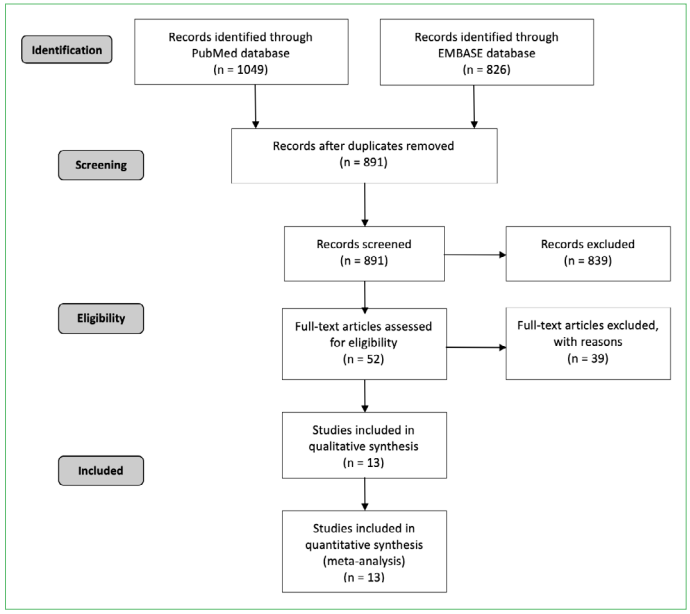

Figure 1. Flowchart of search and study selection.

Table 1. Characteristics of the studies

Ref.	Trial	Year	Arms	No. pts	Endpoint	PFS (m)
[7]	Pharmacia	2003	I-w vs I	95 vs 196	OS	4.0 vs 3.0
[8]	Sanofi	2003	OF vs O	152 vs 156	ORR	4.6 vs 1.6
[9]	BOND 2	2004	IC vs I	218 vs 111	ORR	4.1 vs 1.5
[10]	ACCUP	2008	IO vs I	317 vs 310	OS	5.3 vs 2.8
[11]	NO 16967	2008	OX vs OF	313 vs 314	PFS	4.7 vs 4.8
[12]	EPIC	2008	IC vs I	648 vs 650	PFS	4.0 vs 2.6
[13]	N9841	2009	OF vs I	245 vs 246	OS	6.2 vs 4.4
[14]	20050181(a)	2010	IFP vs IF	303 vs 294	OS/PFS	5.9 vs 3.9
[14]	20050181 (b)	2010	IFP vs IF	238 vs 248	OS/PFS	5.0 vs 4.9
[15]	Confirm 2	2011	OFV vs OF	426 vs 429	OS	5.6 vs 4.2
[16]	Velour	2012	IFA vs IF	612 vs 614	OS	6.9 vs 4.7
[17]	ML 18147	2013	ChtB vs Cht	419 vs 411	OS	5.7 vs 4.1
[18]	RAISE	2015	IFR vs IF	536 vs 536	OS	5.7 vs 4.5
[19]	AXEPT	2018	IXB vs IFB	326 vs 324	OS	8.4 vs 7.2

Legend. A, aflibercept. B, bevacizumab. C, cetuximab. Cht, chemotherapy. F, fluorouracil. I, irinotecan. O, oxaliplatin. P, panitumumab. R, ramucirumab. V, Vascular endothelial growth receptor inhibitor PTK/ZK. X, capecitabine. W, weekly.

Table 2. Differences between arms of treatment-related myeloid toxicities

Trial	Anemia (%)	G3-4 (%)	Neutro (%)	G3-4 (%)	Platelet (%)	G3-4 (%)
Pharmacia	17 vs 18	1 vs 4	43 vs 42	29 vs 34	3 vs 4	0 vs 1
Sanofi	81 vs 64	2 vs 1	73 vs 7	44 vs 0	64 vs 30	5 vs 3
BOND 2	-	4,7 vs 2,6	-	9,4 vs 0	-	-
ACCUP	-	-	25 vs 13	-	-	-
NO 16967	-	-	19 vs 48	5 vs 35	14 vs 16	4 vs 2
EPIC	87,2 v 85,3	3,2 vs 2,6	62,4 vs 55,6	31,8 vs 25,4	28,1 vs 26,8	1,8 vs 0,7
N9841	-	-	-	55 vs 39,5	-	5,8 vs 4,1
20050181(a)	-	-	-	20 vs 23	-	-
20050181 (b)	-	-	-	14 vs 17	-	-
Confirm 2	-	-	37,2 vs 38,8	29,4 vs 29	-	5,5 vs 4
Velour	-	-	67,8 vs 56,3	36,7 vs 29,5	47,4 vs 33,8	3,4 vs 1,6
ML 18147	-	-	65 vs 52	-	-	-
RAISE	17 vs 21	2 vs 4	58 vs 46	10 vs 9	29 vs 14	4 vs 1
AXEPT	71 vs 81	4 vs 5	56 vs 86	17 vs 43	36 vs 35	2 vs 1

Table 4 summarizes the Pearson rho results of the differences between arms in PFS (Δ PFS) and toxicity rates (Δ toxicity rates). In contrast to diarrhea and vomiting, MY-tox deltas correlate with Δ PFS significantly, while no conclusions can be drawn for the low number of studies that evaluated stomatitis.

Discussion

The most important result of the study is the confirmation of the relationship between MY-tox, in particular neutropenia and thrombocytopenia, with the activity of chemotherapy in terms of PFS, while this relationship is not evident for GI-tox. The number of studies that have evaluated stomatitis, in our opinion, is limited to draw definitive conclusions on the relationship between the occurrence of stomatitis and PFS; this number is also low due to the impossibility of including some studies that reported separately the cases of stomatitis and oral mucositis.[18]

We decided to evaluate the second-line chemotherapy trials because in this setting a lower PFS and an increase in the frequency of toxicities are expected, therefore the possible relationships between the variables could have been easier to detect, but it cannot be excluded that a reduction of the bone marrow reserve after first-line chemotherapy may have accentuated MY-tox compared to GI-tox. Although the risk of myelodysplasia and acute

Table 3. Differences between arms of treatment-related gastro-intestinal toxicities

Trial	Diarrhea (%)	G3-4 (%)	Stomatitis (%)	G3-4 (%)	Vomiting (%)	G3-4 (%)
Pharmacia	82 vs 76	36 vs 19	-	-	40 vs 42	6 vs 13
Sanofi	67 vs 46	11 vs 4	37 vs 14	3 vs 0	40 vs 37	9 vs 4
BOND 2	-	21,2 vs 1,7	-	2,4 vs 0,9	-	7,1 vs 4,3
ACCUP	28 vs 23	-	-	-	15 vs 14	-
NO 16967	57 vs 51	20 vs 6	14 vs 30	1 vs 1	43 vs 34	3 vs 3
EPIC	81,2 vs 71,9	15,7 vs 28,4	-	-	38,4 vs 34,5	5,2 vs 5,4
N9841	-	10,7 vs 31,3	-	-	-	12,8 vs 20,6
20050181(a)	-	14 vs 9	-	8 vs 3	-	-
20050181 (b)	-	14 vs 11	-	9 vs 4	-	-
Confirm 2	62,1 vs 48,6	16,4 vs 8,3	21,3 vs 13,8	-	60,2 vs 37,9	9,5 vs 5,2
Velour	69,2 vs 56,5	19,3 vs 7,8	54,8 vs 34,9	13,8 vs 5	32,9 vs 33,4	2,8 vs 3,5
ML 18147	40 vs 34	-	13 vs 4	-	14 vs 13	-
RAISE	60 vs 51	11 vs 9	31 vs 22	4 vs 3	30 vs 28	4 vs 3
AXEPT	50 vs 42	7 vs 3	27 vs 37	2 vs 3	27 vs 29	2 vs 2

Table 4. Correlation coefficient (Pearson rho) of differences in toxicities between arms with differences in PFS

Myeloid toxicity	No. comparisons	Correlation coefficient (Pearson rho)	p
Anemia			
All grades	7	0.844	0.017
G1-G2	6	0.915	0.011
G3-G4	7	0.323	0.480
Neutropenia			
All grades	10	0.817	0.004
G1-G2	12	0.764	0.004
G3-G4	8	0.672	0.068
Piastrinopenia			
All grades	7	0.847	0.016
G1-G2	7	0.847	0.016
G3-G4	9	0.221	0.567
Gastro-intestinal toxicity	**No. comparisons**	**Correlation coefficient (Pearson rho)**	**p**
Diarrhea			
All grades	10	0.554	0.097
G1-G2	8	0.431	0.287
G3-G4	12	0.112	0.730
Stomatitis			
All grades	6	0.913	0.011
G1-G2	4	0.971	0.029
G3-G4	7	0.266	0.565
Vomiting			
All grades	10	0.031	0.932
G1-G2	7	-0.736	0.059
G3-G4	9	0.340	0.370

myeloid leukemia does not increase statistically for colon cancer,[20] clonal hemopoiesis of uncertain significance is present after chemotherapy, and when it does not evolve to myelodysplastic syndromes it could affect anemia, as well as increase the risk of death from tumor or cardiovascular event.[21] Then, although pre-treated patients may develop clonal hemopoiesis, we believe that the time from first-line chemotherapy was limited and the amount of cytotoxic drugs received often insufficient.

Contrary to stomatitis, though the number of studies that reported anemia is congruous, the interpretation of the relationship between the post-chemotherapy anemia and the better PFS is not simple. This is because it is difficult to distinguish the contribution of the baseline anemia, which is often iron-deficient or chronic disease-related in mCRC, from the occurrence of chemotherapy-related anemia. Furthermore, given the development and recovery timing of chemotherapy anemia, even if the reported anemia were only chemotherapy-related anemia it would not be easy to attribute it to the first- or the second-line regimen, nor the data on the erythropoietic stimulating agents treatment are available in the studies. However, the fact that in our experience anemia after second-line chemotherapy correlated with better PFS supports the hypothesis that the response to chemotherapy could have an effect on all myeloid series. In this context, a later progressive improvement of anemia in responding patients would be expected, but the absence of longitudinal data on the toxicity and characteristics of anemia does not allow to verify the behavior of the anemia in relation to the response of the tumor.

Although it seems logic that more toxicity can be associated with more activity of antineoplastic drugs in terms of PFS, the different relationships based on the type of toxicity evaluated is unclear. For this reason it seems rather simplistic to dismiss the MY-tox of cytotoxic chemotherapy as a direct exclusive effect of the drug dose on the bone marrow. In addition, the reported difference between MY-tox and GI-tox does not appear explainable by the drugs and regimens, since both toxicities are reported for most of the involved antineoplastic drugs, and given the heterogeneity of the regimens in the selected studies throughout the time.

With this consideration we certainly do not want to diminish the variability related to the various drugs, which in various ways could affect the results of the study. The rather different toxicity profiles of cytotoxic drugs are well known, even within the same class, such as fluoropyrimidines,[22,23] and the variability of the toxicity profiles of a single drug such as fluorouracil with its multiple schedules of administration. An individual patient analysis of 1219 cases found a significant difference in neutropenia and hand-foot syndrome rates between bolus and infusional fluorouracil, and a relationship of some variables (age, sex, performance status) with the risk of toxicity.[24] Another study found that the risk of diarrhea increased in the presence of primary cancer and previous episodes of chemotherapy-related diarrhea.[25]

In support of this wide variability, pharmacogenomic variations in the population have been documented, relating in particular to the efficiency of the enzymes responsible for detoxifying drugs, although they explain only part of the severe toxicities. A study evaluating the phenotype of dihydro-pyridin-dehydrogenase (DPYD), which is primarily responsible for the elimination of fluorouracil, concluded that an enzyme deficiency is associated with severe fluorouracil toxicity, but in that experience, contrary to severe GI-tox, DPYD deficiency was not associated with significantly higher rates of severe MY-tox.[26] Conversely, although diarrhea is the dose-limiting irinotecan related side effect, an enzyme deficiency of UGT1A1 increases more the irinotecan-related severe MY-tox than the GI-tox.[27] Further data lead us to reflect on the relationship between drugs and side effects, such as a meta-analysis of 51 phase-1 studies that documented SAEs in 19.8% of patients who received drug therapy compared to 5.6% of those receiving a placebo, such that the authors conclude that adverse effects, even the serious ones, are not only and always the effect of the drug.[28]

The explanation that we suggest is that MY-tox could reflect not only the direct toxicity of the drugs but also a chemotherapy-related tumor response mechanism. The hypothesis is that what we define as MY-tox, differently from the GI-tox, is only partly attributable to the direct effect of the chemotherapy on the myeloid series, while the depression of the myolid lines during chemotherapy in metastatic disease could be, to some extent, an effect of the interaction between the host and the tumor.

The issue, however, is further complicated by the activation of the systemic inflammatory response (SIR), usually characterized by an increase in the counts of neutrophils and platelets in the peripheral blood.[29] This phenomenon is common in advanced tumors, and in particular in some subgroups of CRC such as the consensus molecular subgroup (CMS) 4.[30] Although the SIR activation is associated with more chemoresistance, the activity of chemotherapy sometimes reduces SIR activation itself. However, this mechanism may be more difficult to detect when baseline systemic inflammation is activated than when it is not, because the absolute neutropenia is more likely to be detected when the baseline neutrophil count is normal.

All the limitations of the current retrospective and trial-level analysis must be considered, as well as the failure to define the timing of the toxicity assessment, the various chemotherapy regimens, the different schedules of the drugs, the absence of pharmacogenomic data, the lacking reports about the use of bone marrow growth factors, the total number of cycles of chemotherapy, the adjustment based on the baseline neutrophil and platelet counts in the individual patient, and the molecular characteristics of tumors (in particular CMS). Furthermore, the toxicity concerns the whole treatment time and does not allow a cross-sectional evaluation at predefined times, the same toxicity evalua-

tion criteria have changed over time, so that the studies are not exactly comparable.

Conclusion

Despite all this, the study suggests that a direct effect on the myeloid series by cytotoxic drugs in mCRC could be less relevant than the indirect effect mediated by the host response to the tumor during chemotherapy. This finding is associated with a number of other evidences on the predictive role of chemotherapy efficacy by early neutropenia after chemotherapy. Therefore, a prospective evaluation of early neutropenia and thrombocytopenia, adjusted with respect to baseline values of neutrophils and platelets, CMS, and the use of growth factors, is strongly recommended in chemotherapy-based studies of mCRC, since it could allow to define useful intermediate endpoints, and enable a better understanding of the physiology and kinetics of response to chemotherapy.

Disclosures

Ethics Committee Approval: This article does not contain any studies with human participants or animals performed by any of the authors. Therefore, ethical approval approval is not necessary.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – G.A.C.; Design – G.A.C., A.V.; Supervision – A.V.; Materials – G.A.C; Data collection and processing – G.A.C., A.V.; Analysis and interpretation: G.A.C., A.V.; Literature search – G.A.C.; Writing – G.A.C.; Critical review – A.V.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	5-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8-9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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