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Metronomic chemotherapy for paediatric extracranial solid tumours: a systematic review and meta-analysis of randomised clinical trials

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ABSTRACT

Background Metronomic chemotherapy ('less is more, regularly') could be an alternative to the maximum tolerated dose ('the more, the better') in the chemotherapeutic cancer treatment of high-risk malignant solid extracranial tumours in children or young adults.

Objective To evaluate the efficacy of metronomic chemotherapy compared with placebo or stop treatment in paediatric patients with extracranial malignant solid tumours.

Methods We searched the databases MEDLINE and CENTRAL on 8 September 2023 and included randomised clinical trials (RCTs). Primary outcome was overall survival, and the main outcome measure was the HR.

Results We identified three RCTs with parallel assignment and intention-to-treat analyses of data from 775 people. The studies primarily reported on participants with rhabdomyosarcoma, neuroblastoma and osteosarcoma. The HR favoured the metronomic chemotherapy group (0.75 (95% CI 0.56 to 0.98)).

Conclusions The evidence base is compatible with a favourable effect of metronomic chemotherapy on children and young adults with high-risk extracranial malignant solid tumours, especially other than bone tumours, when compared with placebo or stop treatment. Statistical heterogeneity is low while clinical heterogeneity is substantial. Thus, the results must be interpreted with caution and applicability of the results is limited. Future RCTs could provide more data on individual tumour entities and subsequently add information on tumour-specific responses.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The present systematic review is based on a comprehensive search.
⇒ Three included studies are characterised by a considerable number of participants and signs of low statistical heterogeneity among them.
⇒ The essential HR of overall survival was deduced from Kaplan-Meier curves.
⇒ Blinding was difficult to assess concerning the treatment of serious diseases, and we judged an unclear risk when blinding was not reported or not applied.
⇒ Applicability is limited due to the substantial clinical heterogeneity.

INTRODUCTION

Description of the condition

In the present systematic review, diseases of interest are malignant extracranial solid neoplasms that occur during childhood.[1] This heterogeneous group of cancers represents approximately 40% of all paediatric malignancies in infants and young children.[2] In children 0 to 14 years of age, the most common solid tumours are soft tissue sarcoma (7%), neuroblastoma (6%), nephroblastoma (5%) and malignant bone tumours (4%).[2] Common presenting signs and symptoms of paediatric solid tumours are for example, abdominal mass, constipation, shortness of breath, back pain, bone pain, fever and arterial hypertension.[2] Peripheral nervous cell tumours (such as neuroblastoma), bone sarcomas (such as osteosarcomas and Ewing sarcomas) and soft tissue sarcomas (such as rhabdomyosarcoma) separately affect about 1 child in 6000 to 7200 children under 18 years of age.[3] More and more complex and intense treatment protocols have been established, and long-term survival significantly improved in recent decades.[4] Nevertheless, survival after malignant extracranial solid tumour relapse is still poor. For instance, the reported 5 year overall survival rate after relapse from high-risk neuroblastoma is about 20% despite intense relapse treatments.[5] New treatment strategies are urgently needed.[6]

Description of the intervention

Chemotherapy for paediatric extracranial high-risk tumours is usually based on the concept of maximum tolerated dose (MTD, 'the more, the better').[7] High-dose chemotherapy aims to kill tumour cells but at the same time also threatens for example, bone marrow and organ function often leading to

severe adverse events. Therefore, treatment-free intervals are needed to allow cell recovery. In contrast, metronomic chemotherapy (MC) is defined as the frequent administration of chemotherapeutic drugs at doses significantly below the MTD with no prolonged drugfree breaks ('less is more, regularly').[8] As a multi-target treatment, MC is thought to affect the tumour microenvironment and the cancer cell. Effects on tumour angiogenesis and anticancer immunity have been shown.[9] Additionally, MC is often combined with nonchemotherapeutic drugs that is, in the context of drug repurposing.[10] The feasibility and the low toxicity profile in the heavily pretreated patients encouraged physicians to perform more clinical trials with metronomic treatment for solid tumours over the last years.

Objective

This systematic review aimed to evaluate the efficacy of MCcompared with placebo or stop treatment in paediatric patients with extracranial malignant solid tumours.

METHODS

While preparing this systematic review, we endorsed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, adhere to its principles and followed its checklist.[11] Patients and the public were not involved in this systematic review.

Search strategy

We performed an unrestricted electronic literature database search in MEDLINE via PubMed (US National Library of Medicine) on 8 September 2023. Due to automated term mapping, use of an asterisk (*) as a wild card for truncation, different spelling or use of synonyms was not necessary. We conducted an additional electronic literature database search in the Cochrane Central Register of Controlled Trials (CENTRAL) of The Cochrane Library via Wiley based on the PubMed search strategy. MeSH terms were combined with text terms to ensure a comprehensive and up-to-date search. We searched the online trial registries ClinicalTrials.gov (CT.gov, https://clinicaltrials.gov/, US National Library of Medicine) and International Clinical Trials Registry Platform (ICTRP, https://trialsearch.who.int, WHO) on 18 August 2023. The original and updated search strategies are shown in online supplemental table S1. We extended the search by using Google, reference lists of recent publications and PubMed tools including *similar articles* and *clinical queries*.

Study selection

Inclusion criteria. We considered randomised controlled trials (RCTs) with parallel assignment of paediatric patients with extracranial malignant solid tumours. The test intervention was MC which generally followed standard treatment. MC was defined as the frequent administration of chemotherapeutic drugs at doses significantly below the MTD with no prolonged drugfree breaks.[8] The control intervention was placebo or stop treatment. Exclusion criteria. We did not consider publications as follows: article abstracts, meeting abstracts, ongoing studies, trial registries, comments, letters, narrative reviews, systematic reviews duplicate publications.

Outcomes

Primary beneficial outcome measure was overall survival. Primary adverse outcome was treatment-related mortality. Secondary outcomes were progression-free survival, disease-free survival, event-free survival, toxicity grade 3 to 4 and health-related quality of life.

Data collection and analysis

FP imported the bibliographic data into Excel (Microsoft) and EndNote X9 (Clarivate), and FP and MH selected relevant studies in a two-step screening process. In the first step, selecting potentially relevant references was based on title and/or abstract. In the second step, including relevant studies was based on full text. Reasons were provided for excluding the rest of formerly potentially relevant articles. FP and MH also independently extracted information on study design, participants and outcomes into Word (Microsoft). Differences in opinions were resolved by discussion, and the assistance of a third author was not necessary. The main extracted data fields include the study characteristics (registry ID, design, sponsor, participating hospitals and enrolment), the participants (disease, age, gender, tumour histology, performance status, pathology, primary tumour invasiveness, regional lymph node involvement, tumour size and surgery), the interventions (pretreatment before and after randomisation and MC after randomisation), the comparators after randomisation, the treatment duration, the follow-up and the outcomes (overall survival, disease-free survival, progression free survival, event-free survival, health-related quality of life, death, treatment-related mortality, neutropenia grade 3 to 4, neurology adverse events grade 3 to 4 and nephrotoxicity grade 3 to 4).

Concerning time-to-event data, such as overall survival, we re-enacted the survival functions by deducing survival data from the survival curves depicted in the corresponding article. We used the Excel tool provided by Tierney *et al*[12] to estimate the HR and the corresponding log(HR) by using the 'data from curve with numbers at risk given', which is based on the method by Parmar *et al*.[13] If the numbers at risk were not given, we used the 'data from curve read where wished and assuming constant censoring'. We made sure that the constructed graph based on input data was like the published graph. Data were analysed using the Cochrane Review Manager 5 (The Cochrane Collaboration): statistical method: inverse variance; analysis model: random effects and effect measure: HR. The procedure can be detailed as follows: first, the Kaplan-Meier plot is enlarged and printed. In general, time intervals are plotted on the x-axis and the probability of overall survival is plotted on the y-axis. The

values of the time points are usually given in months such as 0, 12, 24 etc. The values of the probabilities are usually given as per cent such as 100% at time point 0. Second, a perpendicular is drawn between a specific time point of the x-axis and the corresponding point of the curve and the distance is measured. This is exerted twice, for the test group and for the control group. Third, the values of distance are converted in values of probability. The time point at 0 and the corresponding probability of 100% or 1.0 serve as a reference for the conversion. Fourth, the time points, the corresponding probability and the number of participants at risk are typed into the downloaded spreadsheet. It is important to make certain that the re-enacted curve mirrors the original curve perfectly. Fifth, the application calculates the HR and the log(HR). These figures are then transferred to the Cochrane Review Manager analysis tool.

Concerning dichotomous outcomes (eg, adverse events), we extracted the number of patients in each treatment arm and the number of patients who experienced the outcome of interest. Data were analysed using the Cochrane Review Manager 5 (The Cochrane Collaboration): statistical method: Mantel-Haenszel; analysis model: random effects and effect measure: risk ratio. We did not identify continuous data.

Subgroups and heterogeneity

We assessed clinical reasons for heterogeneity and estimated the percentage heterogeneity between trials that cannot be ascribed to sampling variation using the index of heterogeneity (I^2 statistic).[14] An I^2 statistic equal to or greater than 50% was regarded as considerable heterogeneity. The studies did not separately report on bone sarcomas versus other than bone sarcomas, thus, it was not possible to conduct a sensitivity analysis in this regard. We conducted a subgroup analysis of studies on solid tumours other than bone sarcomas.

Assessment of risk of bias in included studies

Two authors independently appraised the risk of bias of the included studies. Differences in opinions were resolved by discussion and the assistance of a third author was not necessary. We used the items listed within Cochrane's tool for assessing risk of bias.[15] We assessed selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The criteria for judging an unclear, low or high risk of bias with respect to seven items are shown in online supplemental table S2.

Patient and public involvement

Patients and the public were not involved. There were no study participants since the study was based only on published study data.

RESULTS

Search results

Figure 1 shows the literature retrieval and reference flow. We retrieved 285 references from electronic databases and additional sources such as references lists. We excluded 241 references based on title/abstract information. We excluded another 40 references with reasons based on full-text evaluation. We included four references[16–19] which include the original study data of three RCTs[16–18] and a follow-up report on health-related quality of life.[19] During the 2022 Annual Meeting of the American Society of Clinical Oncology (ASCO), a poster referred to a study which appears to fulfil the inclusion criteria.[20] Unfortunately, the study data relevant for the inclusion in this systematic review will not be available soon. Online supplemental table S3 lists the primary references for the three included studies and 10 associated references. Online supplemental table S4 lists the exclusion reasons for 40 references including the 10 references related to the included studies.

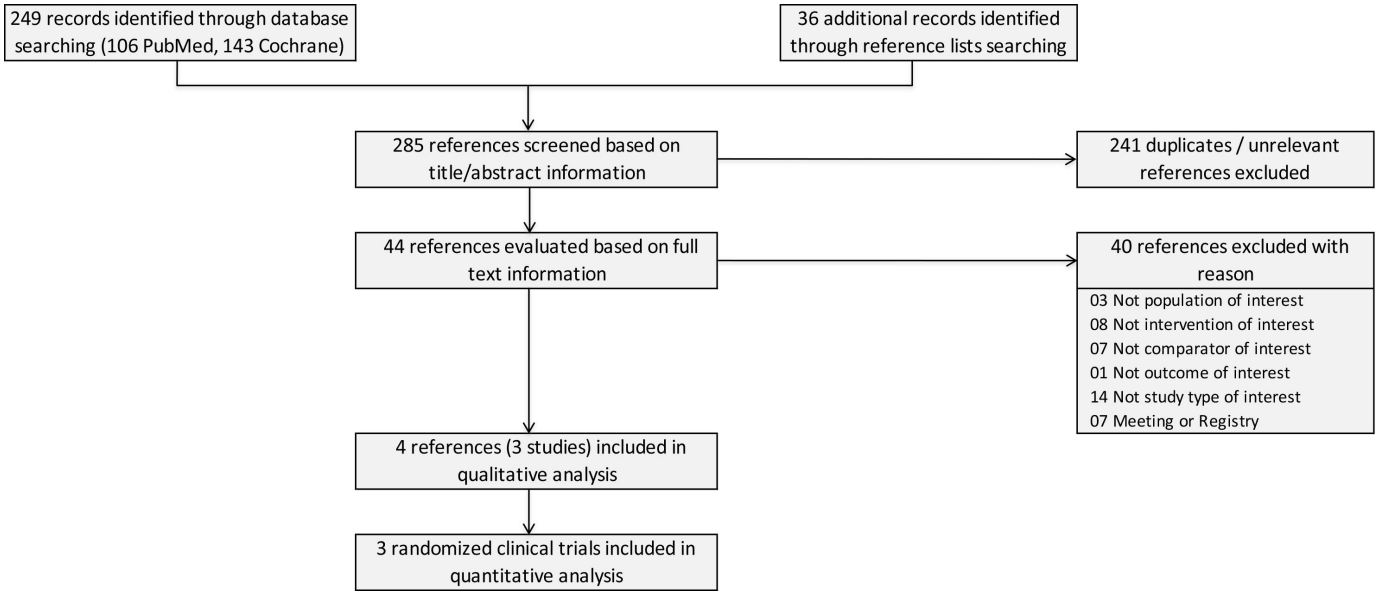

Figure 1 Literature search and flow.

Table 1 Inclusion criteria and study characteristics according to the included RCTs

	Bisogno[16]	Pramanik 2017[17]	Senerchia[18]
Registries	NCT00339118; EudraCT 2005-000217-35	NCT01858571; CTRI/2013/06/003734	n.r.
Study name	RMS 2005	n.r.	n.r.
Design	Randomised, parallel assignment, phase 3, no masking	Randomised, parallel assignment, phase 3, masking: double (participant, care provider)	Randomised, parallel assignment, phase 3, no masking
Sponsor	EpSSG, European paediatric Soft tissue sarcoma Study Group	AIIMS, All India Institute of Medical Sciences	UNIFESP, Universidade Federal de Sao Paulo
Participating hospitals	102 hospitals in 14 countries: Argentina, Belgium, Brazil, Czech Republic, France, Ireland, Israel, Italy, Norway, Switzerland, Slovenia, Spain, the Netherlands, the UK	AIIMS, a tertiary care referral cancer centre in North India	27 hospitals in three countries: Argentina, Brazil, Uruguay
Enrolment	Apr 2006 to Dec 2016: 670 screened, 371 enrolled	Oct 2013 to Dec 2015: 123 screened, 108 enrolled	May 2006 to Jul 2013: 422 screened, 296 enrolled
Population	Patients aged 6 months to 21 years with nonmetastatic high-risk rhabdomyosarcoma at the time of diagnosis and complete remission or with minimal abnormalities on imaging studies at the end of the standard treatment (nine cycles of ifosfamide, vincristine and dactinomycin with or without doxorubicin, and surgery or radiotherapy or both)	Patients aged 5 to 18 years with primary extracranial, nonhematopoietic solid malignant tumours that were refractory/ progressive after treatment with at least 2 lines of chemotherapy (not specified) and had no other curative treatment options	Patients 30 years or younger with newly diagnosed high-grade nonmetastatic osteosarcoma and complete resection of the primary tumour after 10 weeks of preoperative therapy with intravenous MAP (methotrexate, adriamycin and platinum); cisplatin in part replaced by dexrazoxane from week 11 to week 31
Intervention	MC (n=185): six cycles of intravenous vinorelbine 25 mg/m^2 on days 1, 8 and 15, and oral cyclophosphamide 25 mg/ m^2 on days 1 to 28.	MC(n=56): daily oral celecoxib and daily oral thalidomide with alternating periods of oral etoposide and oral cyclophosphamide	73 weeks MC (n=139): oral cyclophosphamide 25 mg/m^2) daily and oral methotrexate 1.5 mg/m^2 two times per daily two times per week after chemotherapy from week 32 through week 104
Comparator	Stop treatment (n=186)	Placebo (n=52)	Stop treatment (n=157)
Outcome: primary	Disease-free survival	Progression-free survival (proportion of patients without disease progression at 6 months)	Event-free survival (events: recurrence, disease progression, secondary malignancy or death)
Outcome: secondary	Overall survival and toxicity	Overall survival and progression-free survival duration	Overall survival
Duration of treatment	Six 4 week cycles continuously for 24 weeks	Treatment was continued until progression was documented	Until week 104
Follow-up	Median 60.3 months	Median 2.9 months	n.r.
Kaplan-Meier interval	Up to 132 months	Up to 15 months	Up to 80 months

CTRI, Clinical Trials Registry – India; EudraCT, European Union Drug Regulating Authorities Clinical Trials Database; MAP, methotrexate, adriamycin (= doxorubicin) and platinum (= cisplatin); MC, metronomic chemotherapy; NCT, ClinicalTrials; n.r., not reported; RCTs, randomised clinical trials.

Baseline data

Table 1 provides an overview of the main characteristics of the study design. Briefly, the three RCTs were published between 2017 and 2019. The screening of 1215 people resulted in enrolment and analysis of data of 775 participants from 16 countries (South America, Europe and Asia). All studies applied an intention-to-treat analysis and were sponsored by public institutions.

Table 2 provides an overview of the main characteristics of the participants. Most participants were children or adolescents with slightly more males than females. The authors reported a variety of solid tumours mainly

Table 2 Characteristics of study participants

	Treatment group	Bisogno *et al*[16]	Pramanik *et al*[17]	Senerchia *et al*[18]
Age	MC	1 year or younger: 6% (n=11)	Median (range): 13 years (5 to 18)	Mean (SD) in years: 13.23 (4.61)
		> 1 year to 9 years: 74% (n=136)		
		10 years to 17 years: 18% (n=34)		
		18 years or older: 2% (n=4)		
	Comparator	1 year or younger: 1% (n=2)	Median (range): 15 years (5 to 18)	Mean (SD) in years: 13.85 (4.10)
		> 1 year to 9 years: 77% (n=143)		
		10 years to 17 years: 19% (n=36)		
		18 years or older: 3% (n=5)		
Gender	MC	Male: 57% (n=105)	Male: 75.0% (n=42)	Male: 52.5%
	Comparator	Male: 56% (n=104)	Male: 76.9% (n=40)	Male: 59.9%
Tumour histology	MC	Alveolar RMS: 33% (n=61)	Osteosarcoma, PNET: 71% (n=40)	n.r.
		Embryonal RMS: 59% (n=109)	Neuroblastoma: 9% (n=5)	
		Botryoid RMS: 6% (n=11)	Rhabdomyosarcoma: 5% (n=3)	
		Other RMS: 2% (n=4)	Esthesioneuroblastoma: 2% (n=1)	
			Nonrhabdomyosarcoma STS: 4% (n=2)	
			Retinoblastoma: 4% (n=2)	
			Others: 5% (n=3)	
	Comparator	Alveolar RMS: 33% (n=62)	Osteosarcoma, PNET: 61% (n=32)	n.r.
		Embryonal RMS: 61% (n=113)	Neuroblastoma: 10% (n=5)	
		Botryoid RMS: 3% (n=5)	Rhabdomyosarcoma: 11% (n=6)	
		Other RMS: 3% (n=6)	Esthesioneuroblastoma: 2% (n=1)	
			Non-rhabdomyosarcoma STS: 8% (n=4)	
			Retinoblastoma: 2% (n=1)	
			Others: 6% (n=3)	
Performance status	MC	n.r.	0: 5% (n=3)	n.r.
			1: 32% (n=18)	
			2: 44% (n=25)	
			3: 17% (n=10)	
	Comparator	n.r.	0: 2% (n=1)	n.r.
			1: 36% (n=19)	
			2: 40% (n=21)	
			3: 21% (n=11)	
Pathology	MC	Favourable: 66% (122)	n.r.	n.r.
	Comparator	Favourable: 65% (120)	n.r.	n.r.
Primary tumour invasiveness	MC	T1: 39% (n=72)	n.r.	n.r.
		T2: 58% (n=108)		
		Tx: 3% (n=5)		
	Comparator	T1: 47% (n=88)	n.r.	n.r.
		T2: 52% (n=97)		
		Tx: 1% (n=1)		
Regional lymph node involvement	MC	N0: 80% (n=148)	n.r.	n.r.
		N1: 17% (n=31)		
		Nx: 3% (n=6)		

Continued

Table 2 Continued

	Treatment group	Bisogno *et al*[16]	Pramanik *et al*[17]	Senerchia *et al*[18]
	Comparator	N0: 83% (n=154)	n.r.	n.r.
		N1: 16% (n=29)		
		Nx: 2% (n=3)		
Tumour size (diameter in cm)	MC	5 cm or less: 28% (n=52)	n.r.	Mean (SD): 10.76 (4.87)
		More than 5 cm: 70% (n=130)		
		Not evaluable: 2% (n=3)		
	Comparator	5 cm or less: 33% (n=61)	n.r.	Mean (SD): 11.06 (5.19)
		More than 5 cm: 67% (n=125)		
		Not evaluable: (n=0)		
Surgery (amputation)	MC	n.r.	n.r.	35.5%
	Comparator	n.r.	n.r.	38.2%

MC, metronomic chemotherapy; n.r., not reported; PNET, primitive neuroectodermal tumour; RMS, rhabdomyosarcoma; STS, soft-tissue sarcoma.

rhabdomyosarcoma, osteosarcoma and neuroblastoma. Patients of all three studies had previous treatments and were subjected to a high risk of relapse. Patients with cranial tumours were not included.

Online supplemental table S5 provides an overview of the main characteristics of the treatment. Patients in the test group received continuous low-dose chemotherapy in all three studies. Patients in the control group received placebo[17] or stop treatment.[16 18] Bisogno *et al*[16] and Pramanik *et al*[17] started the comparison at the time of the randomisation. Senerchia *et al*[18] continued the pretreatment scheme for 18 weeks in both treatment groups after randomisation before starting the actual comparison.

Outcomes

Table 3 shows the extracted outcome data and adds the results of a re-enactment of overall survival data across all three included studies.

Primary outcomes

Figure 2 shows that the pooled estimate of overall survival favours MC when compared with placebo or stop treatment of malignant rhabdomyosarcoma, osteosarcoma and neuroblastoma: HR 0.75 (95% CI 0.56 to 0.98, p=0.04 and I^2=6%). The results remained constant with a fixed effects model (data not shown). The funnel plot is compatible with a low publication bias and a sufficient number of included studies (online supplemental figure 1). We conducted a subgroup analysis to focus on tumours other than bone sarcomas and included the data from the study by Bisogno *et al* [16] and data of a separate analysis on tumours other than bone sarcoma from the study by Pramanik *et al*.[17] Online supplemental figure 2 shows that the pooled estimate of overall survival favours MC when compared with placebo or stop treatment of malignant solid tumours other than bone sarcomas: HR 0.56 (95% CI 0.38 to 0.84, p=0.005 and I^2=0%). Bisogno *et al*[16] did not detect regimen-related deaths. Pramanik *et al*[17] reported that there were no toxic deaths in both groups. Senerchia *et al*[18] reported a regimen-related toxicity of 2% in both groups.

Secondary outcomes

Grade 3 to 4 toxicity appeared manageable, and there was no significant difference between groups. Pramanik *et al*[17] reported health-related quality of life in a follow-up paper Pramanik *et al*,[19] and the study did not detect a significant difference between groups.

Assessment of risk of bias in the included studies

Online supplemental table S6 lists the reasons for judging the risk of bias of the three included studies. Most items resulted in low or unclear risk of bias. A summary of the results of the risk of bias assessment is provided in figure 2 and online supplemental figure S2.

DISCUSSION

Summary of main results

The findings from three RCTs suggest that MC for children and young adults with extracranial malignant solid tumours could improve overall survival when compared with placebo or stop treatment. One included study investigated the health-related quality of life and found no significant difference between groups. We did not identify any previously published meta-analysis.

Overall completeness and applicability of evidence

We believe that we have identified the relevant randomised trials studies sufficiently through searching CENTRAL, MEDLINE and ClinicalTrials.gov. CENTRAL is the result of actively screening for information on RCTs

Table 3 Type and results of reported outcomes

	Bisogno *et al*[16]	Pramanik *et al*[17]	Senerchia *et al*[18]
Extractions from articles			
Overall survival	HR 0.52 (95% CI 0.32 to 0.86) p=0.0097	HR 0.74 (95% CI 0.50 to 1.09) p=0.13	HR 0.9 (95% CI n.r.) p=0.9
Overall survival other than bone sarcoma	HR 0.52 (95% CI 0.32 to 0.86) p=0.0097	HR 0.43 (95% CI n.r.) p=0.02	n.r.
Disease-free survival	HR 0.68 (95% CI 0.45 to 1.02) p=0.061	n.r.	n.r.
Progression-free survival	n.r.	HR 0.69 (95% CI 0.47 to 1.03) p=0.07	n.r.
Progression-free survival other than bone sarcoma	n.r.	HR 0.39 (95% CI: 0.18 to 0.81) p=0.01	n.r.
Event-free survival	n.r.	n.r.	HR 1.2 (95% CI n.r.) p=0.4
PedsQL Cancer Module: child, mean total score (SD)*	n.r.	−1.9 (20.22) vs −1.3 (22.92), p=0.87	n.r.
PedsQL Cancer Module: parent, mean total score (SD)*	n.r.	0.2 (20.81) vs −4.2 (20.51), p=0.33	n.r.
Death	13% (24 of 182) vs 22% (42 of 185)	n.r.	n.r.
Treatment-related mortality	n.r.	0	3% (4 of 139) vs 2% (3 of 157)
Neutropenia, grade 3 to 4	81% (148 of 181)	10% (6 of 56) vs 0%	n.r.
Neurology adverse events, grade 3 to 4	2% (3 of 181)	0% vs 0%	n.r.
Nephrotoxicity, grade 3 to 4	1% (1 of 181)	0% vs 0%	n.r.
Re-enacted data			
Overall survival	HR 0.55 (95% CI 0.34 to 0.90)	HR 0.82 (95% CI 0.55 to 1.21)	HR 0.91 (95% CI 0.52 to 1.61)
Overall survival other than bone sarcoma	HR 0.55 (95% CI 0.34 to 0.90)	HR 0.58 (95% CI 0.29 to 1.15)	n.r.

*PedsQL Cancer Module: results extracted from the associated study by Pramanik *et al*.[19]
ID, identifier; n.r., not reported; PedsQL Cancer Module, Paediatric Quality of Life Inventory in paediatric cancer version 3.

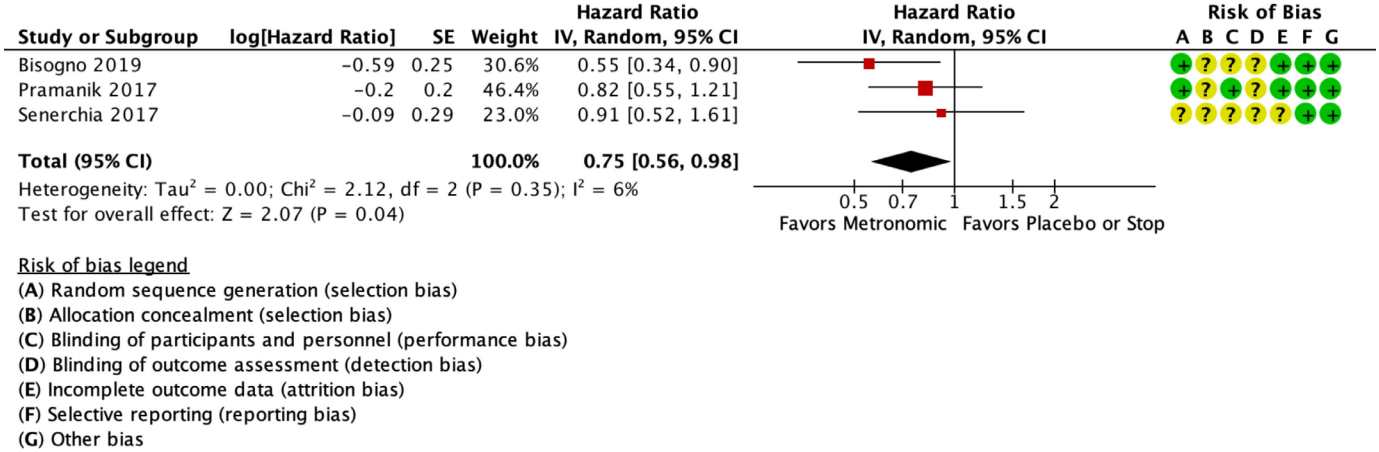

Figure 2 Forest plot of metronomic chemotherapy versus placebo or stop treatment, outcome overall survival. I^2, index of heterogeneity (the smaller the value the lesser the heterogeneity); IV, inverse variance (statistical method); P, probability; Random, random effects (analysis model).

in various literature databases.[21] According to Egger *et al* quote, "Investigators should consider the type of literature search and the degree of comprehensiveness that are appropriate for the review in question."[22] According to Peinemann *et al*, of 11 published RCTs on negative pressure wound therapy, all 11 were obtained from CENTRAL, 10 from MEDLINE, 9 from Embase and 3 from CINAHL.[23] According to AMSTAR 2 quote, "at least two bibliographic databases should be searched."[24] All three included studies were published between 2017 and 2019, and we presume that the principal treatment procedures may not deviate considerably from the current practice. The studies were conducted by academic institutions, and a financial conflict of interest was not obvious. Senerchia *et al*[18] reported a noteworthy number of dropouts but explained the reasons. We did not consider results on two biomarkers including those reported by Pramanik *et al*.[25] The studies provided information required by the Consolidated Standards of Reporting Trials statement.[26] All included studies have an explanatory attitude. In general, this means enrolment of highly selected participants in an *ideal* setting in contrast to an everyday medical practice.[27] In addition, clinical heterogeneity among the included studies is substantial. Thus, the results have to be interpreted with caution and the applicability of the results is certainly limited.

Subgroups and heterogeneity

We assume significant clinical heterogeneity since various tumours were included within or across studies. The type of and the response to pretreatment varied among studies and included complete remission, refractory/progressive status and complete resection of the primary tumour. The Kaplan-Meier intervals ranged from 15 to 132 months. The drugs and their application (oral or intravenous) used for MC varied among studies. This obvious clinical heterogeneity may have a considerable impact on the applicability of the findings. MC is an umbrella term and may be applied with various active substances and doses. An identical MC plan may have different effects depending on the type of tumour.[28] A subgroup analysis of other than bone sarcoma suggested that a possible favourable effect of MC may be primarily associated with rhabdomyosarcoma but not with bone sarcomas. We believe that populations and interventions were similar enough to be combined meaningfully in a meta-analysis. We included only paediatric patients and only interventions clearly defined as metronomic treatments. The I^2 statistic of 6% is in line with the interpretation that there is not an important level of inconsistency. The random effects method and the fixed effect method gave identical results supporting a low heterogeneity among the studies. We chose the random effects model presumably giving a more conservative estimate of effect. The number of three included studies appears appropriate, especially in view of the inclusion of a total number of data from 775 participants. According to Ryan quote, "Two studies is a sufficient number to perform a meta-analysis, provided that those two studies can be meaningfully pooled and provided their results are sufficiently *similar*."[29]

Potential biases in the review process

This systematic review applied a literature search with a degree of comprehensiveness appropriate to finding all available truly randomised studies. We chose overall survival as the primary outcome because it is the most reliable, patient-centred, sound and hard outcome in cancer studies. Grey *et al* listed examples of hard outcomes by clinical specialty.[30] All three studies reported the Kaplan-Meier curves on overall survival but not all reported the HR and the corresponding log(HR), of which both values are necessary to pool the data. According to Higgins *et al*[31] quote, "Conducting a meta-analysis using summary information from published papers or trial reports is often problematic as the most appropriate summary statistics often are not presented." These statistics can be extracted from survival curves, and we deduced the essential data from the published Kaplan-Meier plots. Though the statistical heterogeneity was low, we used the random effects model as a precautional measure to calculate a conservative estimate. Nevertheless, clinical heterogeneity is obviously substantial. Therefore, the results have to be interpreted with caution and applicability of the study data to every day practice is certainly limited or possibly not warranted. Blinding is a challenge, or it is not possible when treating children with life-threatening diseases. Therefore, we judged an unclear risk when blinding was not reported or not applied.

Agreements and disagreements with other studies or reviews

We did not find a systematic review evaluating MC in children, and it does not seem meaningful to compare child cancer such as rhabdomyosarcoma and osteosarcoma with adult cancer such as breast cancer and colorectal cancer. This review substantially updates and improves the previous work in this area. The findings of this review generally agree with the findings in a recent summary review.[28 32] One systematic review by Chen *et al* evaluated RCTs on metastatic colorectal cancer.[33] The authors did not perform a meta-analysis due to substantial heterogeneity. With respect to overall survival, in all four included RCTs there was no significant difference between treatment arms. With respect to progression-free survival, there was no significant difference between treatment arms in two RCTs, and two RCTs reported in favour of MC. We do not agree with the results of the risk of bias assessment, and search strategies were not reported. Several other review type articles labelled 'systematic reviews' did not match the requirements defined by the PRISMA statement[11] and AMSTAR 2.[24] According to Sataloff *et al* quote, "Authors often submit articles that include the term *systematic* in the title without realizing that that term requires strict adherence to specific criteria."[34]

Outlook

We believe that further RCTs are necessary to clarify the role of MC in the treatment of malignant solid tumours. Since different tumour entities or characteristics may react differently to this treatment, RCTs on specific neoplasms could provide important additional results. Health-related quality of life should be considered in studies on MC since this outcome is also critical for medical decision-making.

Conclusions

The evidence base is compatible with a favourable effect of MC on children and young adults with extracranial malignant solid tumours, especially other than bone tumours, when compared with placebo or stop treatment. Statistical heterogeneity is low while clinical heterogeneity is substantial. Thus, the results must be interpreted with caution and applicability of the results is limited. Future RCTs could provide more data on individual tumour entities and subsequently add information on tumour-specific responses.

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Patient consent for publication Not applicable.

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32 Bisogno G, Minard-Colin V, Zanetti I, *et al*. Nonmetastatic Rhabdomyosarcoma in Children and Adolescents: Overall Results of the European Pediatric Soft Tissue Sarcoma Study Group RMS2005 Study. *J Clin Oncol* 2023;41:2342–9.
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Supplemental Tables

Supplemental Table S1 Search strategies

Source	Query		Retrieval	Search date
1 MEDLINE via PubMed using automated term mapping; no limits used	#1	((oral OR low dose) AND maintenance) AND chemotherapy		
	#2	metronomic AND chemotherapy		
	#3	#1 OR #2		
	#4	random AND child AND cancer		
	#5	#3 AND #4	105 references	16 Jun 2023
	Update search			
	#6	#5 AND 2023/06/16:2023/09/08[edat]	106 references	08 Sep 2023
2 Cochrane Library via Wiley using combinations of MeSH terms and text (searched in title, abstract, and keywords); no limits used	#01	MeSH descriptor: [Administration, Oral]		
	#02	(oral):ti,ab,kw		
	#03	#1 or #2		
	#04	MeSH descriptor: [Maintenance Chemotherapy]		
	#05	(maintenance AND chemotherapy):ti,ab,kw		
	#06	#4 or #5		
	#07	#3 and #6		
	#08	MeSH descriptor: [Administration, Metronomic]		
	#09	(metronomic AND chemotherapy):ti,ab,kw		
	#10	#08 or #9		
	#11	#7 or #10		
	#12	MeSH descriptor: [Random Allocation]		
	#13	MeSH descriptor: [Randomized Controlled Trial]		
	#14	MeSH descriptor: [Randomized Controlled Trials as Topic]		
	#15	random*		
	#16	#12 or #13 or #14 or #15		
	#17	MeSH descriptor: [Adolescent]		
	#18	MeSH descriptor: [Child]		
	#19	MeSH descriptor: [Infant]		
	#20	pediatric* or paediatric* or child* or adolescent* juvenile* or toddler* or infant* or neonate*		
	#21	#17 or #18 or #19 or #20		
	#22	MeSH descriptor: [Neoplasm]		
	#23	cancer* or malignanc* or neoplasm* or tumor* or tumour* or carcinoma* or sarcoma* or neuroblastoma* or rhabdomyosarcoma* or RMS or osteosarcoma* or Ewing sarcoma* OR primitive neuroectodermal or PNET or esthesioneuroblastoma* or non-rhabdomyosarcoma soft-tissue sarcoma*		
	#24	#22 or #23		
	#25	#11 and #16 and #21 and #24	142 trials	16 Jun 2023
	Update search			
	#26	#25 with Cochrane Library publication date from Jun 2023 to Sep 2023, in Trials	143 trials	08 Sep 2023
3 ClinicalTrials.gov; limits used as indicated	Condition or disease: Neoplasm; Intervention/Treatment: Metronomic; Age: Child (birth to 17 years); Study phase: Phase 2 or Phase 3; Study type: Interventional		0 additional references	18 Aug 2023
4 ISRCTN registry; limits used as indicated	Neoplasm Metronomic (Phase 2 or Phase 3)		0 additional references	18 Aug 2023
Reference lists	–		36 references	–

Supplemental Table S2 Risk of bias assessment decision criteria

Item	Criteria for judging an unclear, low, or high risk of bias
Random sequence generation (selection bias)	Low: If adequately described Unclear: If not reported High: If not adequately described
Allocation concealment (selection bias)	Low: If adequately described Unclear: If not reported High: If not adequately described
Blinding of participants and personnel (performance bias)	Low: If blinding was addressed though not necessarily performed Unclear: If not reported High: If negated
Blinding of outcome assessment (detection bias)	Low: If adequately described Unclear: If not reported High: Not applicable because blinding of outcome assessment was regarded not appropriate
Incomplete outcome data (attrition bias)	Low: If the authors explained the excluded data and the attrition (lost other than death) was less than 10% in a single arm Unclear: If the attrition (lost other than death) was 10% or more but less than 20% in a single arm High: If the attrition (lost other than death) was 20% or more in a single arm
Selective reporting (reporting bias)	Low: If patient flow and primary/secondary outcomes were provided and treatment groups were evenly balanced for baseline characteristics and an intention-to-treat analysis was applied, and if there were no significant differences between the two treatment groups with respect to condition, treatment, or outcome measurement. Unclear: If there were no pertinent reporting. High: If patient flow and primary/secondary outcomes were not provided, or treatment groups were not evenly balanced for baseline characteristics, or if the authors based their conclusions on invalid biomarkers. Unclear: If there were no reports that favor either low or high risk. High: If patient flow and primary/secondary outcomes were not provided, or treatment groups were not evenly balanced for baseline characteristics, or if the authors based their conclusions on invalid biomarkers.
Other bias	Low: If funding was not industry based Unclear: If funding and conflicts of interest were not reported High: If the sponsor provided industry-based funding and if authors were employees or consultants of the sponsor, or if the early discontinuation of the study was not predefined

Supplemental Table S3 Included studies (n=3)

Study ID	I vs C	Info	Reference	PM	Trials
Bisogno 2019	**MC vs Stop**	**Primary reference for the study**	**Bisogno G, De-Salvo GL, Bergeron C, Gallego-Melcon S, Merks JH, Kelsey A, et al. Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20(11):1566-1575.** [16]	**PM**	**Trials**
		NCT00339118; EudraCT 2005-000217-35	EpSSG (European Soft Tissue Sarcoma Study Group) protocol for non-metastatic rhabdomyosarcoma in children	–	Trials
		2018 ASCO Meeting	Bisogno G, De-Salvo GL, Bergeron C, Jenney M, Merks JHM, Minard-Colin V, et al. Maintenance low-dose chemotherapy in patients with high-risk (HR) rhabdomyosarcoma (RMS): A report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). J Clin Oncol. 2018;36(18_suppl).	–	Trials
		Review of various data of the RMS2005 study	Bisogno G, Minard-Colin V, Zanetti I, Ferrari A, Gallego S, Davila Fajardo R, et al. Nonmetastatic Rhabdomyosarcoma in Children and Adolescents: Overall Results of the European Pediatric Soft Tissue Sarcoma Study Group RMS2005 Study. J Clin Oncol. 2023;41(13):2342-2349.	PM	–
Pramanik 2017	**MC vs Placebo**	**Primary reference for the study**	**Pramanik R, Agarwala S, Gupta YK, Thulkar S, Vishnubhatla S, Batra A, et al. Metronomic chemotherapy vs best supportive care in progressive pediatric solid malignant tumors: A randomized clinical trial. JAMA Oncol. 2017;3(9):1222-1227.** [17]	**PM**	**Trials**
		Follow-up report on quality of life	Pramanik R, Agarwala S, Sreenivas V, Dhawan D, Bakhshi S. Quality of life in paediatric solid tumours: A randomised study of metronomic chemotherapy versus placebo. BMJ Support Palliat Care. 2023;13(2):234-237.	**PM**	**Trials**
		NCT01858571	Low-dose chemotherapy versus best supportive care in progressive pediatric malignancies	–	Trials
		CTRI/2013/06/003734	Low-dose chemotherapy versus best supportive care in progressive and/or refractory pediatric malignancies	–	Trials
		2016 ASCO Meeting	Pramanik R, Bakhshi S, Agarwala S, Gupta YK, Thulkar S, Vishnubhatla S, et al. Metronomic therapy versus best supportive care in progressive pediatric solid malignancies: A double-blind placebo controlled randomized study. J Clin Oncol. 2016;34(15_suppl).	–	Trials
		2017 SIOP Meeting	Pramanik R, Batra A, Bakhshi S, Thulkar S, Sreenivas V, Dhawan D, et al. Progressive paediatric solid tumours other than bone-sarcomas benefit from metronomic chemotherapy: A subgroup analysis from a double-blind placebo controlled randomized study. Pediatr Blood Cancer. 2016;63:S7-S8.	–	Trials
		Biomarker study	Pramanik R, Tyagi A, Agarwala S, Vishnubhatla S, Dhawan D, Bakhshi S. Evaluation of vascular endothelial growth factor (VEGF) and thrombospondin-1 as biomarkers of metronomic chemotherapy in progressive pediatric solid malignancies. Indian Pediatr. 2020;57(6):508-511.	PM	Trials
Senerchia 2017	**MAP–MC vs MAP**	**Primary reference for the study**	**Senerchia AA, Macedo CR, Ferman S, Scopinaro M, Cacciavillano W, Boldrini E, et al. Results of a randomized, prospective clinical trial evaluating metronomic chemotherapy in nonmetastatic patients with high-grade, operable osteosarcomas of the extremities: A report from the Latin American Group of Osteosarcoma Treatment. Cancer 2017;123(6):1003-1010.** [18]	**PM**	**Trials**
		2011 ASCO Meeting	Petrilli AS, Macedo CR, Toledo SRC, Pavoni-Ferreira PC, Grings M, Scopinaro M, et al. Preliminary safety and outcome report of the metronomic chemotherapy from the Latin American osteosarcoma treatment protocol 2006. J Clin Oncol. 2011;29(15_suppl):10032.	–	Trials

Abbreviation. ASCO: American Society of Clinical Oncology; CTRI: Clinical Trials Registry – India; I vs C: intervention versus comparator; MAP: methotrexate, adriamycin, and platinum; MC: Metronomic chemotherapy; NCT: ClinicalTrials.gov identifier (National Clinical Trial number); PM: retrieved from PubMed; SIOP: Societe Internationale d'Oncologie Pediatrique (International Paediatric Oncology Congress); Trials: retrieved from Trials, the Cochrane Central Register of Controlled Trials (CENTRAL)

Supplemental Table S4 Excluded references (n=40)

Registry/Meeting	Reference	Comment	Not of interest:	PM	Trials
NCT00567567	[No author]. Comparing two different myeloablation therapies in treating young patients who are undergoing a stem cell transplant for high-risk neuroblastoma	Comparing two different HDCT	Intervention	–	Trials
EudraCT: 2007-001478-10-PL	[No author]. CWS-2007-HR: A randomised phase-III trial of the Cooperative Weichteilsarkom Studiengruppe for localised high-risk rhabdomyosarcoma and localised rhabdomyosarcoma-like soft tissue sarcoma in children, adolescents, and young adults. CN-01841204	MC vs no therapy, parents refused randomization	Study type	–	Trials
NCT00339118	[No author]. EpSSG (European Soft Tissue Sarcoma Study Group) protocol for non-metastatic rhabdomyosarcoma in children	Related to Bisogno 2019 [16]	Registry	–	Trials
ACTRN12616001524482	[No author]. EWING 2008 Clinical trial for the treatment of Localized and Disseminated Ewing sarcoma	HDCT	Intervention	–	Trials
NCT00078988	[No author]. High-dose chemotherapy plus autologous stem cell transplantation compared with intermediate-dose chemotherapy plus autologous stem cell transplantation with or without isotretinoin in treating young patients with recurrent high-grade gliomas	Gliomas	Population	–	Trials
NCT01858571	[No author]. Low-dose chemotherapy versus best supportive care in progressive pediatric malignancies	Related to Pramanik 2017 [17]	Registry	–	Trials
CTRI/2013/06/003734	[No author]. Low-dose chemotherapy versus best supportive care in progressive and/or refractory pediatric malignancies	Related to Pramanik 2017 [17]	Registry	–	Trials
EudraCT: 2018-000096-32	[No author]. Metro-PD1: A phase I/II trial evaluating anti-PD1 (Nivolumab) in combination with metronomic chemotherapy in children and teenagers with refractory /relapsing solid tumors or lymphoma.	MC vs MC + Nivolumab	Comparator	–	Trials
NCT01467986	[No author]. Multimodal molecular targeted therapy to treat relapsed or refractory high-risk neuroblastoma (RIST-rNB-2011)	Comparing two molecular targeted therapies	Intervention	–	Trials
NCT03585465	[No author]. Nivolumab in combination with metronomic chemotherapy in paediatrics refractory / relapsing solid tumors or lymphoma.	MC vs MC + Nivolumab	Comparator	–	Trials
NCT00688376; EUCTR2007-005442-20-GB.	[No author]. Randomized, double-blind, placebo-controlled study of efficacy and safety of donepezil hydrochloride in preadolescent and adolescent children with attention impairment following cancer treatment - amend 02.	Attention Impairment; Donepezil vs Placebo	Population	–	Trials
–	Andre N, Rome A, Coze C, Padovani L, Pasquier E, Camoin L, et al. Metronomic etoposide/cyclophosphamide/celecoxib regimen given to children and adolescents with refractory cancer: a preliminary monocentric study. Clin Ther. 2008;30(7):1336-1340.	MC in a single-arm study	Study type	–	Trials
–	Andre N, Corradini N, Shaked Y. Metronomic maintenance therapy for rhabdomyosarcoma. Trends Cancer. 2019;5(12):756-759.	Letter relates to NCT00339118	Study type	PM	–
NCT00526318	Berthold F, Boos J, Burdach S, Erttmann R, Henze G, Hermann J, et al. Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: A randomised controlled trial. Lancet Oncol. 2005;6(9):649-658.	MC vs HDCT	Comparator	PM	Trials
NCT00526318	Berthold F, Ernst A, Hero B, Klingebiel T, Kremens B, Schilling FH, et al. Long-term outcomes of the GPOH NB97 trial for children with high-risk neuroblastoma comparing high-dose chemotherapy with autologous stem cell transplantation and oral chemotherapy as consolidation. Br J Cancer. 2018;119(3):282-290.	MC vs HDCT	Comparator	PM	Trials
2018 ASCO Meeting	Bisogno G, De-Salvo GL, Bergeron C, Jenney M, Merks JHM, Minard-Colin V, et al. Maintenance low-dose chemotherapy in patients with high-risk (HR) rhabdomyosarcoma (RMS): A report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). J Clin Oncol. 2018;36(18_suppl).	Related to Bisogno 2019 [16]	Meeting	–	Trials

–	Bisogno G, Minard-Colin V, Zanetti I, Ferrari A, Gallego S, Davila Fajardo R, et al. Nonmetastatic Rhabdomyosarcoma in Children and Adolescents: Overall Results of the European Pediatric Soft Tissue Sarcoma Study Group RMS2005 Study. J Clin Oncol. 2023;41(13):2342-2349.	Related to Bisogno 2019 [16]	Study type	PM	–
–	Bisogno G, Minard-Colin V, Jenney M, Ferrari A, Chisholm J, Di Carlo D, et ak. Maintenance Chemotherapy for Patients with Rhabdomyosarcoma. Cancers (Basel). 2023;15(15):4012.	Review related to Bisogno 2019 [16]	Study type	PM	–
NCT00278070	Briasoulis E, Aravantinos G, Kouvatseas G, Pappas P, Biziota E, Sainis I, et al. Dose selection trial of metronomic oral vinorelbine monotherapy in patients with metastatic cancer: a hellenic cooperative oncology group clinical translational study. BMC Cancer. 2013;13:263.	Breast, Prostate, and Non Small Cell Lung Cancer	Population	–	Trials
–	Casanova M, Ferrari A, Bisogno G, Merks JH, De-Salvo GL, Meazza C, et al. Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European rhabdomyosarcoma protocol. Cancer. 2004;101(7):1664-1671.	MC + HDCT in a single-arm study	Study type	–	Trials
NCT00643565	Chisholm JC, Merks JHM, Casanova M, Bisogno G, Orbach D, Gentet JC, et al. Open-label, multicentre, randomised, phase II study of the EpSSG and the ITCC evaluating the addition of bevacizumab to chemotherapy in childhood and adolescent patients with metastatic soft tissue sarcoma (the BERNIE study). Eur J Cancer. 2017;83:177-184.	CT + Bevacizumb (monoclonal antibody) vs CT	Intervention	PM	–
NCT00061893	Felgenhauer JL, Nieder ML, Krailo MD, Bernstein ML, Henry DW, Malkin D, et al. A pilot study of low-dose anti-angiogenic chemotherapy in combination with standard multiagent chemotherapy for patients with newly diagnosed metastatic Ewing sarcoma family of tumors: A Children's Oncology Group (COG) Phase II study NCT00061893. Pediatr Blood Cancer. 2013;60(3):409-414.	MC + standard chemotherapy in a single-arm study	Study type	–	Trials
NCT00538239; 2012, ASPHO Meeting	Iannone R, Yang Y, Elias A, Peylan-Ramu N, Judson I, Nunes J, et al. Ridaforolimus as maintenance therapy in advanced sarcoma patients following clinical benefit from prior chemotherapy: Pediatric data from the phase 3 sarcoma multi-center clinical evaluation of the efficacy of ridaforolimus (SUCCEED) trial. Pediatr Blood Cancer. 2012,58(7),1081	Ridaforolimus (protein inhibitor) vs Placebo	Intervention	–	Trials
–	Klingebiel T, Boos J, Beske F, Hallmen E, Int-Veen C, Dantonello T, Treuner J, Gadner H, Marky I, Kazanowska B, Koscielniak E. Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial. Pediatr Blood Cancer. 2008;50(4):739-745.	MC vs HDCT	Comparator	–	Trials
–	Koscielniak E, Blank B, Vokuhl C, Kazanowska B, Ladenstein R, Niggli F, et al. Long-term clinical outcome and prognostic factors of children and adolescents with localized rhabdomyosarcoma treated on the CWS-2002P protocol. Cancers (Basel). 2022;14(4):899.	MC vs no therapy, based on the decision of the treating physician	Study type	PM	–
2017 GPOH Meeting	Koscielniak E, Sparber-Sauer M, Scheer M, Klingebiel T. CWS-2007-HR A randomised phase-III trial for localised high-risk rhabdomyosarcoma and rhabdomyosarcoma-like soft tissue sarcoma (STS) in children, adolescents, and young adults. Status update. Monatsschr Kinderheilkd. 2017;165(7):645. CN-01572093.	MC vs no therapy, parents refused randomization	Study type	–	Trials
–	Kyr M, Polaskova K, Kuttnerova Z, Merta T, Neradil J, Berkovcova J, et al. Individualization of treatment improves the survival of children with high-risk solid tumors: Comparative patient series analysis in a real-life scenario. Front Oncol. 2019;9:644.	Comparative case series analysis including MC	Study type	PM	–
NCT01704716	Ladenstein R, Pötschger U, Pearson ADJ, Brock P, Luksch R, Castel V, et al. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): An international, randomised, multi-arm, open-label, phase 3 trial. Lancet Oncol. 2017;18(4):500-514.	Two HDCT arms, all patients received MC	Intervention	PM	Trials
NCT03585465	Leblond P, Probst A, Entz-Werle N, Defachelles AS, Aerts I, Bogart E, et al. Metro-Pd1: A phase-1 feasability study evaluating anti-Pd1 (nivolumab) in combination with metronomic chemotherapy in children and teenagers with refractory/relapsing solid tumors or lymphoma.	MC vs MC + Nivolumab	Comparator	–	Trials
–	Longhi A, Cesari M, Serra M, Mariani E. Long-term follow-up of a randomized study of oral etoposide versus viscum album fermentatum pini as maintenance therapy in osteosarcoma patients in complete surgical remission after second relapse. Sarcoma. 2020;2020:8260730.	MC vs European mistletoe	Comparator	–	Trials

–	Minard-Colin V, Ichante JL, Nguyen L, Paci A, Orbach D, Bergeron C, et al. Phase II study of vinorelbine and continuous low doses cyclophosphamide in children and young adults with a relapsed or refractory malignant solid tumour: good tolerance profile and efficacy in rhabdomyosarcoma--a report from the Societe Francaise des Cancers et leucemies de l'Enfant et de l'adolescent (SFCE). Eur J Cancer. 2012 Oct;48(15):2409-2416.	MC in a single-arm study	Study type	–	Trials
2017 ASPHO Meeting	Ortiz D, Harden A, Ruiz-Mesa C, Podda A. Combination of bevacizumab and taxane containing regimen, hyperthermic intraperitoneal chemotherapy (HIPEC) and tyrosine kinase inhibitor (TKI) trametenib for the treatment of aggressive metastatic pediatric angiosarcoma. Pediatr Blood Cancer. 2017;64:S82.	Case report on bevacizumab (monoclonal antibody) for angiosarcoma	Intervention	–	Trials
2011 ASCO Meeting	Petrilli AS, Macedo CR, Toledo SRC, Pavoni-Ferreira PC, Grings M, Scopinaro M, et al. Preliminary safety and outcome report of the metronomic chemotherapy from the Latin American osteosarcoma treatment protocol 2006. J Clin Oncol. 2011;29(15_suppl):10032.	Related to Senerchia 2017 [18]	Meeting	–	Trials
2016 ASCO Meeting	Pramanik R, Bakhshi S, Agarwala S, Gupta YK, Thulkar S, Vishnubhatla S, et al. Metronomic chemotherapy versus best supportive care in progressive pediatric solid malignancies: A double-blind placebo controlled randomized study. J Clin Oncol. 2016;34(15_suppl).	Related to Pramanik 2017 [17]	Meeting	–	Trials
2017 SIOP Meeting	Pramanik R, Batra A, Bakhshi S, Thulkar S, Sreenivas V, Dhawan D, et al. Progressive paediatric solid tumours other than bone-sarcomas benefit from metronomic chemotherapy: A subgroup analysis from a double-blind placebo controlled randomized study. Pediatr Blood Cancer. 2016;63:S7-S8.	Related to Pramanik 2017 [17]	Meeting	–	Trials
NCT01858571	Pramanik R, Tyagi A, Agarwala S, Vishnubhatla S, Dhawan D, Bakhshi S. Evaluation of vascular endothelial growth factor (VEGF) and thrombospondin-1 as biomarkers of metronomic chemotherapy in progressive pediatric solid malignancies. Indian Pediatr. 2020;57(6):508-511.	Related to Pramanik 2017 [17]	Outcome	PM	–
NCT00643565	Schoot RA, Chisholm JC, Casanova M, Minard-Colin V, Geoerger B, Cameron AL, et al. Metastatic rhabdomyosarcoma: Results of the European Paediatric Soft Tissue Sarcoma study group MTS 2008 study and pooled analysis with the concurrent BERNIE study. J Clin Oncol. 2022;40(32):3730-3740.	CT + Bevacizumb (monoclonal antibody) vs CT	Intervention	PM	–
–	Simon T, Hero B, Faldum A, Handgretinger R, Schrappe M, Klingebiel T, et al. Long term outcome of high-risk neuroblastoma patients after immunotherapy with antibody ch14.18 or oral metronomic chemotherapy. BMC Cancer. 2011;11:21.	MT vs no therapy, not randomized	Study type	–	Trials
–	Traore F, Togo B, Pasquier E, Dembele A, Andre N. Preliminary evaluation of children treated with metronomic chemotherapy and valproic acid in a low-income country: Metro-Mali-02. Indian J Cancer. 2013;50(3):250-253.	MC in a single-arm study	Study type	–	Trials
–	Zapletalova D, Andre N, Deak L, Kyr M, Bajciova V, Mudry P, et al. Metronomic chemotherapy with the COMBAT regimen in advanced pediatric malignancies: a multicenter experience. Oncology. 2012;82(5):249-260.	MC in a single-arm study	Study type	–	Trials

Abbreviation. ACTRN: Australian New Zealand Clinical Trials Registry (ANZCTR) registration number; ASCO: American Society of Clinical Oncology; ASPHO: American Society of Pediatric Hematology/Oncology; CT: chemotherapy; EUCTR: European Union Clinical Trials Register; EudraCT: European Union Drug Regulating Authorities Clinical Trials Database; GPOH: Gesellschaft für Pädiatrische Onkologie und Hämatolgie (Society for Pediatric Oncology and Hematology); HDCT: high-dose chemotherapy; MC: Metronomic chemotherapy; NCT: ClinicalTrials.gov identifier (National Clinical Trial number); PM: retrieved from PubMed; SIOP: Societe Internationale d'Oncologie Pediatrique (International Paediatric Oncology Congress); Trials: retrieved from Trials, the Cochrane Central Register of Controlled Trials (CENTRAL)

Supplemental Table S5 Characteristics of interventions

	Bisogno 2019[(a)] [16]	**Pramanik 2017**[(b)] [17]	**Senerchia 2017**[(c)] [18]
Pretreatment before randomization	Concerning both groups: Standard chemotherapy comprised nine cycles of the IVA or IVADo chemotherapy, and surgery or radiotherapy, or both. IVA Ifosfamide 3 g/sqm days 1 and 2 Vincristine 1.5 mg/sqm weekly during the first 7 weeks then only on day 1 of each cycle (maximum dose 2 mg) Actinomycin D (= Dactinomycin) 1.5 mg/sqm on day 1 (maximum dose 2 mg) IVADo IVA plus doxorubicin 30 mg/sqm on days 1 and 2 in the initial four cycles of chemotherapy. Surgery: Marginal resection was acceptable, provided it was followed by radiotherapy. Radiotherapy 41.4 Gy to 50.4 Gy)	n.r.	Concerning both groups: Induction with two 5-week MAP chemotherapy cycles during weeks 1 to 10 followed by complete resection of the primary tumor in week 11 or 12. MAP Methotrexate 12 g/sqm Adriamycin (= doxorubicin) 75 mg/sqm Platinum (= cisplatin) 120 mg/sqm Adriamycin (= doxorubicin) and platinum (= cisplatin) were administered in weeks 1 and 6, and methotrexate was administered in weeks 4, 5, 9, and 10.
Pretreatment after randomization	n.r.	n.r.	Concerning both groups: After surgery, consenting patients were randomly assigned to complete 31 weeks of MAP with cisplatin replaced by intravenous dexrazoxane (375 mg/sqm on days 1 and 2) in the last 2 cycles.
Metronomic chemotherapy after randomization	Metronomic chemotherapy (n=185): Six 4-week cycles of intravenous vinorelbine 25 mg/sqm on days 1, 8, and 15; during the same time: oral cyclophosphamide 25 mg/sqm per day given continuously for 24 weeks on an outpatient basis.	Metronomic chemotherapy (n=56): Alternating cycles of cycle A and B (each cycle included 3 weeks of drug administration) and best supportive care[(a)] Cycle A: Daily oral thalidomide (3mg/kg), daily oral celecoxib 200 mg to 800 mg, and daily oral etoposide (50 mg/sqm). Cycle B: Daily oral thalidomide (3mg/kg), daily oral celecoxib 200 mg to 800 mg, and daily oral cyclophosphamide 2.5 mg/kg to a maximum of 100 mg/day.	Treatment continued after 31 weeks chemotherapy. Metronomic chemotherapy was applied from week 32 to week 104: oral cyclophosphamide (25 mg/sqm daily) and oral methotrexate (1.5 mg/sqm twice daily twice per week)
Comparator after randomization	Stop treatment (n=186)	Placebo (n=52): Capsules of same size and color as used in metronomic chemotherapy and best supportive care[(a)]	Treatment stopped after 31 weeks chemotherapy.

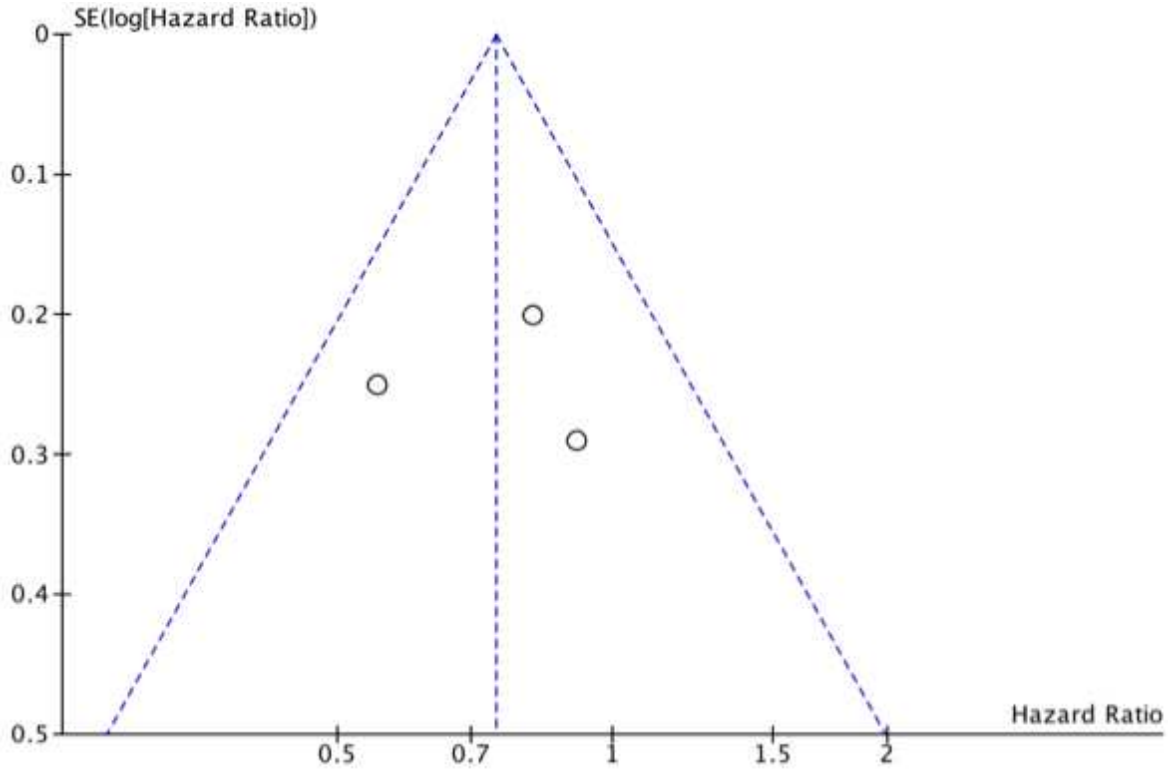
Abbreviations. IVA: ifosfamide, vincristine, and actinomycin D (= dactinomycin); IVADo: ifosfamide, vincristine, actinomycin D (= dactinomycin), and doxorubicin; MAP: methotrexate, adriamycin (= doxorubicin), and platinum (= cisplatin); sqm: square meter = m^2;

[(a)] Pramanik 2017 [17]: Best supportive care included management of pain as per the World Health Organization standard for pain management, blood product transfusion, management of infection, and malodorous necrotic masses.

Supplemental Table S6 Risk of bias assessment results

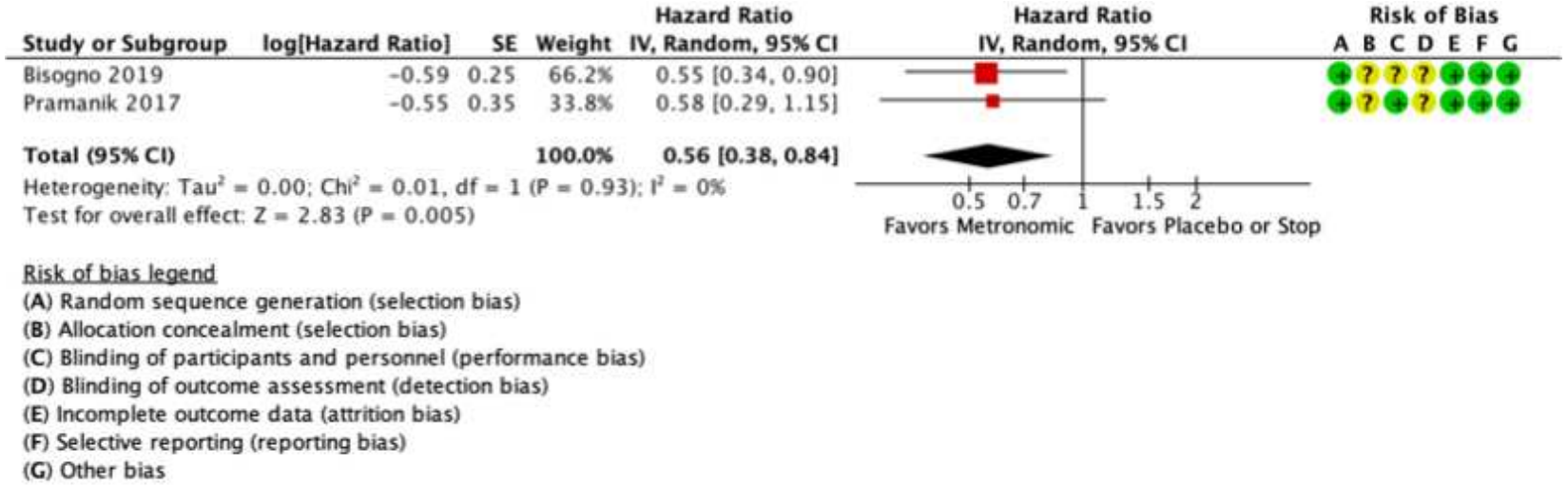
Item	**Bisogno 2019** [16]	**Pramanik 2017** [17]	**Senerchia 2017** [18]
Random sequence generation (selection bias)	Randomisation was done with a web-based system provided by CINECA (Bologna, Italy), a non-profit, inter-university consortium thus LOW.	Randomization was based on a computer-generated table of random numbers, thus LOW.	Not reported, thus UNCLEAR.
Allocation concealment (selection bias)	Not reported, thus UNCLEAR.	Not reported, thus UNCLEAR.	Not reported, thus UNCLEAR.
Blinding of participants and personnel (performance bias)	Neither investigators nor patients were masked to treatment allocation, but we believe that these issues may not influence the results, thus UNCLEAR.	Masking was double blind (subject, caregiver), thus LOW.	Not reported, thus UNCLEAR.
Blinding of outcome assessment (detection bias)	Not reported, thus UNCLEAR.	Not reported, thus UNCLEAR.	Not reported, thus UNCLEAR.
Incomplete outcome data (attrition bias)	Attrition rates (lost other than death) were low and comparable between groups, thus LOW.	Attrition rates (lost other than death) were low and comparable between groups, thus LOW.	Attrition (lost other than death) was more than 20% in a single arm. We are unsure whether this affects the outcome since the authors applied an intention-to-treat analysis. Thus, we judged the risk of bias to be UNCLEAR.
Selective reporting (reporting bias)	Patient flow and primary/secondary patient-centered outcomes were provided, characteristics were balanced, and intention-to-treat analysis was applied, thus LOW.	Patient flow and primary/secondary patient-centered outcomes were provided, characteristics were balanced, and intention-to-treat analysis was applied, thus LOW.	Patient flow and primary/secondary patient-centered outcomes were provided, characteristics were balanced, and intention-to-treat analysis was applied, thus LOW.
Other bias	Sponsor was the European paediatric Soft tissue sarcoma Study Group (EpSSG), thus LOW.	Sponsor was All India Institute of Medical Sciences (AIIMS), thus LOW.	Sponsor was the Federal University of Sao Paulo (Portuguese: Universidade Federal de Sao Paulo, UNIFESP), thus LOW.

Supplemental Figures



Supplemental Figure S1 Funnel plot Metronomic chemotherapy versus Placebo or Stop treatment, outcome Overall Survival, related to Fig. 1.

Caption. SE: standard error of log[Hazard Ratio]



Supplemental Figure S2 Forest plot Metronomic chemotherapy versus Placebo or Stop treatment, outcome Overall Survival not bone tumors

Caption. 95% CI: 95% confidence interval; I^2: index of heterogeneity (the smaller the value the lesser the heterogeneity); IV: inverse variance (statistical method); P: probability; Random: random effects (analysis model); SE: standard error of log[Hazard Ratio]