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

Gianni Bisogno, Gian Luca De Salvo, Christophe Bergeron, Soledad Gallego Melcón, Johannes H Merks, Anna Kelsey, Helene Martelli, Veronique Minard-Colin, Daniel Orbach, Heidi Glosli, Julia Chisholm, Michela Casanova, Ilaria Zanetti, Christine Devalck, Myriam Ben-Arush, Peter Mudry, Sima Ferman, Meriel Jenney, Andrea Ferrari*, for the European paediatric Soft tissue sarcoma Study Group*

Lancet Oncol 2019; 20: 1566–75

Published Online September 24, 2019 https://doi.org/S1470-2045(19)30617-5

See Comment page 1476

*Contributed equally

Haematology Oncology Division, Department of Women's and Children's Health, University of Padova, Padova, Italy (G Bisogno MD, I Zanetti BSc); Clinical Research Unit, Istituto Oncologico Veneto IOV–IRCCS, Padova, Italy (G L De Salvo MD); Institut d'Hématologie et d'Oncologie Pédiatrique, Centre Léon Bérard, Lyon, France (C Bergeron MD); Servicio de Oncología y Hematología Pediatrica, Hospital Universitari Vall d'Hebron, Barcelona, Spain (S Gallego Melcón MD); Princess Máxima Center for Paediatric Oncology, Utrecht, Netherlands (JH Merks MD); Department of Paediatric Oncology, Emma Children's Hospital-Academic Medical Center Amsterdam, Netherlands (JH Merks); Department of Paediatric Histopathology, Royal Manchester Children's Hospital, Manchester, UK (A Kelsey MD); Department of Paediatric Surgery, Hôpital Bicêtre-Hôpitaux Universitaires Paris Sud, Assistance Publique-Hôpitaux de Paris, Le Kremlin Bicêtre, Paris, France (Prof H Martelli MD); Department of Paediatric and Adolescent Oncology, Gustave-Roussy, Villejuif, France (V Minard-Colin MD); SIREDO Oncology Center, Institut Curie, PSL University, Paris, France (D Orbach MD); Department of Paediatric Research and Department of Paediatric and Adolescent Medicine,

Summary

Background For more than three decades, standard treatment for rhabdomyosarcoma in Europe has included 6 months of chemotherapy. The European paediatric Soft tissue sarcoma Study Group (EpSSG) aimed to investigate whether prolonging treatment with maintenance chemotherapy would improve survival in patients with high-risk rhabdomyosarcoma.

Methods RMS 2005 was a multicentre, open-label, randomised, controlled, phase 3 trial done at 102 hospitals in 14 countries. We included patients aged 6 months to 21 years with rhabdomyosarcoma who were considered to be at high risk of relapse: those with non-metastatic incompletely resected embryonal rhabdomyosarcoma occurring at unfavourable sites with unfavourable age (≥10 years) or tumour size (>5 cm), or both; those with any non-metastatic rhabdomyosarcoma with nodal involvement; and those with non-metastatic alveolar rhabdomyosarcoma but without nodal involvement. Patients in remission after standard treatment (nine cycles of ifosfamide, vincristine, dactinomycin with or without doxorubicin, and surgery or radiotherapy, or both) were randomly assigned (1:1) to stop treatment or continue maintenance chemotherapy (six cycles of intravenous vinorelbine 25 mg/m² on days 1, 8, and 15, and daily oral cyclophosphamide 25 mg/m², on days 1–28). Randomisation was done by use of a web-based system and was stratified (block size of four) by enrolling country and risk subgroup. Neither investigators nor patients were masked to treatment allocation. The primary outcome was disease-free survival in the intention-to-treat population. Secondary outcomes were overall survival and toxicity. This trial is registered with EudraCT, number 2005-000217-35, and ClinicalTrials.gov, number NCT00339118, and follow-up is ongoing.

Findings Between April 20, 2006, and Dec 21, 2016, 371 patients were enrolled and randomly assigned to the two groups: 186 to stop treatment and 185 to receive maintenance chemotherapy. Median follow-up was 60·3 months (IQR 32·4–89·4). In the intention-to-treat population, 5-year disease-free survival was 77·6% (95% CI 70·6–83·2) with maintenance chemotherapy versus 69·8% (62·2–76·2) without maintenance chemotherapy (hazard ratio [HR] 0·68 [95% CI 0·45–1·02]; p=0·061), and 5-year overall survival was 86·5% (95% CI 80·2–90·9) with maintenance chemotherapy versus 73·7% (65·8–80·1) without (HR 0·52 [95% CI 0·32–0·86]; p=0·0097). Toxicity was manageable in patients who received maintenance chemotherapy: 136 (75%) of 181 patients had grade 3–4 leucopenia, 148 (82%) had grade 3–4 neutropenia, 19 (10%) had anaemia, two (1%) had thrombocytopenia, and 56 (31%) had an infection. One (1%) patient had a grade 4 non-haematological toxicity (neurotoxicity). Two treatment-related serious adverse events occurred: one case of inappropriate antidiuretic hormone secretion and one of a severe steppage gait with limb pain, both of which resolved.

Interpretation Adding maintenance chemotherapy seems to improve survival for patients with high-risk rhabdomyosarcoma. This approach will be the new standard of care for patients with high-risk rhabdomyosarcoma in future EpSSG trials.

Funding Fondazione Città della Speranza, Association Léon Berard Enfant Cancéreux, Clinical Research Hospital Program (French Ministry of Health), and Cancer Research UK.

Introduction

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and young adults. This form of cancer is nonetheless rare, with an annual incidence of four cases per million in individuals aged 0–19 years and approximately 400 new cases each year in Europe.[1] Although rhabdomyosarcoma is regarded as a tumour typical of paediatric age (with highest incidence before

Research in context

Evidence before this study

We searched PubMed for all randomised trials published in English between Jan 1, 1980, and Dec 1, 2018, involving patients with rhabdomyosarcoma. We also searched for published papers with the search terms "rhabdomyosarcoma" and "maintenance". We did not find any randomised trials investigating the role of maintenance chemotherapy or the duration of chemotherapy in rhabdomyosarcoma.
One non-randomised trial suggested that oral maintenance chemotherapy is better than intravenous high-dose chemotherapy in patients with metastatic rhabdomyosarcoma.

Added value of this study

To our knowledge, this study is the first randomised trial to show some improvement in survival with maintenance chemotherapy (six cycles of intravenous vinorelbine 25 mg/m² on days 1, 8, and 15, and daily oral cyclophosphamide 25 mg/m² on days 1–28) for patients with rhabdomyosarcoma. Maintenance chemotherapy administered to patients with high-risk rhabdomyosarcoma in complete remission after standard chemotherapy improved overall survival and was well tolerated. However, the improvement in disease-free survival was not significant.

Implications of all the available evidence

Maintenance chemotherapy improves survival for patients with high-risk rhabdomyosarcoma and will be further investigated in future European paediatric Soft tissue sarcoma Study Group (EpSSG) trials as the new standard of care for this subgroup.

Oslo University Hospital, Oslo, Norway (H Glosli MD); **Children and Young Peoples Unit, Royal Marsden Hospital, Sutton, Surrey, UK** (J Chisholm MD); **Paediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy** (M Casanova MD, A Ferrari MD); **Paediatric Haematology and Oncology, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium** (C Devalck MD); **Joan and Sanford Weill Pediatric Hematology Oncology and Bone Marrow Transplantation Division, Ruth Rappaport Children's Hospital, Rambam Medical Center, Haifa, Israel** (Prof M Ben-Arush MD); **University Children´s Hospital Brno, Czech Republic** (P Mudry MD); **Instituto Nacional de Câncer, Rio de Janeiro, Brazil** (S Ferman MD); **and Department of Paediatric Oncology, Children's Hospital for Wales, Heath Park, Cardiff, UK** (M Jenney MD)

Correspondence to:
Prof Gianni Bisogno, Haematology Oncology Division, Department of Women's and Children's Health, University of Padova, Padova, Italy
gianni.bisogno@unipd.it

age 6 years), around 40% of all cases occur in adults.[2] This aggressive tumour is thought to derive from primitive mesenchymal cells committed to developing into striated muscles, but an origin from endothelial progenitors has also been suggested.[3]

Two main histotypes exist: the embryonal subtype, which accounts for approximately 80% of all paediatric rhabdomyosarcomas, and the more aggressive alveolar subtype, which comprises 15–20% of cases and is characterised by a chromosomal translocation involving the fusion of the transcription factor genes *FOXO1* and either *PAX3* or *PAX7*.

Survival of patients with non-metastatic rhabdomyosarcoma is around 70% with the risk-adapted multimodal treatment strategy. This strategy has been refined since the 1970s as a result of several studies coordinated by international cooperative groups, the largest being the Children's Oncology Group (COG) in the USA and the more recently founded European paediatric Soft tissue sarcoma Study Group (EpSSG).[4] These groups have adopted an alkylating agent (ie, cyclophosphamide or ifosfamide) combined with vincristine and dactinomycin, administered every 3 weeks for 6–10 months,[5,6] as the standard chemotherapy regimen for patients with non-metastatic rhabdomyosarcoma. In a series of randomised trials done in the past five decades, attempts to intensify this chemotherapy regimen have not been successful in improving outcomes.[5–13] These trials have shown that most patients with rhabdomyosarcoma achieve complete remission by the end of their treatment, which also includes surgery, radiotherapy, or both. However, the fact that up to one in three patients relapses within 5–9 months after the end of treatment[5,6] suggests that minimal residual active disease is escaping detection through existing radiological methods and is resistant to standard treatment, and thus remains an obstacle to improving survival outcomes. This obstacle might be overcome by introducing new, more effective drugs or adopting new strategies, or through a combination of these approaches.

When the RMS 2005 trial was planned, evidence was available to suggest that vinorelbine is an effective drug against relapsing rhabdomyosarcoma.[14] Some initial claims had also been made that maintenance chemotherapy might be effective against rhabdomyosarcoma.[15] After a pilot study confirmed the effectiveness of vinorelbine combined with low-dose continuous cyclophosphamide,[16] the EpSSG included this novel regimen in the RMS 2005 study and aimed to investigate whether prolonging treatment with a less intensive but continuous chemotherapy regimen could improve outcomes in patients with high-risk rhabdomyosarcoma.

Methods

Study design and participants

RMS 2005 was an investigator-initiated, prospective, international, phase 3, randomised, controlled, open-label trial done at 102 hospitals in 14 countries (Argentina, Belgium, Brazil, Czech Republic, France, Ireland, Israel, Italy, Norway, Switzerland, Slovenia, Spain, the Netherlands, and the UK; appendix p 1).

See **Online** for appendix

After undergoing diagnostic work-up, each patient was assigned to a specific risk group based on six prognostic factors according to the EpSSG stratification system (appendix p 7). The high-risk group comprised patients with non-metastatic, incompletely resected, embryonal rhabdomyosarcoma occurring at unfavourable sites, age 10 years or older or with a tumour size larger than 5 cm, or both; those with any non-metastatic embryonal rhabdomyosarcoma with nodal involvement; or those with any non-metastatic alveolar rhabdomyosarcoma without nodal involvement. Patients in the low-risk, standard-risk, and very-high-risk groups were not eligible for this study and were treated according to specific recommendations included in the RMS 2005 study.

Patients in the high-risk group were eligible for enrolment into two consecutive independent randomised trials to investigate the benefit of early dose intensification with doxorubicin and the value of maintenance chemotherapy for patients in complete remission after standard therapy. The results of the first trial have been reported elsewhere.[17] Patients were considered for the second trial independently of whether or not they were included in the first trial. The first trial was closed on Dec 17, 2013. After this date, patients were eligible for enrolment into the second trial only.

Eligibility criteria were age older than 6 months at the time of randomisation to younger than 21 years at the time of diagnosis, a pathologically confirmed diagnosis of rhabdomyosarcoma, no evidence of metastatic lesions at the time of diagnosis, no previous illness preventing treatment, no previous malignancies, and no severe vincristine-related neuropathy. Patients also had to be in complete remission or with minimal abnormalities on imaging studies at the end of the standard treatment. These minimal radiological abnormalities were defined as residual signs compatible with fibrosis (which would not have prompted the clinician responsible for the patient to defer stopping treatment). No central radiological review was in place. Patients had to be randomly assigned within 8 weeks after the end of standard treatment, which was defined as the last day of the ninth chemotherapy cycle, the date of surgery, or the date of the end of radiotherapy if done after the ninth cycle of chemotherapy.

Histopathological material had to be available for central diagnostic review, although risk grouping and randomisation were based on local assessments. Molecular confirmation of the presence of a *PAX–FOXO1* translocation was recommended but not mandatory for alveolar subtyping, and was not always done. Patients were removed from the study only if they withdrew consent or did not comply with study procedures.

The trial was designed and overseen by a trial management committee. An independent data monitoring committee reviewed safety and efficacy during the trial. The study was done in accordance with the Declaration of Helsinki and good clinical practice guidelines. All participating centres were required to obtain written approval from their local authorities and ethical committees, as well as written informed consent from patients or their parents or legal guardians.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to stop treatment or continue with maintenance chemotherapy. Randomisation was done with a web-based system provided by CINECA (Bologna, Italy), a non-profit, inter-university consortium. Patients were stratified in a block size of four by enrolling country and high-risk subgroup (E, F, and G, as described in the EpSSG risk classification, appendix p 7). Neither investigators nor patients were masked to treatment allocation.

Procedures

The diagnostic work-up comprised CT or MRI scans, or both, of the primary tumour, chest CT scan, radionuclide bone scan, bone marrow aspirates, and biopsy. ^{18}F-fluorodeoxyglucose PET was optional. Primary tumour resection was recommended only if a complete resection was considered feasible without harming the patient; otherwise, a biopsy was obtained to establish the diagnosis.

Patients received nine cycles of the IVA chemotherapy regimen: ifosfamide 3 g/m² given as a 3 h intravenous infusion with mesna (3 g/m²) and hydration on days 1 and 2; vincristine 1·5 mg/m² given as a single intravenous injection, weekly during the first 7 weeks then only on day 1 of each cycle (maximum dose 2 mg); and dactinomycin 1·5 mg/m² on day 1 given as a single intravenous injection (maximum dose 2 mg). From Oct 1, 2005, to Dec 17, 2013, patients were invited to participate in the randomised trial comparing standard IVA with IVADo (IVA plus doxorubicin 30 mg/m² on days 1 and 2 in the initial four cycles of chemotherapy).[17] After the trial closed on Dec 17, 2013, the trial management committee recommended treating patients with high-risk rhabdomyosarcoma with nine cycles of IVA (ie, the standard treatment). Local treatment of the primary tumour—including surgery, radiotherapy, or both—was planned after assessing tumour response at week 9, and was implemented at week 13. When a residual mass was identified, surgical resection was encouraged if free margins were achievable without organ or functional impairment. Marginal resection at sites where complete resection was deemed unfeasible was acceptable, provided it was always followed by radiotherapy.

Radiotherapy was the only possible local treatment for patients not able to undergo to secondary surgery because of the tumour's location (eg, parameningeal rhabdomyosarcoma). Radiotherapy doses varied from 41·4 Gy to 50·4 Gy, depending on tumour histology, response to chemotherapy, and surgical outcome. A boost of 5·4 Gy to the residual tumour was recommended for large tumours responding poorly to chemotherapy.

After the ninth cycle of chemotherapy, a full assessment of the tumour was done and patients meeting eligibility criteria were invited to participate in the maintenance chemotherapy trial. Patients were randomly assigned (1:1) to either stop treatment or continue with six 4-week cycles of intravenous vinorelbine 25 mg/m² on days 1, 8, and 15 and oral cyclophosphamide 25 mg/m² per day given continuously for 24 weeks. This treatment was given on an outpatient basis. In the event of neutropenia ($<1\times10^9$ neutrophils per L) or thrombocytopenia ($<80\times10^9$ platelets per L), or both, during the maintenance therapy phase, cyclophosphamide was stopped until the cell counts recovered, and the third dose of vinorelbine in the subsequent course also withheld if necessary.

If further haematological toxicity occurred, the dose of vinorelbine was reduced to 66% of the full dose on

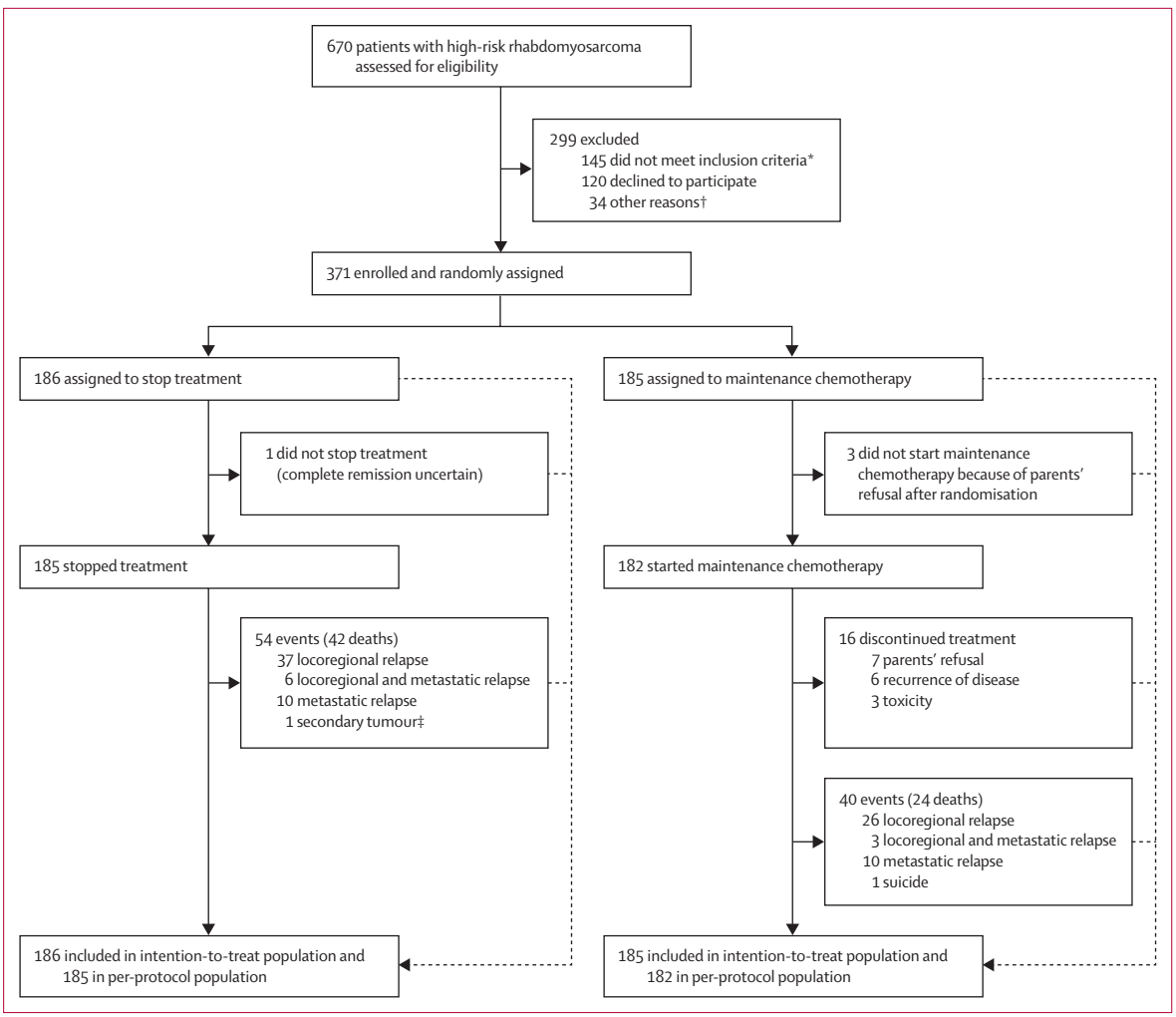

Figure 1: **Trial profile**

*Nine patients were aged older than 21 years at diagnosis, 81 were not in complete remission at the end of standard treatment, 18 had vincristine neuropathy, and in 37 the interval between the end of treatment and the evaluation for the second randomisation was longer than 8 weeks. †27 exclusions were due to the physician's decision, one due to the patient's condition, and six due to organisational reasons. ‡High-grade glioma.

days 1 and 8 (and the third dose omitted), to minimise interruptions in treatment.

Adverse events were monitored at least weekly, and were assessed according to National Cancer Institute Common Toxicity Criteria, version 3. All patients were monitored for possible tumour relapse with CT or MRI scans every 3 months during the first year, every 4 months during the second and third year, and yearly in the fourth and fifth year.

Outcomes

The primary outcome was disease-free survival, which was assessed by the investigator at each centre and not centrally reviewed, and was defined as the time from randomisation to tumour relapse or death from any cause or time of the latest follow-up in patients without an event. Secondary outcomes were overall survival, measured as the time from randomisation to death from any cause, or time to the latest follow-up in patients without an event, and toxicity. Median follow-up time is reported for patients who were alive at the time of data cutoff.

Statistical analysis

The trial was originally designed to enrol 388 patients and observe 200 events to detect an absolute increase in 3-year disease-free survival from 55% in patients who stopped treatment to 67% in those receiving maintenance chemotherapy. This difference would correspond to a relative reduction in the proportion of relapse of 33% in the maintenance treatment group, with 80% statistical power and an alpha of 5% (two-sided log-rank test). The sample size was calculated for a three-step, group sequential design (two interim analyses plus the final analysis) with an O'Brien-Fleming efficacy boundary and the Harrington-Fleming-O'Brien process

	Stop treatment group (n=186)	Maintenance chemotherapy group (n=185)
Age at diagnosis, years		
≤1 year	2 (1%)	11 (6%)
>1–9 years	143 (77%)	136 (74%)
10–17 years	36 (19%)	34 (18%)
≥18 years	5 (3%)	4 (2%)
Sex		
Female	82 (44%)	80 (43%)
Male	104 (56%)	105 (57%)
Histology of rhabdomyosarcoma		
Alveolar	62 (33%)	61 (33%)
Botryoid	5 (3%)	11 (6%)
Embryonal	113 (61%)	109 (59%)
Not otherwise specified	4 (2%)	2 (1%)
Spindle cells or leiomiomatous	2 (1%)	2 (1%)
Pathology		
Favourable	120 (65%)	122 (66%)
Unfavourable	66 (35%)	63 (34%)
Presence of *FOXO* and *PAX3* or *PAX7* translocation		
No	85 (46%)	102 (55%)
Yes	41 (22%)	43 (23%)
Investigation not done	60 (32%)	40 (22%)
Post-surgical tumour staging (IRS)		
Group I*	5 (3%)	5 (3%)
Group II	20 (11%)	21 (11%)
Group III	161 (86%)	159 (86%)
Primary tumour invasiveness		
T1: localised to the organ or tissue of origin	88 (47%)	72 (39%)
T2: extending beyond the tissue or organ of origin	97 (52%)	108 (58%)
Tx: insufficient information about the primary tumour	1 (1%)	5 (3%)
(Table 1 continues in next column)		

	Stop treatment group (n=186)	Maintenance chemotherapy group (n=185)
(Continued from previous column)		
Tumour size		
≤5 cm	61 (33%)	52 (28%)
>5 cm	125 (67%)	130 (70%)
Not evaluable	..	3 (2%)
Regional lymph node involvement		
N0: no evidence of lymph node involvement	154 (83%)	148 (80%)
N1: evidence of regional lymph node involvement	29 (16%)	31 (17%)
Nx: no information about lymph node involvement	3 (2%)	6 (3%)
Site of origin of primary tumour		
Orbit	7 (4%)	5 (3%)
Head and neck non-parameningeal	11 (6%)	14 (8%)
Parameningeal	56 (30%)	64 (35%)
Bladder prostate	25 (13%)	27 (15%)
Genitourinary non-bladder prostate	5 (3%)	7 (4%)
Extremities	36 (19%)	27 (15%)
Other sites	46 (25 %)	41 (22%)
Subgroup risk		
E	91 (49%)	91 (49%)
F	29 (16%)	31 (17%)
G	66 (35%)	63 (34%)

Data are n (%). IRS=Intergroup Rhabdomyosarcoma Studies. *All IRS group I patients had alveolar histology.

Table 1: **Clinical characteristics of randomised patients by treatment group**

of repeated testing of the alternative hypothesis at an alpha level of 0·005 for futility monitoring. Since the number of patients enrolled and the number of events were lower than planned, on Dec 1, 2011, the independent data monitoring committee recommended re-estimating the sample size and extending the recruitment period, reducing the hazard ratio to be detected to 0·5, and increasing the statistical power to 87%. Based on these assumptions, a new sample size of 370 patients and 79 events, and an interim analysis after observing 50% of the events was planned. At the time of the planned interim analysis in December, 2012, the independent data monitoring committee recommended continuing randomisation as planned. Accrual of patients ended on Dec 21, 2016, and data collected up to Nov 2, 2017, were analysed. The baseline characteristics of the treatment groups were compared with the χ^2 test. Survival probabilities were estimated according to the intention-to-treat principle (ie, including patients in the group to which they were assigned, whether or not they actually received the allocated treatment), by use of the Kaplan-Meier method and the two-sided stratified log-rank test, adjusting for the stratification factors at randomisation to compare the treatment groups at a significance level of 5%. A sensitivity analysis was done for the primary and secondary outcomes in the per-protocol population (ie, eligible patients who received the allocated treatment). 5-year disease-free survival and overall survival were reported with 95% CIs, calculated with Greenwood's method. Hazard ratios (HRs) were estimated with Cox's regression models, adjusted for stratification factors at randomisation, and 95% CIs were calculated according to Wald's method. The proportional hazards assumption was assessed with the score test based on scaled Schoenfeld residuals and was met (p=0·0793). Cox's regression models for disease-free survival and overall survival were estimated to examine possible interactions between treatment efficacy and clinical subgroups. For post-hoc subgroup analyses, no adjustments were made for multiplicity and so these analyses should be interpreted as only being descriptive. Patients who received at least one dose of study treatment were included in the safety analysis,

and toxicities were analysed according to the actual treatment received. All analyses were done with SAS, version 9.4.

This trial is registered with EUDRACT, number 2005-000217-35, and ClinicalTrials.gov, number NCT00339118.

Role of the funding source

EpSSG designed and coordinated the trial. The funders had no role in the design of the study, data collection, data analysis, data interpretation, or writing of the report. GB, IZ, and GLDS had full access to the raw data and had final responsibility for the decision to submit for publication, on behalf of the EpSSG board members.

Results

Between April 20, 2006, and Dec 21, 2016, 670 patients with characteristics of high-risk rhabdomyosarcoma were assessed for eligibility and 371 eligible patients were randomly assigned: 186 (50%) to stop treatment and 185 (50%) to receive maintenance chemotherapy (figure 1). One patient continued with maintenance chemotherapy despite being randomly assigned to stop treatment because their physician was uncertain as to whether the patient's tumour was in complete remission. Three children randomly assigned to the maintenance treatment group did not start the treatment because of parental refusal afterwards. All four patients were included in the intention-to-treat analysis but were excluded from the per-protocol analysis. Central diagnostic review was done in 282 (76%) patients: 146 (79%) of those who stopped the treatment and 136 (74%) of those who received maintenance chemotherapy. Clinical characteristics of patients were well balanced between the two groups (table 1) and were similar to those of non-randomised patients (appendix p 9). The interval from the end of treatment to randomisation was reasonable and similar in the two groups: median 29 days (IQR 17–42) in the group that stopped treatment and 31 days (22–44) in the group that received maintenance chemotherapy.

The treatment received before randomisation was similar in the two groups: 227 (61%) patients received IVA (120 in the maintenance chemotherapy group and 107 in the stop treatment group), and 144 (39%) received IVADo (65 in the maintenance chemotherapy group and 79 in the stop treatment group). More patients received IVA than IVADo because this was the regimen recommended after the first trial was closed on Dec 17, 2013. Complete data about treatment adherence and toxicity were available for 181 (99%) of the 183 patients who started maintenance chemotherapy (since we did a per-protocol analysis of toxicity, we included one patient who was randomly assigned to stop treatment but received maintenance chemotherapy), which was completed by 165 (90%) of 183 patients. The median time from randomisation to the end of maintenance chemotherapy was 5·75 months (IQR 5·45–5·98). Treatment was interrupted at the request of parents in seven children, because of disease recurrence in six, and because of toxicity in three (neurotoxicity in two [one grade 2 and one grade 3] and bone infection in one [grade 3]). 144 (80%) of 181 patients had at least one cycle

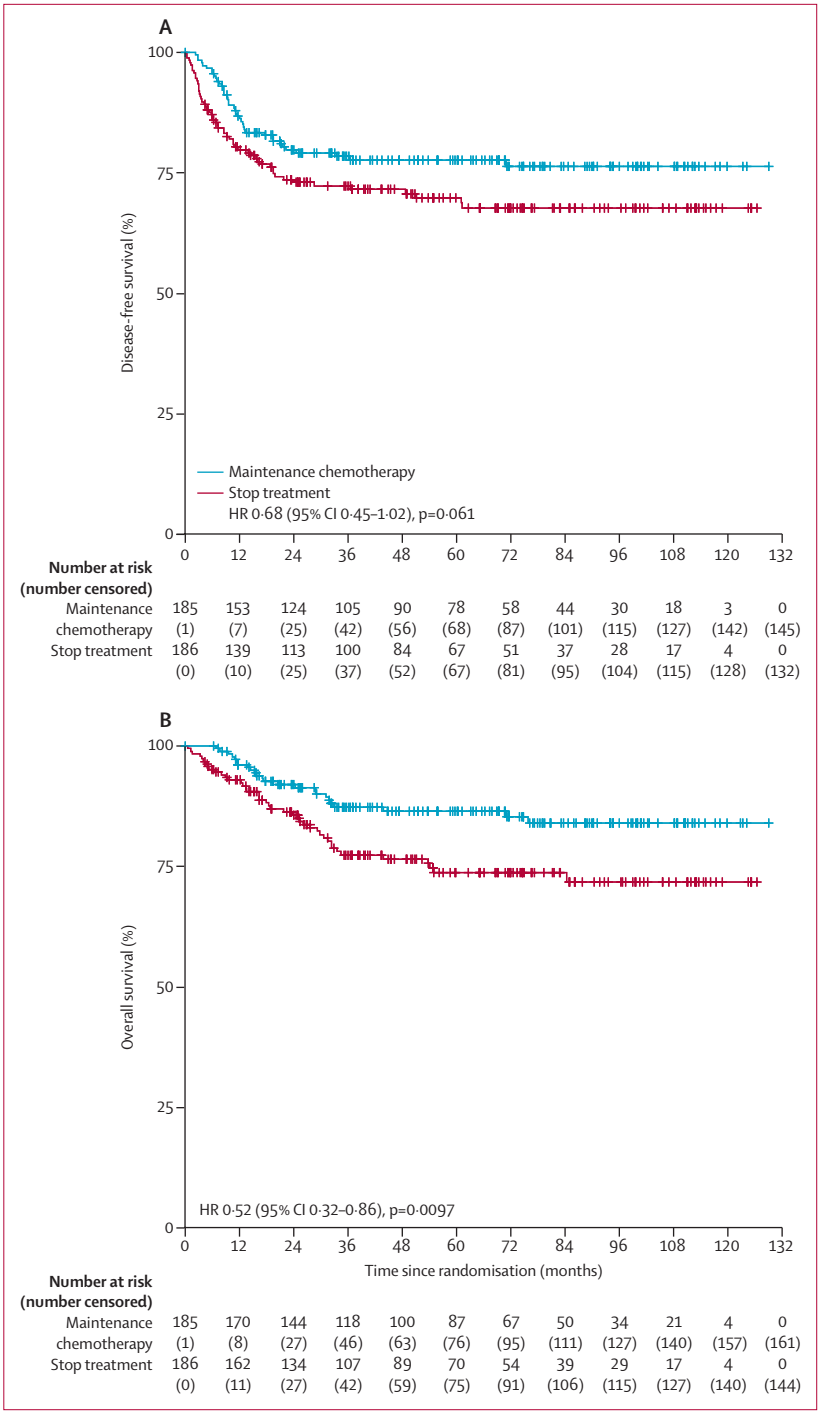

Figure 2: **Kaplan-Meier estimates of disease-free survival (A) and overall survival (B)**
HR=hazard ratio.

	Stop treatment group (n=186)	Maintenance chemotherapy group (n=185)
All events	54	40
Local relapse or regional lymph node relapse	37 (69%)	26 (65%)
Local or regional lymph node relapse and metastasis	6 (11%)	3 (8%)
Metastases	10 (19%)	10 (25%)
Death	1* (2%)	1† (3%)

Data are n or n (%). *Died by suicide. †Died after second tumour (high-grade glioma). One patient who died from a surgical complication and one who died from H1N1 influenza are not reported here because these were not the first events.

Table 2: **First events by randomised group**

	Grade 1–2	Grade 3	Grade 4
Haematological toxicity			
Anaemia	128 (71%)	16 (9%)	3 (2%)
Leucopenia	26 (14%)	86 (48%)	50 (28%)
Neutropenia	16 (9%)	66 (37%)	82 (45%)
Thrombocytopenia	28 (16%)	1 (1%)	1 (1%)
Non-haematological toxicity			
Cardiac	1 (1%)	..	..
Infection	33 (18%)	56 (31%)	..
Fever and neutropenia	4 (2%)	44 (24%)	..
Fever without neutropenia	26 (14%)	9 (5%)	..
Other infection	3 (2%)	3* (2%)	..
Nephrotoxicity	14 (8%)	1 (1%)	..
Neurology	21 (12%)	2 (1%)	1 (1%)†
Nausea or vomiting	34 (19%)	1 (1%)	..
Gastrointestinal	41 (23%)	9 (5%)	..
Allergy	4 (2%)	..	..
Dermatological	7 (4%)	1 (1%)	..
Other‡	37 (20%)	1 (1%)‡	..

Data are n (%). Toxicity data were only available for 181 patients. *Bone infection in one patient and pulmonary infection in two patients. †Steppage gait with limb pain that completely resolved after 1 month. ‡Hypokalemia.

Table 3: **Adverse events reported in 181 patients during maintenance chemotherapy**

modification: drug doses were reduced in accordance with the recommendations of the protocol to deal with neutropenia or thrombocytopenia in 74 (51%) patients; reduced because of toxicity in 63 (44%), and reduced for other reasons in seven (5%; appendix p 11).

At the time of data cutoff, the median follow-up for patients who were still alive was 60·3 months (IQR 32·4–89·4), so the 5-year results are reported here. In the intention-to-treat population, 5-year disease-free survival was 77·6% (95% CI 70·6–83·2) for patients who received maintenance chemotherapy versus 69·8% (62·2–76·2) for patients who stopped treatment (HR 0·68 [95% CI 0·45–1·02]; p=0·061). 5-year overall survival was 86·5% (95% CI 80·2–90·9) for patients who received maintenance chemotherapy versus 73·7% (65·8–80·1) for patients who stopped treatment (HR 0·52 [95% CI 0·32–0·86]; p=0·0097; figure 2). 367 patients met the criteria for the per-protocol analysis. 5-year disease-free survival was 69·6% (95% CI 62·0–76·0) in the group given no further treatment and 77·8% (70·8–83·4) in the group given maintenance chemotherapy (HR 0·67 [95% CI 0·44–1·01]; p=0·053). 5-year overall survival was 73·5% (95% CI 65·6–79·9) in the group given no further treatment and 86·3% (79·9–90·8) in the group given maintenance chemotherapy (HR 0·53 [95% CI 0·32–0·87]; p=0·011).

94 (25%) of 371 patients had a relapse event, with local and metastatic relapses similarly distributed in the two groups (table 2). The median time to relapse calculated from the randomisation date to the event was 6·9 months (IQR 3·0–16·1) in the group given no further treatment and 10·1 months (6·9–15·4) in the maintenance chemotherapy group.

66 (18%) patients died: 42 (23%) of 186 in the group given no further treatment and 24 (13%) of 185 in the maintenance therapy group. All deaths were related to tumour relapse except for two patients in the group given no further treatment (one from a surgical complication after a local relapse and one from suicide), and two in the maintenance chemotherapy group (an infection with H1N1 influenza after metastasis to the lung in one patient and high-grade glioma occurring as a second tumour 69·7 months after rhabdomyosarcoma in the other patient).

A post-hoc exploratory subgroup analysis, taking into account clinical variables known to be of prognostic value—such as age at diagnosis, histological subtype, primary tumour invasiveness, nodal involvement, tumour size and site, and Intergroup Rhabdomyosarcoma Studies group—showed no differences in any subgroup of patients between the two groups (appendix p 12).

The randomised comparison between the IVA and the IVADo regimens, which was part of the RMS 2005 study, did not differ significantly in terms of disease-free survival and overall survival between the two groups.[17] In a post-hoc analysis, a possible interaction between the initial standard chemotherapy (IVA or IVADo) and any subsequent maintenance chemotherapy was ruled out with Cox's regression models, for both disease-free survival (p=0·54) and overall survival (p=0·84; appendix p 13).

In view of the greater difference between the two groups in overall survival than in disease-free survival, a post-hoc analysis was done on the distribution of the characteristics that might have a prognostic effect for patients with a relapse: all variables were found to be well balanced between the two groups (appendix p 14). We noted a difference among countries in the number of patients considered in complete remission at the end of standard treatment and therefore eligible for the randomised study (appendix page 8). This difference was more evident in countries that enrolled a small number of patients.

Toxicity data are summarised in table 3. Grade 4 neutropenia was the most common adverse event, occurring in 82 (45%) patients, and grade 3 infection was reported in 56 (31%). 136 (75%) of 181 patients had grade 3–4 leucopenia, 148 (82%) had grade 3–4 neutropenia, 19 (10%) had anaemia, and two (1%) had thrombocytopenia. One patient (1%) had grade 4 non-haematological toxicity (neurotoxicity). Two treatment-related serious adverse events occurred: one patient had inappropriate antidiuretic hormone secretion and the other had a severe steppage gait with limb pain. Both events were resolved but maintenance treatment was permanently discontinued in the patient who had inappropriate antidiuretic hormone secretion.

Discussion

The results of this international randomised trial show that maintenance chemotherapy with vinorelbine and low-dose oral cyclophosphamide after standard treatment improves overall survival of patients with high-risk, non-metastatic rhabdomyosarcoma. In three decades of international cooperative trials,[4–13] this randomised study is, to the best of our knowledge, the first to show a survival benefit related to an experimental chemotherapy regimen.

The improvement in overall survival was significant and clinically important, whereas the improvement in disease-free survival—the primary endpoint—was not. However, in the per-protocol analysis (in which only a few patients were excluded in comparison with the intention-to-treat analysis) both disease-free and overall survival were significantly improved with maintenance chemotherapy, thus lending support to the activity of this regimen. Whether or not post-relapse treatment had any effect on survival could not be verified, because patients received different types of chemotherapy, with or without radiotherapy or surgery, or both. Previous studies identified factors that predict survival after relapse[18] and these factors were well balanced in our study population. Maintenance chemotherapy might have led to selection of patients in some way (eg, outcomes after late relapses are reported to be better, and in our cohort the median time to an event was 3 months later in patients randomly assigned to maintenance chemotherapy than in those assigned to stop treatment). Finally, the effectiveness of maintenance chemotherapy in the experimental group is also supported by the results of the per-protocol analysis, which show a significant improvement in disease-free survival in patients who received further treatment.

We were unable to identify subgroups of patients in whom maintenance chemotherapy was more effective and we ruled out any possible influence of previous treatments.

A limitation of the study was the high proportion of potentially eligible patients who were not randomly assigned, mainly because of parents' refusal. However, not including these patients is unlikely to have influenced the results substantially because the characteristics of non-randomised patients were similar to those of randomised patients. The inability to achieve complete tumour remission at the end of standard treatment, based on radiology investigations, was another reason for exclusion of several patients from this study. No central radiological review was in place but national coordinators were available to discuss difficult cases. We found some differences among countries in the number of patients not considered in complete remission, but randomisation was stratified by enrolling countries, thus preventing possible bias.

When the EpSSG RMS 2005 protocol was developed, the idea of a possible effect of maintenance therapy was based on sparse clinical evidence. The use of low-dose chemotherapy to maintain remission is a key concept in paediatric acute lymphoblastic leukaemia,[19] but such a strategy has been rarely investigated in solid tumours. In paediatric soft tissue sarcomas, the German Cooperative Group used oral maintenance chemotherapy (trofosfamide plus etoposide or idarubicin) as an alternative to high-dose chemotherapy with stem-cell rescue after standard therapy in children with metastatic disease. Although the study had some major limitations (ie, it was not randomised and the treatment was chosen at the discretion of the physician), it did suggest a promising role for maintenance chemotherapy.[15]

When the EpSSG RMS 2005 trial was developed, the activity of vinorelbine as a single agent in rhabdomyosarcoma had been documented in a single study,[14] which was subsequently supported by a second study showing 36% of patients achieving a response in relapsing rhabdomyosarcoma.[20] Cyclophosphamide had already been used successfully at low doses (2·5 mg/kg per day for up to 2 years).[7,8] A potentially anti-angiogenic and immunomodulatory effect has been suggested for both vinca alkaloids and continuous low-dose cyclophosphamide.[21–25] Additionally, these two drugs were not part of the initial chemotherapy regimen adopted in the RMS 2005 study, making chemoresistance issues less likely. All these reasons made this combination ideal as a maintenance therapy in the RMS 2005 trial. Moreover, before starting the trial, the new combination was tested in a pilot study, which showed that it was well tolerated and active.[16] This result was later confirmed by a larger phase 2 study.[26]

Our trial shows the feasibility of delivering this drug combination after standard chemotherapy. More than 90% of patients completed the treatment, although 80% required drug dose modification according to the protocol guidelines to avoid excessive myelosuppression. Although administration of cyclophosphamide should not increase the risk related to the cumulative doses of ifosfamide previously administered, the risk of long-term toxicity remains to be established, particularly the possibility of an increased risk of gonadal damage and secondary malignancies.

The observed improvement in overall survival could be explained in many ways. Prolonging chemotherapy might have improved survival in children with a small amount of residual disease remaining at the end of standard treatment. The optimal duration of chemotherapy for rhabdomyosarcoma has yet to be established. The duration has gradually decreased over the years, without apparently impairing the results of treatment. For example, treatment duration was reduced from 2 years to 1 year from the IRS-I study to the IRS-IV study,[7–10] and most patients receive 42 weeks of treatment in contemporary COG protocols. In Italian studies, treatment duration was reduced from 52 weeks or 78 weeks (depending on the risk group) in the first study to 22–37 weeks in the second, and 25 weeks in the third, without jeopardising patient outcomes.[27] However, the results of a retrospective analysis on extremity rhabdomyosarcoma, pooling data from US and European protocols, showed an improved outcome for patients treated with longer periods of chemotherapy compared with those who received a shorter duration of treatment.[28] Other differences in treatment strategies used by the various cooperative groups might, however, also account for these results.

An alternative hypothesis to explain the improved outcome for patients treated with maintenance therapy might be the effectiveness of the drugs involved (ie, vinorelbine and low-dose cyclophosphamide). In previous studies, the proportion of patients achieving a response to single-agent vinorelbine was similar to those achieving a response to vinorelbine combined with low-dose cyclophosphamide,[14,16,20,26] so the additive effect of the combination is unclear. But fully assessing the relative contribution of each drug by comparing the results of different studies is difficult. That said, the combined regimen might have killed any residual tumour cells resistant to the drugs administered during the standard treatment. This benefit seemed to be more evident in preventing locoregional rather than metastatic events. Since locoregional relapse is the most frequent cause of treatment failure and death, the effect of maintenance treatment might have been more evident in this group of patients.

When the RMS 2005 trial was started, the possibility of adding the effect of a metronomic approach to the effect of conventional chemotherapy was appealing. The prolonged exposure of tumour cells to chemotherapy, together with possible anti-angiogenic and immunomodulatory effects, are reportedly behind the mechanism of action of drugs given continuously at low doses.[24,25]

Finally, the effectiveness of maintenance chemotherapy could also relate to the compound effect of a longer period of chemotherapy and the efficacy of the drugs used in the maintenance phase.

For the **EpSSG website** see https://www.epssgassociation.it/en/

In the RMS 2005 trial, the role of maintenance chemotherapy was investigated in patients with high-risk disease (according to the EpSSG definition) with no evidence of an active residual tumour at the end of standard treatment. Although additional maintenance chemotherapy might not be considered necessary in patients with low-risk or standard-risk rhabdomyosarcoma, which has an excellent prognosis with standard treatment, this new strategy might be of benefit for children at higher risk of failure (ie, those with metastatic disease at diagnosis).

Maintenance chemotherapy was designed by taking into account the overall structure of the RMS 2005 trial and we do not know whether or not this strategy could be adopted for patients treated according to other protocols with a longer treatment duration (eg, COG protocols). This strategy might lead to an overall treatment duration that is less acceptable to patients and additional concerns about long-term toxicity. One option is to consider maintenance therapy in lieu of several more intense cycles of chemotherapy, to minimise toxicity while maintaining outcomes.

The role of maintenance therapy in the treatment of rhabdomyosarcoma, and possibly of other paediatric solid tumours, needs to be better elucidated. Further studies have been planned by the EpSSG to investigate the effectiveness of this strategy in patients with metastatic disease, whose prognosis is still largely unsatisfactory. The possible benefit of a longer duration of the maintenance phase will also be addressed in a randomised trial. Different drug combinations could also be investigated, and the mechanism of action behind the effect of maintenance therapies needs to be better understood.

In conclusion, this study showed that maintenance treatment with vinorelbine and low-dose oral cyclophosphamide for patients with high-risk rhabdomyosarcoma in complete remission after standard treatment improves overall survival and is safe and well tolerated. This approach has now been adopted by the EpSSG as the new standard of care for patients with high-risk rhabdomyosarcoma.

Contributors

All authors contributed to the study design, data collection, and interpretation, management of the clinical trial, writing and review of the paper, and approval of the final version. GB acted as principal investigator and was part of the trial management committee, along with CB, MJ, SGM, and AF. GB, GLDS, CB, MJ, AK, HM, SGM, and AF wrote the protocol and organised data collection. JHM, VMC, HG, JC, MC, CD, MBA, PM, and SF coordinated the protocol in the participating countries. GLDS coordinated the data centre and did the statistical analysis with IZ.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data are not publicly available since this was requirement not anticipated in the study protocol. The protocol can be requested through the EpSSG website.

Acknowledgments

The overall organisation of this study was supported by the Fondazione Città della Speranza, Padova, Italy. In France the study was supported by ALBEC (Association Léon Berard Enfant Cancéreux) grant 2005 and

Clinical Research Hospital Program from the French Ministry of Health (PHRC2004). In the UK, the study was supported by Cancer Research UK. During the course of the RMS 2005 study the EpSSG received unrestricted grants from Chugai and Roche, for unrelated work. JCC was supported by the National Institute for Health Research Biomedical Research Centre of the Royal Marsden NHS Foundation Trust. We acknowledge the work and vision of Odile Oberlin, Modesto Carli, and Michael Stevens who worked together to create the EpSSG, making this trial possible. We also thank Beatrice Coppadoro for statistical analysis and all the investigators who worked at the EpSSG centres and the patients and families who agreed to participate in this trial. Finally, we express our appreciation to James Anderson for representing the members of the independent data monitoring committee.

References

1 Ferrari A, Brecht IB, Gatta G, et al. Defining and listing very rare cancers of pediatric age: consensus of the Joint Action on Rare Cancers (JARC) in cooperation with the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT). *Eur J Cancer* 2019; **110:** 120–26.

2 Sultan I, Qaddoumi I, Yaser S, Rodriguez-Galindo C, Ferrari A. Comparing adult and pediatric rhabdomyosarcoma in the Surveillance, Epidemiology and End Results program, 1973 to 2005: an analysis of 2,600 patients. *J Clin Oncol* 2009; **27:** 3391–97.

3 Drummond CJ, Hanna JA, Garcia MR, et al. Hedgehog pathway drives fusion-negative rhabdomyosarcoma initiated from non-myogenic endothelial progenitors. *Cancer Cell* 2018; **33:** 108–24.

4 Arndt CAS, Bisogno G, Koscielniak E. Fifty years of rhabdomyosarcoma studies on both sides of the pond and lessons learned. *Cancer Treat Rev* 2018; **68:** 94–101.

5 Arndt CA, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group study D9803. *J Clin Oncol* 2009; **27:** 5182–88.

6 Oberlin O, Rey A, Sanchez de Toledo J, et al. Randomized comparison of intensified six-drug versus standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other chemotherapy-sensitive childhood soft tissue sarcomas: long-term results from the International Society of Pediatric Oncology MMT95 study. *J Clin Oncol* 2012; **30:** 2457–65.

7 Maurer HM, Beltangady M, Gehan EA, et al. The Intergroup Rhabdomyosarcoma Study-I. A final report. *Cancer* 1988; **61:** 209–20.

8 Maurer HM, Gehan EA, Beltangady M, et al. The Intergroup Rhabdomyosarcoma Study-II. *Cancer* 1993; **71:** 1904–22.

9 Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol* 1995; **13:** 610–30.

10 Crist WM, Anderson JR, Meza JL, et al. Intergroup Rhabdomyosarcoma Study-IV: results for patients with nonmetastatic disease. *J Clin Oncol* 2001; **19:** 3091–102.

11 Flamant F, Rodary C, Rey A, et al. Treatment of non-metastatic rhabdomyosarcomas in childhood and adolescence. Results of the second study of the International Society of Paediatric Oncology: MMT84. *Eur J Cancer* 1998; **34:** 1050–62.

12 Stevens MC, Rey A, Bouvet N, et al. Treatment of nonmetastatic rhabdomyosarcoma in childhood and adolescence: third study of the International Society of Paediatric Oncology–SIOP Malignant Mesenchymal Tumor 89. *J Clin Oncol* 2005; **23:** 2618–28.

13 Spunt SL, Smith LM, Ruymann FB, et al. Cyclophosphamide dose intensification during induction therapy for intermediate-risk pediatric rhabdomyosarcoma is feasible but does not improve outcome: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Clin Cancer Res* 2004; **10:** 6072–79.

14 Casanova M, Ferrari A, Spreafico F, et al. Vinorelbine in previously treated advanced childhood sarcomas: evidence of activity in rhabdomyosarcoma. *Cancer* 2002; **94:** 3263–68.

15 Klingebiel T, Boos J, Beske F, et al. 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:** 739–45.

16 Casanova M, Ferrari A, Bisogno G, et al. Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European Rhabdomyosarcoma Protocol. *Cancer* 2004; **101:** 1664–71.

17 Bisogno G, Jenney M, Bergeron C, et al. Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a multicentre, open-label, randomised controlled, phase 3 trial. *Lancet Oncol* 2018; **19:** 1061–71.

18 Chisholm JC, Marandet J, Rey A, et al. Prognostic factors after relapse in nonmetastatic rhabdomyosarcoma: a nomogram to better define patients who can be salvaged with further therapy. *J Clin Oncol* 2011 **29:** 1319–25.

19 Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med* 2006; **354:** 166–78.

20 Kuttesch JF Jr, Krailo MD, Madden T, Johansen M, Bleyer A. Phase II evaluation of intravenous vinorelbine (navelbine) in recurrent or refractory pediatric malignancies: a Children's Oncology Group study. *Pediatric Blood Cancer* 2009; **53:** 590–93.

21 Hill SA, Lonergan SJ, Denekamp J, Chaplin DJ. Vinca alkaloids: anti-vascular effects in a murine tumour. *Eur J Cancer* 1993; **29A:** 1320–24.

22 Hill SA, Sampson LE, Chaplin DJ. Anti-vascular approaches to solid tumour therapy: evaluation of vinblastine and flavone acetic acid. *Int J Cancer* 1995; **63:** 119–23.

23 Ma J, Waxman DJ. Modulation of the antitumor activity of metronomic cyclophosphamide by the angiogenesis inhibitor axitinib. *Mol Cancer Ther* 2008; **7:** 79–89.

24 Kamen BA, Rubin E, Aisner J, Glatstein E. High-time chemotherapy or high time for low dose. *J Clin Oncol* 2000; **18:** 2935–37.

25 Hanahan D, Bergers G, Bergsland E. Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. *J Clin Invest* 2000; **105:** 1045–47.

26 Minard-Collin V, Ichante JL, Nguyen L, 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 Société Française des Cancers et Leucémies de l'Enfant et de l'Adolescent (SFCE). *Eur J Cancer* 2012; **48:** 2409–16.

27 Bisogno G, De Rossi C, Gamboa Y, et al. Improved survival for children with parameningeal rhabdomyosarcoma: results from the AIEOP soft tissue sarcoma committee. *Pediatr Blood Cancer* 2008; **50:** 1154–58.

28 Oberlin O, Rey A, Brown KL, et al. Prognostic factors for outcome in localized extremity rhabdomyosarcoma. Pooled analysis from four international cooperative groups. *Pediatr Blood Cancer* 2015; **62:** 2125–31.