A multicenter, open label, randomised phase 3 trial investigating vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma

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SUMMARY

Background For over 3 decades, standard treatment for rhabdomyosarcoma in Europe has included 6 months of chemotherapy. The European paediatric Soft tissue sarcoma Study Group investigated whether prolonging treatment with maintenance chemotherapy improves survival for patients with high-risk rhabdomyosarcoma.

Methods This was a multicentre, open-label, randomised controlled, phase 3 trial involving 102 hospitals from 14 countries. We included patients aged 6 months to 21 years with non-metastatic embryonal rhabdomyosarcoma i) incompletely resected occurring at unfavorable sites with unfavorable age and/or tumor size, or (ii) with nodal involvement and those with alveolar rhabdomyosarcoma but without nodal involvement were considered at high-risk of relapse. Patients with tumour in remission after standard treatment (9 cycles of ifosfamide, vincristine, dactinomycin +/- doxorubicin, surgery and/or radiotherapy) were randomly assigned (1:1) to stop treatment or receive maintenance chemotherapy (6 cycles of i.v. vinorelbine 25 mg/m^2 on days 1,8,15 and daily oral cyclophosphamide 25 mg/m^2, days 1-28). Randomisation was done using 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. Primary endpoint was disease-free survival (DFS) in the intention to treat population. Secondary endpoints were overall survival and toxicity. This trial is registered with EudraCT, number 2005-000217-35 and ClinicalTrials.gov number NCT00339118, and is currently in follow-up.

Findings Between April 20th, 2006 and December 21st, 2016, 371 patients were randomised (186 to stop treatment and 185 to receive maintenance therapy). Median follow up was 60·3-months (IQR 32·4–89·4). The 5-year DFS was 77·6% (95% CI 70·6-83·2) with maintenance vs. 69·8% (95% CI 62·2-76·2) without maintenance chemotherapy (p=0·061), and OS was 86·5% (95% CI 80·2-90·9) and 73·7% (95% CI 65·8-80·1) (p=0·0097), respectively. Toxicity was manageable: grade 3-4

leucopenia in 136 (76%) patients, anaemia in 19 (11%), thrombocytopenia in 2 (2%), infection in 56 [31%] patients. Only 1 (1%) patient suffered of grade 4 non haematological toxicity (neurotoxicity).

Interpretation Adding maintenance chemotherapy improves survival for high-risk rhabdomyosarcoma patients and will be the new standard of therapy for this group in future EpSSG trials.

Funding Fondazione Città della Speranza, Italy; Association Léon Berard Enfant Cancéreux, France; Cancer Research UK;

Introduction

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and young adults. It is nonetheless a rare cancer, with an annual incidence of 4 in a million for 0-19 years old individuals and approximately 400 cases each year in Europe.[1] Although it is regarded as a tumour typical of paediatric age (with its highest incidence before age 6 years), approximately 40% of all rhabdomyosarcomas occur in adults.[2] This aggressive tumour is thought to derive from primitive mesenchymal cells committed to developing into striated muscles but recently an origin from endothelial progenitors has been suggested.[3]

There are two main histotypes, the embryonal (which accounts for approximately 80% of all pediatric rhabdomyosarcomas), and the more aggressive alveolar subtype (15-20% of cases), characterised by a chromosomal translocation involving the fusion of the transcription factor genes *FOXO1* and either *PAX3* or *PAX7*.

The survival of patients with non-metastatic rhabdomyosarcoma is around 70% with the risk-adapted multimodal treatment strategy currently used. This strategy has been refined since the 1970s thanks to several studies coordinated by international cooperative groups, the largest being the North American Children's Oncology Group (COG), and the more recently founded European paediatric Soft tissue sarcoma Study Group (EpSSG).[4] These groups have adopted an alkylating agent (i.e. cyclophosphamide or ifosfamide) combined with vincristine and dactinomycin, administered every 3 weeks for 6 to 10 months,[5,6] as the standard chemotherapy for patients with non-metastatic rhabdomyosarcoma. In a series of randomised trials attempts to intensify this chemotherapy have failed to improve outcome.[5-13] These trials showed that most rhabdomyosarcoma patients achieve complete tumour remission by the end of their treatment, which also includes surgery and/or radiotherapy. The fact that up to one in three patients relapse within a relatively short time[5,6] suggests, however, that minimal residual active disease escaping

detection using current radiological methods and resistant to standard treatment, remains an obstacle to improving the survival. This obstacle might be overcome by introducing new, more effective drugs and/or adopting new strategies.

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

Methods

Study Design and participants

The RMS 2005 was an investigator-initiated prospective international phase III randomised, open label, controlled clinical trial conducted at 102 hospitals in 14 countries (Argentina, Belgium, Brazil, Czech Republic, France, Ireland, Israel, Italy, Norway, Switzerland, Slovenia, Spain, The Netherlands, and United Kingdom) (appendix p 1). 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 conducted 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, and written informed consent from patients and/or their parents or legal guardians

After the 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 included non-metastatic and either i) incompletely resected embryonal rhabdomyosarcoma occurring at unfavourable sites with age $\geq$ 10 years and/or size > 5 cm, or (ii) any embryonal rhabdomyosarcoma with nodal involvement or (iii) any alveolar rhabdomyosarcoma without nodal involvement.

Patients included in the high-risk group were eligible for two consecutive independent randomised trials to investigate: a) the benefit of early dose intensification with doxorubicin and b) the value of maintenance chemotherapy for patients in complete remission after the standard therapy. The results of the first trial have been reported elsewhere. [17]

Patients were considered for the second trial independently from the fact they have been included (or not included for whatever reason) in the first trial. The first trial was closed on December 2013. After this date patients were eligible only for the second trial.

The eligibility criteria were: age >6 months at the time of randomisation to <21 years at the time of diagnosis; a pathologically confirmed diagnosis of rhabdomyosarcoma; no evidence of metastatic lesions at the time of diagnosis; no prior illness preventing treatment; no prior 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 the treatment). No central radiological review was in place. Patients had to be

randomised within 8 weeks after the end of standard treatment defined as the last day of the 9th chemotherapy cycle or the dates of surgery or the date of the end of radiotherapy if performed after the 9th cycle of chemotherapy.

Histopathological material had to be available for central diagnostic review (and 76·0% of cases have been actually reviewed), though 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 undertaken (table 1). Patients were removed from the study only due to consent withdrawal or lack of compliance with study procedures.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to stop treatment or continue with maintenance chemotherapy. Randomisation was done using a web-based system provided by CINECA (an Italian, a not-profit, inter-university consortium). Patients were stratified in 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 included CT and/or MRI 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 9 cycles of IVA chemotherapy comprising ifosfamide 3 g/m^2 given as a 3-h intravenous infusion with mesna (3 g/m^2) and hydration on days 1 and 2, vincristine 1·5 mg/m^2 given as a single intravenous injection, weekly during the first 7 weeks then only on day 1 of each cycles (maximum dose 2 mg), and dactinomycin 1·5 mg/m^2 on day 1 given as a single intravenous injection (maximum dose 2 mg). From October 1st, 2005, to December 17th, 2013, patients were invited to participate in the randomised trial comparing standard IVA with IVADo (IVA plus doxorubicin 30 mg/m^2 on days 1 and 2 in the initial 4 cycles of chemotherapy).[17] After the trial closed, the Trial Management Committee recommended treating high-risk rhabdomyosarcoma patients with 9 cycles of IVA. The 'local treatment' of the primary tumour - including surgery and/or radiotherapy - was planned after assessing tumour response at week 9, and it 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 resections 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 amenable to secondary surgery due to the tumour's location (e.g. parameningeal rhabdomyosarcoma). Radiotherapy doses varied from 41·4 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 9th cycle of chemotherapy, a full assessment of the tumour was mandatory and patients satisfying the eligibility criteria were invited to participate in the maintenance chemotherapy trial, and to be randomised to either stop treatment or continue with six 4-week cycles of intravenous vinorelbine 25 mg/m^2 on days 1, 8 and 15 and oral cyclophosphamide 25 mg/m^2/day given continuously for 24 weeks. This treatment was given on an outpatient basis. In the event of

neutropenia (<1 x10^9/l neutrophils) and/or thrombocytopenia (< 80 x10^9/l platelets) during the maintenance therapy phase, cyclophosphamide was stopped until the count(s) recovered, possibly also withholding the third dose of vinorelbine in the subsequent course.

When further haematological toxicity occurred, the dose of vinorelbine could be reduced to 66% on days 1 and 8 (and the third dose omitted), in an effort to minimize interruptions in the therapy. Adverse events were monitored at least weekly. All patients were followed for possible tumour relapse with CT scan or MRI every 3 months during the first year, every 4 months during the second and third year, yearly in the fourth and fifth year.

Outcomes

The primary endpoint was disease-free survival, assessed by the investigator at each centre and not centrally reviewed and defined as the time from randomisation to tumour relapse or death due to any cause or time of the latest follow up. Secondary outcomes were: overall survival, measured as the time from randomisation to death due to any cause, or time to the latest follow-up; and toxicity, assessed according to NCI-CTC version 3. Median follow up time was reported for alive patients.

Statistical analysis

The trial was originally planned to enrol 388 patients and observe 200 events in order to detect an absolute increase in 3-year disease-free survival from 55% in those who stopped treatment to 67% in those receiving the maintenance therapy. This would correspond to a relative reduction in the proportion of relapse of 33% in the maintenance arm, with an 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) using an O'Brien-Fleming efficacy boundary and the Harrington-Fleming-O'Brien process of repeated testing of the alternative hypothesis at an alpha level 0·005 for futility monitoring. As the number of events and the number of patients enrolled were lower than planned, on the 1st of December 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 one 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 the randomisation as planned. Patients accrual ended on December 21st, 2016 and data collected up to the 2nd of November 2017 were analysed. The baseline characteristics of the treatment groups were compared using the chi-square test. Survival probabilities were estimated according to the intention-to-treat principle, i.e. including patients in the group to which they were assigned, whether they received the allocated treatment or not, using the Kaplan-Meier method and the two-sided stratified log rank test, adjusting for the stratification factors at randomisation to compare the treatment arms on a significance level of 5%. A sensitivity analysis was performed for the primary and secondary end points in the per protocol population, i.e. eligible patients who received the allocated treatment. Five-year disease-free survival and overall survival were reported with 95% confidence intervals (CI), calculated using Greenwood's method. Hazard Ratios (HR) were estimated with Cox's regression models, adjusted for the stratification factors at randomisation and 95% CI were calculated according to Wald's method. The proportional hazards assumption was assessed using 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 of patients. For

subgroup analyses, no adjustments were made for multiplicity and should be interpreted as only descriptive. Patients who received at least one dose of treatment under study were considered in the safety analysis and toxicities were analysed according to the actual treatment received. All analyses were performed with SAS software, version 9·4 (SAS Institute, Cary, NC). This trial is registered with EUDRACT Number 2005-000217-35 and ClinicalTrials.gov number NCT00339118.

Role of funding source

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

Results

The first patient was randomised on April 20th, 2006 and the last on December 21st, 2016. Overall, 670 rhabdomyosarcoma patients with high-risk characteristics were assessed for eligibility and 299 (44·6%) were excluded: 145 (21·6%) patients did not satisfy the eligibility criteria (mainly because the patient was not considered in complete remission at the end of standard treatment, appendix p 8) and 154 (22·9%) eligible patients were not randomised, due largely to parental refusal (120 cases). A total of 371 patients were randomised: 186 (50·1%) to stop treatment and 185 (49·9%) to receive maintenance therapy (Figure 1). One patient continued with maintenance chemotherapy despite being randomised to stop treatment because his/her physician had become uncertain whether the tumour was in complete remission. Three children randomised to the maintenance arm did not start the treatment due to parental refusal afterwards. All these patients

were included in the analysis according to the intention-to-treat principle, but excluded from the per protocol analysis. The characteristics of the patients and their disease were well balanced between the two arms of the trial (Table 1) and similar to those of non-randomised patients (appendix p 9). The interval from the end of treatment to randomization has been reasonable and similar in the 2 arms: 28.5 days (IQR 17 – 42) in the stop treatment arm and 31 days (IQR 22 – 44) in the maintenance arm.

The treatment received prior to randomisation was similar in the two groups: an overall 227 (61·1%) patients had received IVA (120 with maintenance), and 144 (38·9%) IVADo (65 with maintenance). More patients received IVA because this was the regimen recommended after the first trial was closed on December 2013. Complete data on treatment adherence and toxicity were available for 181 (98·9%) of the 183 patients who started the maintenance therapy, which was completed by 165 (90·2%) patients. The median time from randomisation to the end of the maintenance therapy was 5·75 months (inter-quartile range 5·45-5·98). It was interrupted at parents' request in 7 children, due to disease recurrence in 6, and due to toxicity in 3 (neurotoxicity in 2, bone infection in 1). Overall, 144/181 (80%) patients had at least one cycle modification: the drug doses were reduced in accordance with the recommendations of the protocol to deal with neutropenia or thrombocytopenia in 74 (51·4%) cases; due to toxicity in 63 (43·7%); and for other reasons in 7 (4·9%) (appendix p 11).

Toxicity data are provided in Table 2. Grade 4 neutropenia was the most common toxicity issue (in 45% of patients) and grade 3 infection was reported in 31% of patients. Only one patient suffered from grade 4 non-haematological toxicity. Only two treatment-related serious adverse events occurred: one patients suffered from a syndrome of inappropriate antidiuretic hormone secretion and the other from a severe steppage gait with limbs pain. Both events resolved but in the first case maintenance treatment was permanently discontinued.

At the time of data cut-off, the median follow-up for patients still alive was 60·3 months (inter-quartile range 32·4–89·4), so the 5-year results are reported here.

In the intention-to-treat population, the 5-year disease-free survival was 69·8% (95% CI 62·2 – 76·2) for patients who stopped treatment, and 77·6% (95% CI 70·68 – 83·2) for those who received maintenance therapy (HR 0·68, 95%CI 0·45-1·02; p=0·061). The 5-year overall survival was 73·7 (95% CI 65·8-80·1) and 86·5 (95% CI 80·2-90·9) in the arm given no further treatment and the maintenance therapy arm (HR 0·52, 95% CI 0·32-0·86; p=0·0097), respectively (Figure 2).

In all, 94 (25·3%) patients experienced an event, with local and metastatic relapses similarly distributed in the two arms (Table 3).

Sixty-six (17·8%) patients died: 42/186 (22·5%) in the arm given no further treatment and 24/185 (13%) in the maintenance therapy arm. All deaths were related to tumour relapse except for 2 patients in the group given no further treatment (1 surgical complication after a local relapse, and 1 suicide), and 2 in the maintenance therapy group (an infection with H1N1 influenza after metastasis to the lung in 1, and high-grade glioma occurring as second tumour 69·7 months after rhabdomyosarcoma).

The median time to relapse calculated from the randomisation date to the event was 6.9 months (inter-quartile range 3.0 - 16.1) in the stop treatment arm and 10.1 months (inter-quartile range 6.9 – 15.4) in the maintenance arm.

A per-protocol analysis was run according to the treatment actually received (Figure 1). Overall, 367 patients met the criteria for this analysis. The 5-year disease-free survival was 69·6% (95% CI 62·0-76·0) in the group given no further treatment and 77·8% (95% CI 70·8-83·4) in the group given maintenance therapy (HR 0·67, 95% CI 0·44-1·01; p=0·053). The 5-year overall survival was 73·5% (95% CI 65·6-79·9) and 86·3% (95% CI 79·9-90·8), respectively (HR 0·53, 95% CI 0·32-0·87, p=0·011)

A post hoc exploratory analysis, taking into account the 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 IRS group – revealed no differences in any subgroup of patients between the patients in the two arms of the trial (appendix p 12).

The randomised comparison between the IVA and the IVADo regimen, which was part of the RMS 2005 study, did not show any significant differences between the two arms[20]. A possible interaction between the initial standard chemotherapy (IVA or IVADo) and any subsequent maintenance chemotherapy was ruled out using Cox's regression models, for both disease-free survival (p=0·54) and overall survival (p=0·84) (appendix p 13).

Considering the greater difference between the two arms in overall survival than in disease-free survival, a post hoc analysis was conducted on the distribution of the characteristics that can have a prognostic impact for the patients experiencing a relapse: all variables were found well balanced between the two groups (table 4)

Discussion

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

The improvement observed in overall survival in this trial is statistically significant and clinically important, while the improvement in disease-free survival (which was the primary endpoint of the trial) falls just short of the conventional definition of statistical significance. The statistical significance achieved in the per protocol analysis (where only few patients were excluded in

comparison to the intention to treat analysis) both for disease free and overall survival support the activity of maintenance. It was not possible to verify whether post relapse treatment had any impact on survival as patients received a variety of chemotherapy with/without radiotherapy and or surgery. Previous studies identified factors that predict survival after relapse [18] and they were well balanced in our population. It might be possible that maintenance therapy has been able to make some kind of selection, i.e. it is reported that outcomes after "late" relapses are better and, in our cohort, the median time to an event was 3 months later in the patients randomised to the maintenance arm. Finally, the effectiveness of the maintenance therapy in the experimental arm is also supported by the results of the "per-protocol analysis", which demonstrate a statistically significant benefit in disease-free survival for patients receiving further treatment.

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

A limitation of the study was the relatively high-proportion of potentially eligible patients have not been randomized mainly because of parents' refusal. This phenomenon should not have impacted the study as the characteristics of non-randomized patients were similar to those of randomized patients. It is likely that in the light of the results obtained in this study the number of families that will refuse maintenance will be greatly reduced in the future. Another reason to exclude patients from the study was represented by the inability to achieve a complete tumor remission at the end of standard treatment judged on radiology investigations. 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 the randomization was stratified by enrolling countries preventing possible bias.

When the EpSSG RMS 2005 protocol was developed, the idea of a possible effect of maintenance therapy was based on limited 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 suffered from significant limitations (i.e. 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 trial was developed, the activity of vinorelbine as a single agent in rhabdomyosarcoma had been documented by a single study,[14] which was subsequently supported by a second study showing a 36% response rate in relapsing rhabdomyosarcoma.[20] Cyclophosphamide had already been used successfully at low doses (2·5 mg/kg/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] In addition, 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.

Before opening the trial, the new combination was tested in an pilot study, which demonstrated that it was well tolerated and active.[16] This result was later confirmed by a larger phase II study.[26]

Our trial confirmed the feasibility of delivering this drug combination after standard chemotherapy. More than 90% of patients completed the treatment, although the majority (79·4%) required drug dose modification according to the protocol guidelines to avoid excessive myelosuppression. Despite the fact that the administration of cyclophosphamide should not increase the risk related to the cumulative doses of ifosfamide previously administered, long-term

toxicity remains to be established. In particular, the possibility of an increased risk of gonadal damage and secondary malignancies.

The survival improvement may be explained in many ways. Prolonging chemotherapy may have cured a group of children with the persistence of a limited amount of residual disease at the end of standard treatment. The optimal duration of chemotherapy for rhabdomyosarcoma has yet to be established. It has gradually decreased over the years, without apparently impairing the results. For example, it was reduced from 2 years to 1 from the IRS-I study to the IRS-IV,[7-10] and most patients receive 42 weeks of treatment in modern COG protocols. In the Italian studies, treatment duration dropped from 52 or 78 weeks (depending on risk group) in the first study to 22-37 weeks in the second, and 25 in the third, without jeopardizing the outcome.[27] On the other hand, the results of a recent retrospective analysis on extremity rhabdomyosarcoma, pooling data from US and European protocols, demonstrated a better outcome for patients treated with longer periods of chemotherapy.[28] Other differences in the treatment strategies used by the various cooperative groups may, however, account for these results as well.

An alternative hypothesis to explain the better outcome for patients treated with maintenance therapy may be the effectiveness of the drugs involved, i.e. vinorelbine and low-dose cyclophosphamide. In previous studies, the response rate to single-agent vinorelbine seemed similar to the results achieved when it was combined with low-dose cyclophosphamide,[14,16,20,26] so the additive effect of the latter is unclear. But it is difficult to fully assess the relative contribution of each drug comparing the results of different studies. That said, the combined regimen may have killed any residual tumour cells resistant to the drugs administered during the standard treatment. This benefit appeared more evident in preventing locoregional rather than metastatic events. It might be possible that being the locoregional relapse the most frequent cause of treatment failure and death, maintenance effect resulted 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 longer period of chemotherapy *and* the efficacy of the drugs used in the maintenance phase.

In the RMS 2005 trial, the role of maintenance therapy was investigated in patients with high-risk disease (according to the EpSSG definition) with no evidence of active residual tumour at the end of standard treatment. Whilst it may be difficult to suggest a role for additional maintenance therapy in patients with low- or standard-risk rhabdomyosarcoma, which carries an excellent prognosis with current treatment, this new strategy may be interesting for children at higher risk of failure, i.e. those with metastatic disease at diagnosis.

Maintenance chemotherapy was designed taking into account the overall structure of the RMS 2005 trial and we do not know whether this strategy could be adopted for patients treated according to other protocols whose treatment duration is longer (e.g. COG protocols). This might lead to an overall treatment duration that is less acceptable to patients and additional concerns regarding late toxicity. One option is to consider maintenance therapy in lieu of a number of more intense cycles of chemotherapy, aiming to minimise toxicity whilst 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 metastatic patients, 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 may be investigated too, and

the mechanism of action behind the effect of maintenance therapies needs to be better understood.

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

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Research in context

Evidence before this study

We searched PubMed between January 1 1980 and December 1 2018 for all randomised trials in English involving patients with rhabdomyosarcoma. We also searched for published papers with the following search terms: “rhabdomyosarcoma” and “maintenance”. We did not find any randomised trial investigating the role of maintenance chemotherapy or the length of chemotherapy in rhabdomyosarcoma. One non-randomised trial suggested that oral maintenance chemotherapy is better than high dose chemotherapy in metastatic rhabdomyosarcoma patients.

Added value of this study

To our knowledge this is the first randomised study to show an improvement in survival for patients with rhabdomyosarcoma included in the interventional arm. In our trial maintenance chemotherapy (6 cycles of intravenous vinorelbine 25 mg/m^2 on days 1, 8, 15 and daily oral cyclophosphamide 25 mg/m^2, days 1-28) added to patients with high risk rhabdomyosarcoma in complete tumour remission after standard chemotherapy improved overall survival and was well tolerated. However, the increase in disease free survival was not statistically significant.

Implications of all the available evidence

Adding maintenance chemotherapy improves survival for high-risk rhabdomyosarcoma patients and will be the new standard of therapy for this group in future EpSSG trials.

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. In addition GB acted as principal investigator and was part of the Trial Management Committee with CB, MJ, SG, AF. GB, GLDS, CB, MJ, AK, HM, SG, AF wrote the protocol and organized the data collection. JHM, VMC, HG, JC, MC, CD, MBA, PM, SF coordinated the protocol in the participating countries. GLDS coordinated the data centre and performed the statistical analysis with IZ.

Declaration of interest

Authors have no competing interests to disclose.

Data Sharing Statement

Individual participant data are not publicly available since this was not foreseen by the study protocol. The protocol can be requested through the EpSSG website https://www.epssgassociation.it/en/

Acknowledgment:

We would like to 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 centers and the patients/families who agreed to participate in this trial, contributing to its success.

Finally, we would like to express our appreciation to James Anderson in representation of the members of the independent data monitoring committee.

Funding: The overall organization of this study was supported by the Fondazione Città della Speranza, Padova, Italy. In France the study has been supported by ALBEC (Association Léon Berard Enfant Cancéreux) grant 2005. In the United Kingdom the study has been supported by Cancer Research UK. During the course of the RMS 2005 study (but not related to it) the EpSSG received unrestricted grants from Chugai and Roche. Dr. Julia C. Chisholm was supported by the National Institute for Health Research Biomedical Research Center of the Royal Marsden NHS Foundation Trust

Table 1: Clinical characteristics of randomised patients by treatment arm

	Stop Treatment (n=186)	Maintenance Chemotherapy (n=185)
Age (years) at diagnosis		
≤ 1 year	2 (1·1%)	11 (5·9%)
>1 and <10 years	143 (76·9%)	136 (73·5%)
≥10 and <18 years	36 (19·3%)	34 (18·4%)
≥ 18 years	5 (2·7%)	4 (2·2%)
Gender		
Female	82 (44·1%)	80 (43·2%)
Male	104 (55·9%)	105 (56·8%)
Histology		
Alveolar RMS	62 (33·3%)	61 (33·0%)
Botryoid RMS	5 (2·7%)	11 (5·9%)
Embryonal RMS	113 (60·7%)	109 (58·9%)
Not Otherwise Specified RMS	4 (2·2%)	2 (1·1%)
Spindle cells/Leiomiomatous RMS	2 (1·1%)	2 (1·1%)
Pathology		
Favourable	120 (64·5%)	122 (65·9%)
Unfavourable	66 (35·5%)	63 (34·1%)
Presence of FOXO/PAX3 or PAX7 translocation		
No	85 (45·7%)	102 (55·1%)
Yes	41 (22·0%)	43 (23·2%)
Investigation not performed	60 (32·3%)	40 (21·7%)
Post surgical tumour staging (IRS)		
Group I*	5 (2·7%)	5 (2·7%)
Group II	20 (10·8%)	21 (11·4%)
Group III	161 (86·5%)	159 (85·9%)
Primary tumour Invasiveness (T)		
T1 – Localized to the organ or tissue of origin	88 (47·3%)	72 (38·9%)
T2 – Extending beyond the tissue or organ of origin	97 (52·2%)	108 (58·4%)
Tx – Insufficient information about the primary tumour	1 (0·5%)	5 (2·7%)
Tumour size		
≤ 5 cm	61 (32·8%)	52 (28·1%)
> 5 cm	125 (67·2%)	130 (70·3%)
not evaluable	-	3 (1·6%)
Regional lymph node involvement		
N0 – No evidence of lymph node involvement	154 (82·8%)	148 (80·0%)
N1 – Evidence of regional lymph node involvement	29 (15·6%)	31 (16·8%)
Nx – No information on lymph node involvement	3 (1·6%)	6 (3·2%)
Site of origin of primary tumour		
Orbit	7 (8·8%)	5 (2·7%)

	Stop Treatment (n=186)	Maintenance Chemotherapy (n=185)
Head neck non paramenigeal	11 (5·9%)	14 (7·6%)
Parameningeal	56 (30·1%)	64 (34·6%)
Bladder Prostate	25 (13·4%)	27 (14·6%)
Genito-urinary non Bladder Prostate	5 (2·7%)	7 (3·8%)
Extremities	36 (19·4%)	27 (14·6%)
Other sites	46 (24·7 %)	41 (22·1%)
Subgroup risk		
E	91 (48·9%)	91 (49·2%)
F	29 (15·6%)	31 (16·7%)
G	66 (35·5%)	63 34·1%)

*All IRS I patients had alveolar histology

Table 2: Summary of adverse events reported in 181 patients during maintenance chemotherapy

	Grade 1-2	Grade 3	Grade 4
Haematological Toxicity			
Haemoglobin	128 (71%)	16 (9%)	3 (2%)
Leukocytes	26 (14%)	86 (48%)	50 (28%)
Neutrophils	16 (9%)	66 (37%)	82 (45%)
Platelets	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/vomiting	34 (19%)	1 (0·6%)	-
Gastrointestinal	41 (23%)	9 (5%)	-
Allergy	4 (2%)	-	-
Dermatological	7 (4%)	1 (1%)	-
Other#	37 (20%)	1# (1%)	-

* Other infections: Bone infection 1, Pulmonary infection 2

° Neurology: steppage gait with limbs pain completely resolved after 1 month

Other: hypokalemia

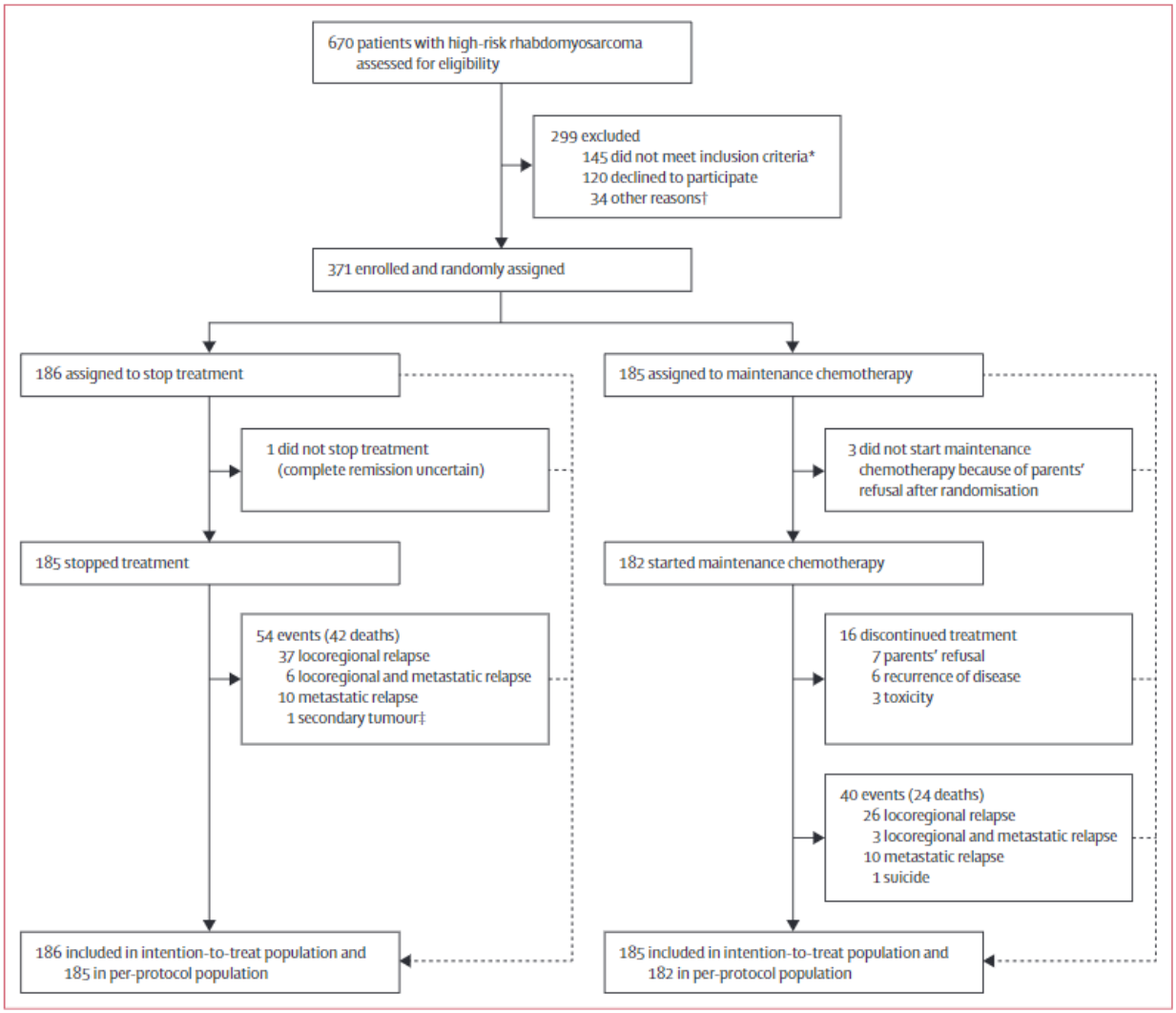
Table 3: Type of first events by randomised arm

TYPE OF EVENT	RANDOMISED ARM		Total
	Stop treatment	Maintenance	
Local relapse and/or regional lymph-node relapse	37 (68·5%)	26 (65·0%)	63
Local and/or regional lymph-node relapse and metastasis	6 (11·1%)	3 (7·5%)	9
Metastases	10 (18·5%)	10 (25·0%)	20
Death	1° (1·8%)	1^ (2·5%)	2
Total	54	40	94

° 1 patient died due to suicide; ^ 1 patient died after second tumour (High grade glioma)

Note: 1 patients that died of surgical complication and 1 patient that died of H1N1 influenza are not reported here because these were not the first event (see text)

Figure 1. Trial Profile



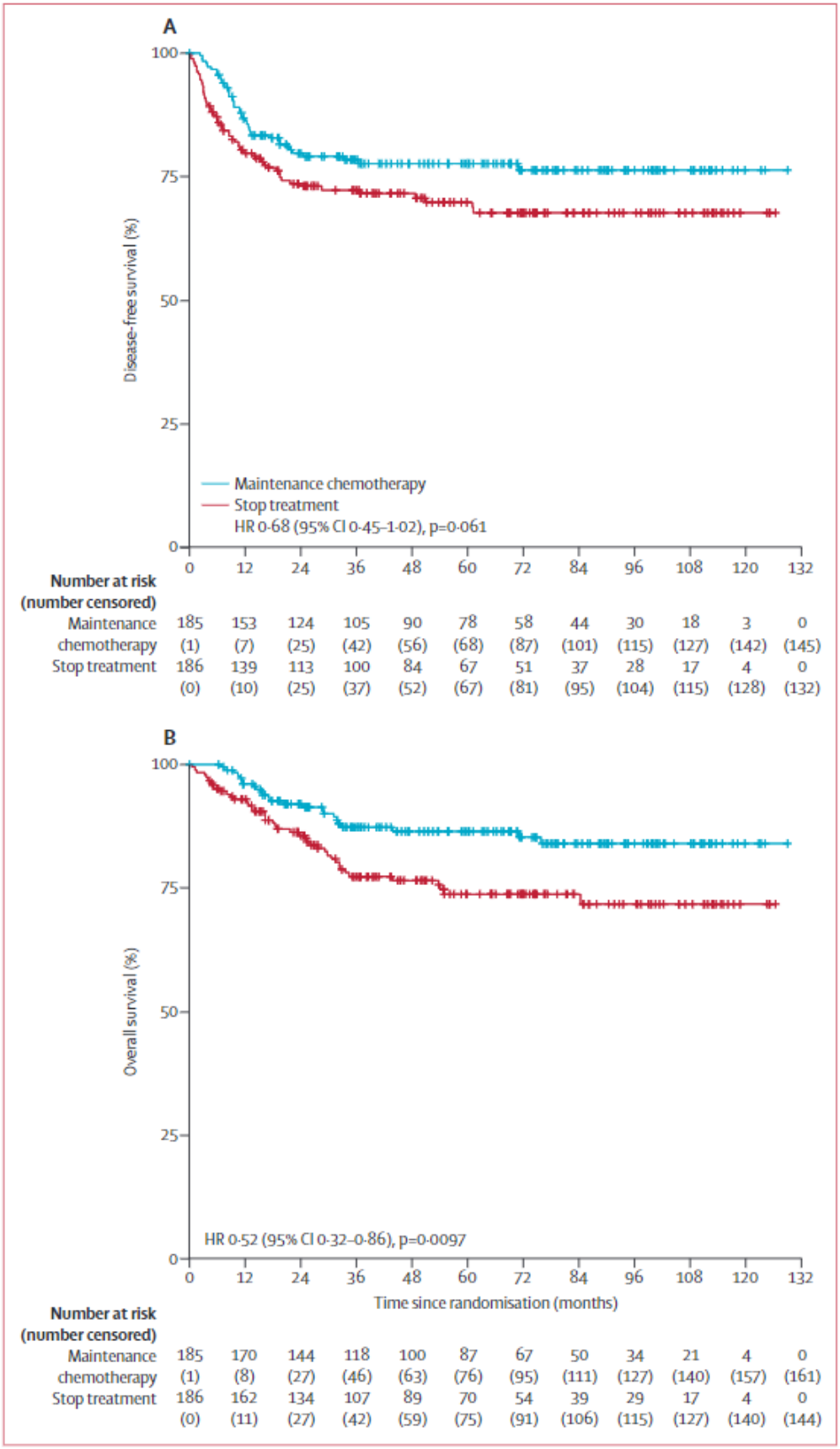
Legend:

* The reasons for exclusion were: 9 patients were > 21 years old 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 randomization was longer than 8 weeks;

** The reasons for exclusion were: 27 physician's decision, 1 patient condition, 6 organizational reasons

*** High-grade glioma

Figure 2. Kaplan-Meier Estimates of Outcome



A Disease Free Survival
B Overall Survival