Comparison of two chemotherapy regimens in patients with newly diagnosed Ewing sarcoma (EE2012) an open-label, randomised, phase 3 trial

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Comparison of two chemotherapy regimens in patients with newly diagnosed Ewing sarcoma (EE2012): an open-label, randomised, phase 3 trial

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Summary

Background Internationally, a single standard chemotherapy treatment for Ewing sarcoma is not defined. Because different chemotherapy regimens were standard in Europe and the USA for newly diagnosed Ewing sarcoma, and in the absence of novel agents to investigate, we aimed to compare these two strategies.

Methods EURO EWING 2012 was a European investigator-initiated, open-label, randomised, controlled phase 3 trial done in 10 countries. We included patients aged 2–49 years, with any histologically and genetically confirmed Ewing sarcoma of bone or soft tissue, or Ewing-like sarcomas. The eligibility criteria originally excluded patients with extrapulmonary metastatic disease, but this was amended in the protocol (version 3.0) in September, 2016. Patients were randomly assigned (1:1) to either the European regimen of vincristine, ifosfamide, doxorubicin, and etoposide induction, and consolidation using vincristine, actinomycin D, with ifosfamide or cyclophosphamide, or busulfan and melphalan (group 1); or the US regimen of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide induction, plus ifosfamide and etoposide, and consolidation using vincristine and cyclophosphamide, or vincristine, actinomycin D, and ifosfamide, with busulfan and melphalan (group 2). All drugs were administered intravenously. The primary outcome measure was event-free survival. We used a Bayesian approach for the design, analysis, and interpretation of the results. Patients who received at least one dose of study treatment were considered in the safety analysis. The trial was registered with EudraCT, 2012-002107-17, and ISRCTN, 54540667.

Findings Between March 21, 2014, and May 1, 2019, 640 patients were entered into EE2012, 320 (50%) randomly allocated to each group. Median follow-up of surviving patients was 47 months (range 0–84). Event-free survival at 3 years was 61% with group 1 and 67% with group 2 (adjusted hazard ratio [HR] 0·71 [95% credible interval 0·55–0·92 in favour of group 1). The probability that the true HR was less than 1·0 was greater than 0·99. Febrile neutropenia as a grade 3–5 treatment toxicity occurred in 234 (74%) patients in group 1 and in 183 (58%) patients in group 2. More patients in group 1 (n=205 [64%]) required at least one platelet transfusion compared with those in group 2 (n=138 [43%]). Conversely, more patients required blood transfusions in group 2 (n=286 [89%]) than in group 1 (n=277 [87%]).

Interpretation Dose-intensive chemotherapy with vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide is more effective, less toxic, and shorter in duration for all stages of newly diagnosed Ewing sarcoma than vincristine, ifosfamide, doxorubicin, and etoposide induction and should now be the standard of care for Ewing sarcoma.

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Introduction

Ewing sarcoma is a cancer of the bone and soft tissue, with 80% of cancers occurring in adolescents and young adults and a peak incidence in the second decade of life.[1] Ewing sarcoma is rare, with fewer than 70 cases per year in the UK, 100 cases per year in France, and 400 cases per year in the rest of Europe; therefore, any randomised trials must be international to yield robust results in a timely manner. With existing multimodal programmes, including combination chemotherapy of doxorubicin, etoposide, cyclophosphamide, vincristine, and ifosfamide, using different doses and schedules of administration, as well as surgery and radiotherapy, the outcome for localised disease is good, with an event-free survival of 65% and overall survival of 75% at 3 years with standard chemotherapy regimens.[2,3] For metastatic disease, 3-year overall survival is 68% for patients with isolated pulmonary or pleural metastases and only 29% for patients with multi-metastatic disease.[4–10]

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Research in context

Evidence before this study

We searched PubMed for randomised trials in Ewing sarcoma published in English between Jan 1, 1990, and Dec 31, 2010. We used the search terms "Ewing sarcoma" and "chemotherapy trials". We did not find any randomised studies comparing different standard regimens of chemotherapy used in Europe and the USA.

Added value of this study

This study established the standard-of care chemotherapy for patients with newly diagnosed Ewing sarcoma in the USA and Europe.

Implications of all the available evidence

Dose-intensive chemotherapy with vincristine, doxorubicin, cyclophosphamide induction plus ifosfamide and etoposide regimen was more effective, less toxic, and shorter in duration than vincristine, ifosfamide, doxorubicin, and etoposide induction was for all stages of newly diagnosed Ewing sarcoma and should be the standard of first-line care for all patients with Ewing sarcoma.

Internationally, a single standard chemotherapy treatment for Ewing sarcoma is not defined. The EURO-EWING 99 trial[11] used induction chemotherapy (six cycles of vincristine, ifosfamide, doxorubicin, and etoposide [VIDE] given approximately every 3 weeks before local control) followed by risk-adapted randomised treatment of either vincristine, actinomycin D, and ifosfamide or cyclophosphamide (VAI or VAC) as consolidation chemotherapy, or high-dose busulfan and melphalan. The toxicity of VIDE induction chemotherapy has been published.[11]

The other widely used treatment regimen for Ewing sarcoma, used mainly in the USA, is from the Children's Oncology Group AEWS0031 trial.[2] In that study, patients with localised Ewing sarcoma received alternating cycles of vincristine, doxorubicin, and cyclophosphamide (VDC), plus ifosfamide and etoposide (IE) as induction chemo-therapy and alternating cycles of IE and vincristine and cyclophosphamide (VC) as consolidation chemotherapy, either every 3 weeks or every 2 weeks. The 2-weekly schedule was significantly more effective, with fewer events and deaths, than the 3-weekly schedule was and is now standard of care in the USA. Because different chemotherapy regimens were standard in Europe and the USA for newly diagnosed Ewing sarcoma, and in the absence of novel agents to investigate, a randomised comparison of these two strategies was considered worthwhile to establish the regimen of choice, taking account of both clinical outcomes (event-free survival and overall survival) and toxicity.

Methods

Study design and participants

EURO EWING 2012 (EE2012) was a European investigator-initiated, open-label, randomised, controlled phase 3 trial done in ten countries and in 110 sites (appendix 1 pp 2–5). All patients with Ewing sarcoma, except for those with widely metastatic disease until the protocol amendment were eligible for randomisation to receive induction chemotherapy. Eligible patients were aged 2–49 years, with any histologically and genetically confirmed Ewing sarcoma of bone or soft tissue, or Ewing-like round-cell sarcomas but negative for *EWSR1* gene rearrangement, who were medically fit to receive trial treatment. The eligibility criteria originally excluded patients with extrapulmonary metastatic disease, but this was amended in the protocol (version 3.0) in September, 2016.

The trial was overseen by trial management and steering groups. An independent data monitoring committee reviewed safety and efficacy during the trial. The study was done in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Informed written consent was obtained from all patients, parents, or legal guardians as per local practice.

The protocol is available online.

Randomisation and masking

Patients were randomly allocated (1:1) to either the European regimen of VIDE induction chemotherapy and VAI or VAC consolidation, or the US regimen of com-pressed VDC plus IE induction chemotherapy and IE plus VC consolidation.

Randomisation was done online by staff at participating centres by using the randomisation function of the electronic remote data capture system designed and maintained by the coordinating sponsor. Randomisation was stratified using minimisation to ensure a balance between treatments within the strata defined by key prognostic factors and country. The minimisation factors were age at randomisation (<14 years or ≥14 years), sex, disease type (absence of metastases or involvement of regional lymph nodes only; lung or pleural metastases only; or other metastases), volume of tumour at diagnosis (<200 mL or ≥200 mL), and country (the UK, France, or other).

Following induction chemotherapy, all patients were eligible for a second randomisation with the addition of zoledronic acid to the consolidation chemotherapy assigned at first randomisation.

No masking or allocation concealment occurred.

Procedures

At diagnosis, the work-up consisted of an MRI or CT scan of the primary tumour and staging, including bone marrow assessment, CT scan of the chest, and radionuclide bone scan (18F-fluorodeoxyglucose PET was an alternative to a bone scan in some trial sites). Resection of the primary tumour at diagnosis was not recommended for most patients, and in these patients a biopsy was obtained to establish the diagnosis.

Patients in group 1 received VIDE induction therapy, and VAI, VAC, or busulfan and melphalan consolidation therapy, administered intravenously (appendix 2 pp 7–11). Induction chemotherapy included six cycles of VIDE and consolidation chemotherapy included one cycle of VAI plus seven cycles of VAC (patients with good-risk localised disease), or one cycle of VAI plus one cycle of busulfan and melphalan (patients with poor-risk localised disease without contraindication to busulfan and melphalan), or eight cycles of VAI (patients with poor-risk localised disease with contraindication to busulfan and melphalan, or with regional lymph node involvement or metastatic disease).

Patients in the second group received VDC plus IE induction, and IE, VC, VAI, and busulfan and melphalan consolidation therapy. Induction chemotherapy included nine cycles of alternating VDC and IE. Consolidation chemotherapy included five cycles of alternating IE and VC (patients with good-risk localised disease or regional lymph node involvement or metastatic disease, or poor-risk localised disease with contraindication to busulfan and melphalan) or one cycle of VAI plus busulfan and melphalan (patients with poor-risk localised disease without contraindication to busulfan and melphalan).

A summary of the enrolment, interventions, and the main assessments has been published,[12] and a Standard Protocol Items: Recommendations for Interventional Trials checklist is supplied in appendix 2 (pp 2–6). The full schedule of treatments is provided in appendix 2 (pp 7–11) and full details of trial treatments and conduct have been published.[12] Following induction chemotherapy, local control of the primary tumour was performed, when feasible with a complete surgical resection or, if not, definitive radiotherapy. The protocol recommended that radiotherapy be given concurrently with consolidation chemotherapy to the primary site. In patients with pulmonary or pleural metastatic disease, whole-lung radiotherapy was recommended to be given on completion of consolidation chemotherapy. Radiotherapy to bone metastases was given either during consolidation or at the end of chemotherapy. Patients who received radiotherapy only as their local control and had measurable disease before radiotherapy had an MRI or CT scan at the end of treatment. If the end-of-treatment scan showed residual disease, another scan was done 6 months after the end of treatment. Adverse events were monitored at least weekly and were assessed according to National Cancer Institute Common Toxicity Criteria (version 4.0). After treatment, patients were followed up with clinical assessment and scanning for a minimum of 5 years or until disease progression or death if sooner.

Outcomes

The primary outcome measure was event-free survival. Event-free survival was defined as the time from randomisation to first event, where an event was the first of progression without complete or partial response, recurrence (following complete or partial remission), second malignancy, or death by any cause without a preceding event; patients who did not have an event were censored at the date they were last seen. The secondary outcome measures were overall survival, defined as the time from randomisation to death, irrespective of the cause, with surviving patients censored at their date last seen; adverse events and toxicity; histological response of the primary tumour to induction chemotherapy if surgery was done; response of the primary tumour, regional lymph nodes, or metastases, using the volume of the whole primary tumour, diameter of the largest node (or group if not separate), and number of lung or pleural and other metastases; and achievement of local control at the end of treatment.

Statistical analysis

Because of the rarity of Ewing sarcoma and the comparison being between two standard chemotherapy regimens, we used a Bayesian approach for the design, analysis, and interpretation of first randomisation. We made no prior assumptions that one chemotherapy group was likely to have better outcomes than the other. With a 5-year accrual period, we anticipated that at least 600 patients could be randomly assigned across participating countries. Hence, the minimum sample size was set at 600 with a minimum of 2 years' and a maximum of 7 years' follow-up, with at least 150 events expected. We used non-informative priors, so the posterior distribution gives parameter data (ie, the probability of the treatment effect). We assumed the hazard ratio (HR) to be normally distributed with variance $4/n$, where n is the total number of events in both groups.[13]

On the basis of the EURO-EWING 99 data, we anticipated 3-year event-free survival to be approximately 70% with VIDE.[3] A 5% absolute difference in 3-year event-free survival corresponds to an HR of 1·21 (or inversely 0·81). We considered different scenarios to establish the probabilities that one treatment was better than the other, or not more than 5% worse, from posterior probability distributions. These distributions were based on a study sample size of 600 patients and a range of observed HRs for the data. Given an observed HR of 1·00 (ie, no apparent difference between randomly assigned groups in terms of event-free survival), the probability that VDC plus IE was more than 5% worse than VIDE would be 10% or more than 5% better would be 7%. Under the premise of no difference in efficacy (event-free survival), one
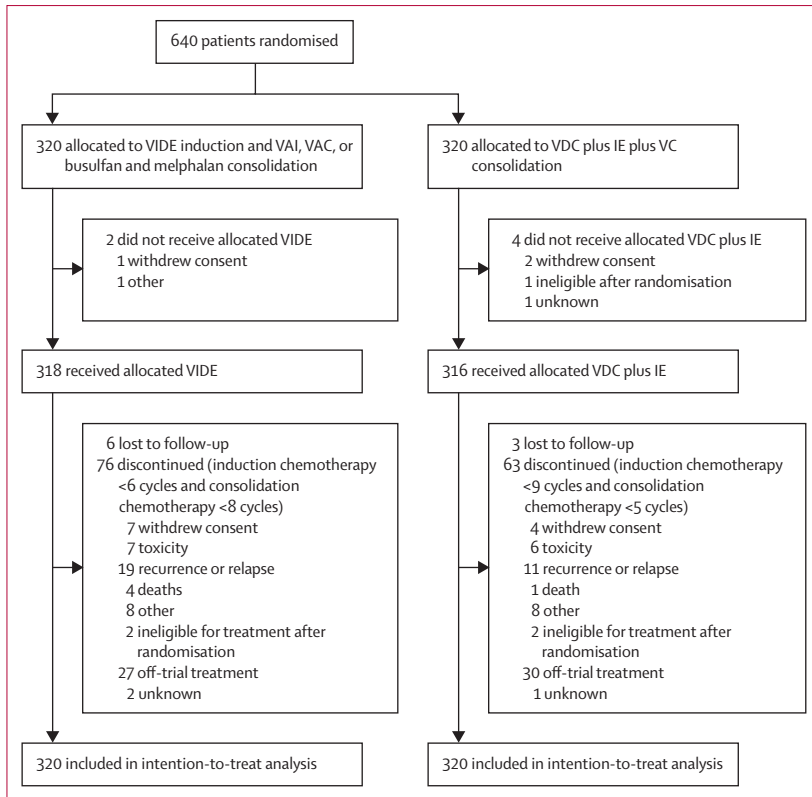
Figure 1: Trial profile
IE=ifosfamide and etoposide. VAC=vincristine, actinomycin, and cyclophosphamide. VAI=vincristine, actinomycin, and ifosfamide. VC=vincristine and cyclophosphamide. VDC=vincristine, doxorubicin, and cyclophosphamide. VIDE=vincristine, ifosfamide, doxorubicin, and etoposide.

	VIDE (n=320)	VDC plus IE (n=320)
Age, years		
<14	132 (41%)	133 (42%)
≥14	188 (59%)	187 (58%)
Median	15 (2–48%)	15 (2–49%)
Sex		
Male	186 (58%)	186 (58%)
Female	134 (42%)	134 (42%)
Disease type		
Localised disease	236 (74%)	236 (74%)
Lung or pleuropulmonary metastases	53 (17%)	53 (17%)
Other metastases	31 (10%)	31 (10%)
Tumour volume, mL²		
<200	180 (56%)	179 (56%)
≥200	140 (44%)	141 (44%)
Country		
UK	122 (38%)	120 (38%)
France	97 (30%)	98 (31%)
Other	101 (32%)	102 (32%)
Ireland	3 (1%)	1 (<1%)
Switzerland	1 (<1%)	0
Denmark	1 (<1%)	1 (<1%)
Netherlands	2 (1%)	3 (1%)
Spain	71 (22%)	77 (24%)
Belgium	8 (3%)	8 (3%)
Czech Republic	9 (3%)	11 (3%)
Hungary	6 (2%)	1 (<1%)
Primary tumour site		
Pelvis	78 (24%)	69 (22%)
Abdomen	14 (4%)	15 (5%)
Spine	24 (8%)	32 (10%)
Chest	65 (20%)	56 (18%)
Head and neck	15 (5%)	22 (7%)
Upper extremity	25 (8%)	19 (6%)
Lower extremity	97 (30%)	107 (33%)
Unknown origin	1 (<1%)	0
Missing	1 (<1%)	0

Data are n (%) or median (range). IE=ifosfamide and etoposide. VDC=vincristine, doxorubicin, and cyclophosphamide. VIDE=vincristine, ifosfamide, doxorubicin, and etoposide.

Table 1: Baseline clinical characteristics

might reasonably decide to recommend the regimen that has a more tolerable toxicity profile. Additionally, with an observed HR of 0·81 (ie, an absolute improvement of approximately 5% in event-free survival with VDC plus IE compared with VIDE, or vice versa), there would be an 8% probability that the apparently better regimen was worse. Finally, with an observed HR of 0·90 (ie, an absolute difference of approximately 2·5% in event-free survival in favour of one group or the other), there would be a probability of 25% that the apparently better regimen was worse and a probability of 3% that the treatment was more than 5% worse. Probabilities from these scenarios were all within the limit of clinical acceptability as per expert opinion at the design stage, confirming that 600 was an acceptable sample size.

For time-to-event outcome measures, we used Cox regression models to compare the treatment groups, adjusted for stratification variables. We assessed the proportional hazards assumption by examining the Schoenfeld residuals. Additionally, we obtained Kaplan-Meier survival estimates at 3 and 5 years. We did exploratory hypothesis-generating subgroup analyses for all stratification variables and interpretation focused on 95% CIs. We tested for heterogeneity using the likelihood ratio test, comparing Cox models with and without an interaction term between the treatment variable and stratification variable. All analyses were intention-to-treat, with all patients analysed in the group to which they were assigned at randomisation. We used Stata (version 17.0) for all statistical analyses.

Role of the funding source

A

Event-free survival (%)

VIDE
VDC plus IE

Number at risk

VIDE	320	(47)	268	(58)	197	(16)	130	(8)	71	(1)	35
VDC plus IE	320	(33)	283	(46)	220	(21)	151	(7)	85	(2)	39

B

Overall survival (%)

Years since randomisation

Number at risk

VIDE	320	(22)	293	(34)	244	(20)	162	(12)	88	(4)	45
VDC plus IE	320	(12)	304	(30)	254	(13)	182	(6)	105	(6)	44

Figure 2: **Kaplan-Meier estimates**
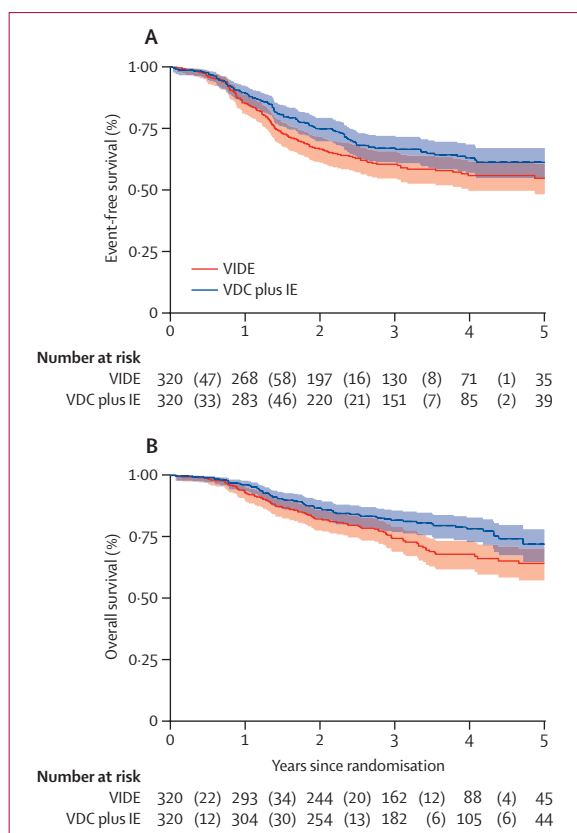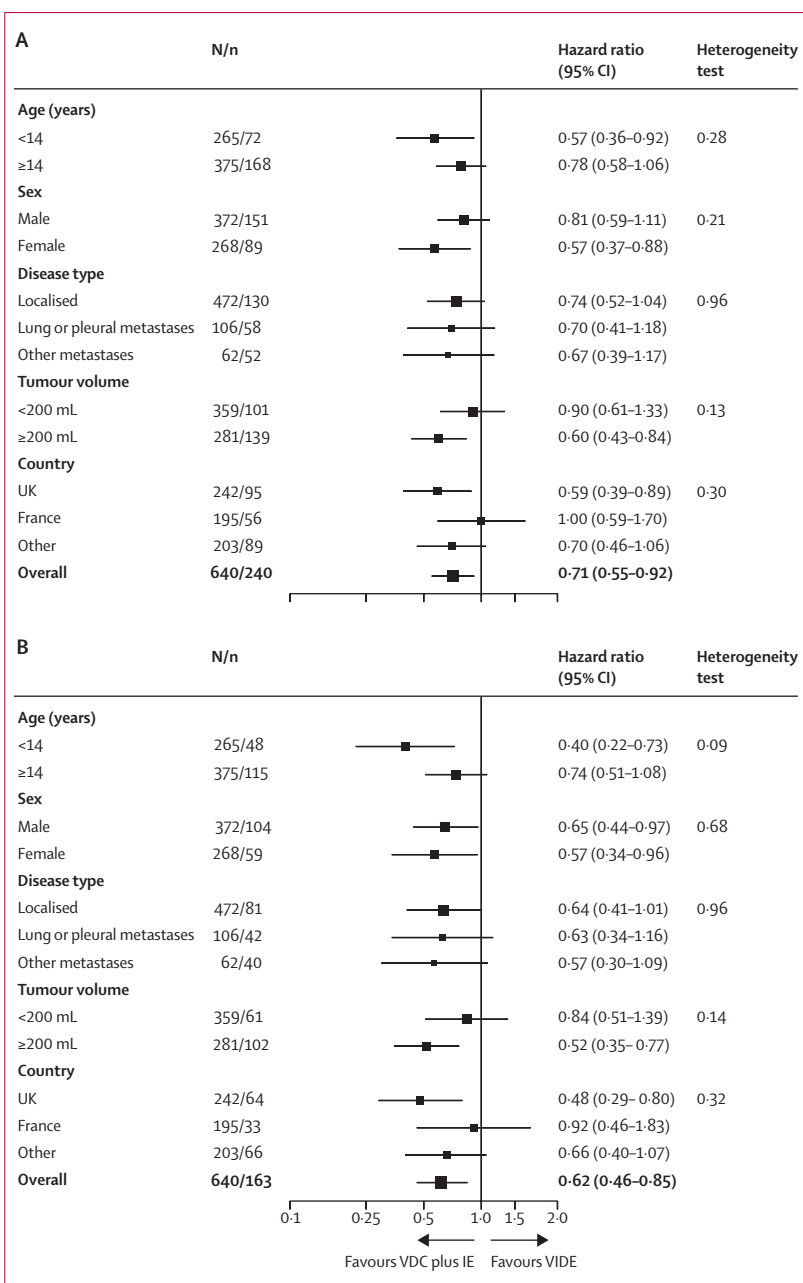(A) Event-free survival. (B) Overall survival. IE=ifosfamide and etoposide. VDC=vincristine, doxorubicin, and cyclophosphamide. VIDE=vincristine, ifosfamide, doxorubicin, and etoposide.

Results

Between March 21, 2014, and May 1, 2019, we enrolled 640 patients into EE2012, with 320 (50%) allocated to each group for the first randomisation (figure 1). At the date of data cutoff, Nov 28, 2021, median follow-up of surviving patients was 47 months (range 0–84). 14 patients formally withdrew consent for further data collection (figure 1). Six patients in the VIDE group and three in the VDC plus IE group were lost to follow-up (figure 1). Baseline clinical characteristics were well balanced across the two groups (table 1). 20 patients had Ewing-like sarcoma: nine (45%) in the VIDE group, and 11 (55%) in the VDC plus IE group. 19 (7%) patients in the VIDE group and six (2%) in the VDC plus IE group received busulfan and melphalan. 134 patients (42%) in the VIDE group and 183 (44%) in the VDC plus IE group were randomly assigned in the second randomisation.

634 (99%) of 640 patients started their allocated treatment (three withdrawals of consent to treatment, one ineligible after randomisation, one reason not given, and one no record to support having treatment or not having treatment; figure 1). In the VIDE group, 304 (95%) patients received all six induction courses and in the

A

	N/n	Hazard ratio (95% CI)	Heterogeneity test
Age (years)			
<14	265/72	0·57 (0·36–0·92)	0·28
≥14	375/168	0·78 (0·58–1·06)	
Sex			
Male	372/151	0·81 (0·59–1·11)	0·21
Female	268/89	0·57 (0·37–0·88)	
Disease type			
Localised	472/130	0·74 (0·52–1·04)	0·96
Lung or pleural metastases	106/58	0·70 (0·41–1·18)	
Other metastases	62/52	0·67 (0·39–1·17)	
Tumour volume			
<200 mL	359/101	0·90 (0·61–1·33)	0·13
≥200 mL	281/139	0·60 (0·43–0·84)	
Country			
UK	242/95	0·59 (0·39–0·89)	0·30
France	195/56	1·00 (0·59–1·70)	
Other	203/89	0·70 (0·46–1·06)	
Overall	**640/240**	**0·71 (0·55–0·92)**	

B

	N/n	Hazard ratio (95% CI)	Heterogeneity test
Age (years)			
<14	265/48	0·40 (0·22–0·73)	0·09
≥14	375/115	0·74 (0·51–1·08)	
Sex			
Male	372/104	0·65 (0·44–0·97)	0·68
Female	268/59	0·57 (0·34–0·96)	
Disease type			
Localised	472/81	0·64 (0·41–1·01)	0·96
Lung or pleural metastases	106/42	0·63 (0·34–1·16)	
Other metastases	62/40	0·57 (0·30–1·09)	
Tumour volume			
<200 mL	359/61	0·84 (0·51–1·39)	0·14
≥200 mL	281/102	0·52 (0·35–0·77)	
Country			
UK	242/64	0·48 (0·29–0·80)	0·32
France	195/33	0·92 (0·46–1·83)	
Other	203/66	0·66 (0·40–1·07)	
Overall	**640/163**	**0·62 (0·46–0·85)**	

Favours VDC plus IE — Favours VIDE

Figure 3: **Forest plot for all subgroups (minimisation factors) with event-free survival as the outcome**
Heterogeneity test is the p value for the interaction term between the treatment variables and the stratification variable. IE=ifosfamide an etoposide. VDC=vincristine, doxorubicin, and cyclophosphamide. VIDE=vincristine, ifosfamide, doxorubicin, and etoposide.

VDC plus IE group, 291 (91%) patients received all nine induction courses. In the VIDE group, 185 (58%) patients received all eight consolidation courses and in the VDC plus IE group, 240 (75%) patients received all five consolidation courses (figure 1).

208 (65%) patients in the VIDE group and 199 (62%) in VDC plus IE group received radiotherapy to the primary tumour (appendix 2 p 12). 34 (64%) patients in the VIDE

	VIDE (n=318)		VDC plus IE (n=316)	
	Induction (n=318)	Consolidation (n=271)	Induction (n=316)	Consolidation (n=272)
Grade 3–5 adverse events				
Blood and lymphatic system disorders	273 (86%)	121 (45%)	248 (78%)	145 (53%)
Anaemia	207 (65%)	83 (31%)	195 (62%)	112 (41%)
Febrile neutropenia	234 (74%)	71 (26%)	183 (58%)	72 (26%)
Gastrointestinal disorders	123 (39%)	36 (13%)	134 (42%)	24 (9%)
Infections and infestations	62 (19%)	31 (11%)	63 (20%)	30 (11%)
Investigations	254 (80%)	185 (68%)	237 (75%)	187 (69%)
Lymphocyte count decreased	81 (25%)	77 (28%)	77 (24%)	70 (26%)
Neutrophil count decreased	178 (56%)	135 (50%)	174 (55%)	135 (50%)
Platelet count decreased	221 (69%)	143 (53%)	178 (56%)	139 (51%)
Nervous system disorders	18 (6%)	8 (3%)	18 (6%)	2 (1%)
Encephalopathy	6 (2%)	0	2 (1%)	0
Serious adverse events				
Blood and lymphatic system disorders	5 (2%)	..	6 (2%)	..
Febrile neutropenia	4 (1%)	..	6 (2%)	..
Gastrointestinal disorders	2 (1%)	..	7 (2%)	..
Infections and infestations	13 (4%)	..	10 (3%)	..
Investigations	1 (<1%)	..	2 (1%)	..
Nervous system disorders	13 (4%)	..	2 (1%)	..
Encephalopathy	6 (2%)	..	0	..
Expected serious adverse events				
Blood and lymphatic system disorders				
Febrile neutropenia	198 (62%)	..	177 (56%)	..
Gastrointestinal disorders				
Other	37 (12%)	..	36 (11%)	..
Infections and infestations				
Other	45 (14%)	..	40 (13%)	..
Investigations				
Other	44 (14%)	..	36 (11%)	..

Data are n (%). Expected serious adverse events are reported separately to non-serious adverse reactions (as serious adverse events) because of their categorisations, which are as follows: febrile neutropenia (neutropenia, fever, and febrile neutropenia); infection and infestation, other (infections); investigations, other (haematological toxicity [eg, haemoglobin, white blood cell, granulocyte, and platelet concentrations]); and gastrointestinal disorders, other (gut toxicity [eg, mucositis or stomatitis, nausea, vomiting, and diarrhoea]). IE=ifosfamide and etoposide. VDC=vincristine, doxorubicin, and cyclophosphamide. VIDE=vincristine, ifosfamide, doxorubicin, and etoposide.

Table 2: Adverse events

group and 30 (57%) in the VDC plus IE group with lung or pleural metastases received lung radiotherapy (appendix 2 p 12).

240 events were recorded: 131 (55%) in the VIDE group and 109 (45%) in the VDC plus IE group (appendix 2 p 12). Event-free survival at 3 years was 61% in the VIDE group and 67% in the VDC plus IE group (HR 0·71 [95% CI 0·55–0·92]; figure 2A) in favour of VDC plus IE. The probability that the true HR was less than 1·0 was greater than 0·99, and the probability that the true HR was less than 0·8 in favour of VDC plus IE was 0·81 (appendix 2 p 13). The proportional hazards assumption held.

We recorded 163 deaths: 95 (58%) in the VIDE group and 68 (42%) in the VDC plus IE group (appendix 2 p 12).

Overall survival at 3 years was 74% in the VIDE group and 82% in the VDC plus IE group (HR 0·62 [95% CI 0·46–0·85]) in favour of VDC plus IE (figure 2B). The probability that the true HR was less than 1·0 was greater than 0·99; the probability that the true HR was less than 0·8 in favour of VDC plus IE was 0·94 (appendix 2 p 13). The proportional hazards assumption held.

We found no evidence that the treatment effect for VIDE compared with VDC plus IE differed across patient and disease subgroups for either event-free survival or overall survival, with all CIs for the interaction effects including values that were consistent with no significant subgroup effects (figure 3). Within all subgroups, the point estimate for the HR was in favour of VDC plus IE (figure 3).

Among patients who started trial treatment, grade 3–5 adverse events occurred in 289 (91%) patients in the VIDE group and in 284 (90%) in the VDC plus IE group during induction chemotherapy and in 179 (66%) patients in the VIDE group and 182 (67%) in the VDC plus IE group during consolidation (table 2). However, febrile neutropenia as a grade 3–5 adverse event occurred in 234 (74%) patients receiving VIDE induction but in 183 (58%) patients receiving VDC plus IE induction (table 2). The difference in febrile neutropenia between the two groups was also seen in expected serious adverse reactions, again greater in the VIDE group than in the VDC plus IE group (table 2). We found no difference in gastrointestinal toxicities and infections and infestations between the two groups (table 2).

205 patients in the VIDE induction group and 138 in the VDC plus IE induction group required at least one platelet transfusion (table 3). Conversely, 286 patients in the VIDE induction group and 277 in the VDC plus IE group required a blood transfusion (table 3). The median number of unscheduled visits required in the VIDE group was 13 (IQR 5–28) and nine (2–21) in the VDC plus IE group (table 3). The length of treatment for VDC plus IE was on average 62 days shorter than that of the VIDE regimen.

In patients who had surgery after induction chemotherapy, 104 patients in the VIDE group and 82 in the VDC plus IE group had good necrosis (>90%) (appendix 2 p 13). Response data were not complete or of sufficient quality for further analysis and reporting.

Discussion

The results of this international randomised trial for 2–50-year-old patients with newly diagnosed Ewing sarcoma show that VDC plus IE chemotherapy was more effective than VIDE for both event-free survival and overall survival, with a greater than 99% chance that the regimen is better for both outcome measures. This benefit was consistent across all baseline stratification parameters, which are also important prognostic factors. We found no excess toxicity with VDC plus IE, fewer supportive care requirements, and the total time to complete treatment

was on average 12 weeks shorter with VDC plus IE compared with VIDE. These findings are all clinically meaningful. Hence, these results have led to a practice change in Europe and many other countries. VDC plus IE chemotherapy has become the standard regimen for all newly diagnosed Ewing sarcomas in Europe, following its earlier adoption in the USA. Furthermore, the trial used Bayesian statistical models for what is a rare tumour, which required fewer patients than with frequentist methodology.

At the time of designing this study, VDC plus IE was the standard of care for Ewing sarcoma, for all stages of disease in the USA as per the Children's Oncology Group research group guidelines, following the Children's Oncology Group AEWS0031 trial, which compared 3-weekly chemotherapy VDC plus IE versus more intensive 2-weekly VDC plus IE.[2] The overall survival for the VDC plus IE group in AEWS0031 was 83% at 5 years versus 87% at 3 years in the VDC plus IE group in EE2012. Although these results seem similar, the AEWS0031 study only included localised Ewing sarcoma versus all stages in EE2012. Pragmatically, VAI plus busulfan and melphalan was allowed in the VDC plus IE group after induction in EE2012, following the results of EE99 R2 loc randomisation for patients with poor-risk localised disease, which showed better overall survival for VAI plus busulfan and melphalan, and therefore differed to AEWS0031, but not significantly, as only six (2%) patients in the VDC plus IE group received busulfan and melphalan.[14]

Furthermore, the median age of participants in AEWS0031 was lower than in E2012, known to confer a better prognosis in Ewing sarcoma.[4] The AEWS0031 study had also compared a more dose-dense chemotherapy, maintaining the doses but reducing the interval between chemotherapy.[2] Their strategy followed Norton's dose-density model and with the use of granulocyte colony-stimulating factor, as in our study, the investigators were able to maintain this dose intensity with superior results.[15] The VIDE group in this study received what is the standard of care in Europe and Israel and Hong Kong from the EURO-EWING 99 trial.[2,4,10] It is difficult to make any direct comparisons because no data have been published for the whole study including all stages of disease.

Previous publications have focused on individual disease types or risk groups related to the extent of disease or stage, either in single-group or randomised studies.[2,4,6,10] In EE2012, all disease groups of Ewing sarcoma were included in the first randomisation, but we had stratification for these disease groups along with other factors such as age and tumour volume. The disease type was balanced between the two groups. We did subgroup analyses for all baseline parameters and used heterogeneity tests (p value of the interaction term between treatment variable and covariate in the adjusted Cox model), shown visually by forest plots, to investigate whether the treatment effect differed between these groups. For both event-free survival

	VIDE (n=320)		VDC plus IE (n=320)	
	Induction (n=320)	Consolidation (n=271)	Induction (n=320)	Consolidation (n=272)
Platelet transfusions				
None	105 (33%)	145 (45%)	177 (55%)	169 (53%)
At least one	205 (64%)	119 (37%)	138 (43%)	95 (30%)
NA	7 (2%)	6 (2%)	1 (<1%)	6 (2%)
Missing	3 (1%)	50 (16%)	4 (1%)	50 (16%)
Blood transfusions				
None	36 (11%)	140 (44%)	30 (9%)	95 (30%)
At least one	277 (87%)	124 (39%)	286 (89%)	172 (54%)
NA	4 (1%)	6 (2%)	0	3 (1%)
Missing	3 (1%)	50 (16%)	4 (1%)	50 (16%)
Unscheduled visits in hospital, n	13 (5–28)	0 (0–5)	9 (2–21)	0 (0–7)
Overall treatment time, days	300 (163–337)	..	238 (209–279)	..
Patients receiving all treatment cycles, n	303 (95%)	186 (58%)	292 (91%)	240 (75%)

Data are n (%) or median (IQR). IE=ifosfamide and etoposide. NA=not applicable. VDC=vincristine, doxorubicin, and cyclophosphamide. VIDE=vincristine, ifosfamide, doxorubicin, and etoposide.

Table 3: Blood product transfusions and days in hospital

and overall survival, the benefit of VDC plus IE was not different for disease type or indeed any other stratification variables. This finding provides evidence to treat all patients with Ewing sarcoma with the VDC plus IE regimen and hence for this regimen to become the standard of care internationally. This finding is particularly important for patients with widely metastatic disease who were not included in the AEWS0031 study.[2] Patients with Ewing-like sarcoma were included in the study, but their numbers were small in both groups and therefore unlikely to have had any effect on the outcomes reported.

A limitation of this study was that patients with widely metastatic disease were not included at the start of the study but only from September, 2016 (and because there was a competing study [COMBINAIR 3] in France, patients were not entered at all from France). Therefore, the percentage of patients with widely metastatic disease was less than expected from the population data.[16] The group with widely metastatic disease was, however, balanced between the two groups and the subgroup analysis showed that the benefit of VDC plus IE was consistent for this disease group along with other disease groups. As a randomised study, the type of local therapy (surgery or not, with or without radiation) received was balanced between groups and, although guidance exists for the dose of and indications for radiotherapy, variability in indications and dose received might exist among sites and countries because the guidance was not mandatory. Going forward, the Ewing sarcoma research community needs to develop an evidence base for radiotherapy doses in Ewing sarcoma because currently there is variability in practice.

A Bayesian approach was chosen because two standard chemotherapy regimens—one European and one North American—were to be compared. Therefore, a less

stringent decision criterion for accepting one as being better than the other was considered appropriate compared with a conventional frequentist p value of 0·05.[17] An informal survey of the trial's lead clinicians revealed that they would be happy to accept a regimen as the standard going forward if there were an 80% chance that it was better than the other. Furthermore, had a frequentist design been used, whether superiority (and which group would be the control) or equivalence should be shown is unclear. With the use of non-informative priors, the Bayesian design is entirely equivalent to a frequentist one, with one minus the posterior probability being the one-sided p value—ie, 1–Prob(trueHR<1·0|data)=1p.[18] Given the 80% decision guideline, we decided that a phase 3 trial with a two-sided alpha of 0·4 might be deemed unacceptable to funders and regulators. We also believe that Bayesian presentation of the results as probabilities that one group is better than the other is more intuitive and easier for clinicians and patients to understand than p values are, which are often misinterpreted. A relaxed decision criterion was not relevant, given that the posterior probabilities for both event-free survival and overall survival were 100%—ie, equivalent to a one-sided p value of less than 0·01, thereby providing very strong evidence that VDC plus IE is superior to VIDE. Another advantage of a Bayesian design is that alternative probabilities can be generated, not just the probability that one treatment is better than the other. In this case, we had a 94% chance that the true HR for overall survival was below 0·8—ie, a 94% chance that the risk of death reduced with VDC plus IE compared with that of VIDE. Advancements in the use of Bayesian methodology since the design of EE2012 mean that if the trial were to be designed again, using a minimally (or weakly) informative prior rather than a non-informative prior would be preferable to exclude unrealistic values for the log(HR). However, this method would not have altered the conclusion of our trial given the large sample size and event rate.

We found little difference in toxicity between the two chemotherapy groups in the proportion of any grade 3–5 events, in both induction and consolidation. However, on review of specific events, less overall haematological toxicity occurred in the VDC plus IE group compared with in the VIDE group and, hence, reduced requirement for blood product transfusions; more blood transfusions were required in the VDC plus IE group, but even more platelet transfusions were required in the VIDE group. This difference is also apparent in infection events, with admissions for both fever alone and episodes associated with neutropenia occurring less in the VDC plus IE group. Overall, we found more unscheduled hospital visits in the VIDE group than in the VDC plus IE group. The proportions of gastrointestinal events, however, were similar. These findings were expected because the toxicity of the two treatments had been previously described in publications.[2,11] In terms of the feasibility of delivering the different chemotherapy groups, only 58% of patients in the VIDE group received all eight consolidation courses, but in the VDC plus IE group, 75% of patients received all five consolidation courses. The 12-week average reduction in total time to complete treatment with VDC plus IE was also an important factor supporting this as standard of care.

The success of the VDC plus IE treatment and the lower toxicity allows us to think about adding in other non-chemotherapy-targeted therapies; in combination, these therapies might have tolerable toxicity and are certainly needed in patients with poor-prognostic Ewing sarcoma, such as those with metastatic disease, to hopefully improve outcomes.[5,6,14] Early clinical data suggest that strategies adding a multiple tyrosine kinase inhibitor with anti-angiogenic activities might be beneficial in Ewing sarcoma.[19–21] These drugs have been combined with chemotherapy in the ARST1321 trial (ifosfamide and doxorubicin), which included patients younger than 14 years and reported no major toxicities.[22]

In summary, dose-intensive chemotherapy with VDC plus IE was more effective, less toxic, and more convenient than VIDE for all stages of newly diagnosed Ewing sarcoma and should be the standard of first-line care for all patients with Ewing sarcoma.

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