CHAPTER 1
Rhabdomyosarcoma

Katherine K. Matthay
UCSF School of Medicine, San Francisco, CA, USA

Commentary by Meriel Jenney

Philosophy of treatment of rhabdomyosarcoma

Soft tissue sarcomas (STS) account for about 8% of all childhood malignancies. Rhabdomyosarcoma (RMS) is the single most common diagnosis (accounting for approximately 60% of all STS). It is, consequently, the tumor which is best defined, although there are important differences in behavior between RMS and some of the non-RMS STS (e.g. metastatic potential, chemosensitivity).

Historically, there have been important differences in the philosophy of treatment of RMS between the major international collaborative groups. Although there is now good communication, and a convergence toward standard criteria for staging and pathological classification, the experience of reviewing the literature can be confusing, particularly with respect to the previous lack of use of standard terminology for staging and treatment stratification.

One of the most important philosophical differences between the International Society of Paediatric Oncology (SIOP MMT) studies and those of the Intergroup Rhabdomyosarcoma Study Group (IRSG) (and, to some extent, those of the German [CWS] and Italian [ICG] Cooperative Groups) relates to the method and timing of local treatment. In particular, to the place of radiotherapy (RT) in guaranteeing local control for patients who appear to achieve complete remission (CR) with chemotherapy, with or without "significant" surgery. The SIOP strategy recognizes that some patients can be cured without the use of radiotherapy or so-called "significant' surgery," i.e. surgery resulting in considerable long-term morbidity. However, with this approach local relapse rates are generally higher in the SIOP studies than those experienced elsewhere, although the SIOP experience has also made it clear that a significant number of patients who relapse may be cured with alternative treatment (the so-called "salvage gap" between event-free and overall survival). In the context of such differences, *overall* survival rather than *disease-free* or *progression-free* survival becomes the most important criterion for comparing studies and measuring outcome

Treatment: the general approach

Rhabdomyosarcoma can occur almost anywhere in the body (although a number of well-recognized sites have been defined, e.g. bladder, prostate, parameningeal, limb, genitourinary, and head and neck). This leads to a complexity in its treatment and although the majority of clinical trials have explored chemotherapeutic options for the treatment of RMS, the impact of the site of disease should not be overlooked. Experience in all studies has confirmed that a surgical-pathological classification, which groups patients according to the extent of residual

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tumor after the initial surgical procedure, predicts outcome. The great majority of patients (approximately 75%) will have macroscopic residual disease (IRS clinical group III) at the primary site at the start of chemotherapy (this is equivalent to pT3b in the SIOP postsurgical staging system). The additional adverse prognostic influence of tumor site, size (longest dimension >5 cm), histological subtype (alveolar versus embryonal) and patient age (>10 years) adds to the complexities of treatment stratification. All current clinical trials utilize some combination of the best-known prognostic factors to stratify treatment intensity for patients with good or poor predicted outcomes and the impetus for this approach comes as much from wishing to avoid overtreatment of patients with a good prospect for cure as improving cure rates for patients with less favorable disease.

The importance of multiagent chemotherapy, as part of co-ordinated multimodality treatment, has been clearly demonstrated for RMS. Cure rates have improved from approximately 25% in the early 1970s, when combination chemotherapy was first implemented, to the current overall 5-year survival rates of more than 70% that are generally achieved. Nevertheless, it is interesting to see how relatively little the results of randomized controlled trials have actually contributed to decision making in the selection of chemotherapy and to the development of the design of the sequential studies which have shown this improvement in survival over those years.

Lessons from studies of rhabdomyosarcoma

The IRSG was formed in 1972 as a collaboration between the two former pediatric oncology groups in North America (Children's Cancer Group and Pediatric Oncology Group [POG]) with the intention of investigating the biology and treatment of RMS (and undifferentiated sarcoma) in the first two decades of life. This group, whose work and publications have been pre-eminent in the field, now forms the Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG). Results of treatment have improved significantly over time. The percentage of patients alive at 5 years has increased from 55% on the IRS-I protocol [1] to over 70% on the IRS-III and IRS-IV protocols [2,3].

Combinations of vincristine, actinomycin D, and cyclophosphamide (VAC) have been the mainstay of chemotherapy in all IRS studies. Actinomycin-D was originally given in a fractionated schedule but subsequent experience, including a randomized study from Italy [4], showed no advantage in terms of outcome and has suggested that fractionation may increase toxicity; single-dose scheduling is now standard across all studies. There have never been any results in the IRSG studies that challenge the use of these drugs as first-line therapy and the results of all randomized studies which compare other drugs with, or against, VA or VAC have failed to show significant advantage.

One of the most significant differences between the IRSG and European studies has been in the choice of alkylating agent that provides the backbone of first-line chemotherapy. Ifosfamide was introduced into clinical practice earlier in Europe than in the United States and phase II data are available which support its efficacy in RMS. IRS-IV [2, 3] attempted to answer the question of comparative efficacy by randomizing VAC (using an intensified cyclophosphamide dose of 2.2 g/m^2) against vincristine/dactinomycin/ifosfamide (VAI), which incorporated ifosfamide at a dose of 9 g/m^2. A third arm in this randomization included ifosfamide in combination with etoposide (VIE; vincristine, ifosfamide, etoposide). No difference was identified between the higher-dose VAC and the ifosfamide-containing schedules, and VAC remains the combination of choice for future IRSG (now COG) studies. The rationale for this is explained by the lower dose of cyclophosphamide and its shorter duration of administration, together with concern about the nephrotoxicity of ifosfamide. Nevertheless, the European Paediatric Soft Tissue Sarcoma Group (EpSSG) has chosen to retain ifosfamide as its standard combination as the experience of significant renal toxicity at cumulative ifosfamide doses less than 60 g/m^2 is now very small and there are preliminary data suggesting that the gonadal toxicity of ifosfamide may be significantly less than that of cyclophosphamide [5].

Vincristine, actinomycin D, and cyclophosphamide remains the chemotherapy backbone for IRS studies, as there has been little evidence of benefit from other agents. IRS-III included cisplatin and etoposide in a three-way randomization between VAC, VAC with doxorubicin and cisplatin, and VAC with doxorubicin,

cisplatin, and etoposide. No advantage was seen in selected group III and all group IV patients and there were concerns about additive toxicity. IRS-IV (and an earlier IRS-IV pilot) explored the value of melphalan in patients with metastatic RMS or undifferentiated sarcoma. Patients were randomized to receive three courses of vincristine and melphalan (VM) or four of ifosfamide and etoposide (IE) [6]. There was no significant difference in initial complete and partial remission rates. However, patients receiving VM had a lower 3-year event-free and overall survival. Patients receiving this combination had greater hematological toxicity and, therefore, a lower tolerance of subsequent therapy. In the latest published randomized study by the COG (D9803) [7] in patients with intermediate-risk RMS, VAC was compared to a regimen of VAC alternating with vincristine, topotecan, and cyclophosphamide. Again, no benefit was seen with use of these agents.

Alternative agents of particular interest include doxorubicin (Adriamycin), which has been evaluated in a number of IRSG studies. A total of 1431 patients with group III and IV disease were randomized to receive or not receive doxorubicin in addition to VAC during studies in IRS-I to IRS-III. The results did not indicate any significant advantage for those who received doxorubicin. Furthermore, also in IRS-III, patients with group II (microscopic residual) tumors were randomized between vincristine and actinomycin (VA) alone and VA with doxorubicin without any significant difference in survival. Recent European studies (MMT 95 and CWS-ICG 96) both included randomizations between their ifosfamide-based standard chemotherapy options and an intensified six-drug combination, which also included epirubicin (with carboplatin and etoposide). In the MMT 95 study [8], 457 previously untreated patients with incompletely resected embryonal rhabdomyosarcoma, undifferentiated sarcoma, and soft tissue primitive neuroectodermal tumor were randomized to receive IVA (ifosfamide, vincristine, actinomycin D) or a six-drug combination (IVA+carboplatin, epirubicin, etoposide) both delivered over 27 weeks. Overall survival for all patients was 81% (95% confidence interval [CI], 77–84%) at 3 years but there was no significant difference in outcome in either overall or event-free survival between the two arms. Toxicity was significantly greater (infection, myelosuppression, mucositis) in patients in the six-drug arm. However, in this and the previous studies, the dose intensity of the anthracyclines used was low which may have influenced the evaluation.

So doxorubicin remains a drug of interest in soft tissue sarcomas. A SIOP "window" study in chemotherapy-naïve patients with metastatic RMS has provided good new phase II data for the efficacy of doxorubicin, with response rates greater than 65% [9]. This has justified further evaluation of the role of doxorubicin in the treatment of RMS and this is now under investigation in a randomized study being undertaken by the EpSSG. A more intensive scheduling of doxorubicin is being tested within this study.

Other agents that have shown activity in RMS include irinotecan (CPT11), which in combination with vincristine in a recent COG window study had excellent PR and CR rates [10]. There is also evidence of benefit in the phase I setting [11]. The scheduling of this agent in the phase II setting [12] has been evaluated in patients with RMS, undifferentiated sarcoma or ectomesenchymoma at first relapse or with disease progression. Although preclinical models suggested that a prolonged administration schedule of irinotecan would be more effective than a short (more convenient) schedule, this study demonstrated equivalent response rates (26% for prolonged schedule versus 36% for short) in patients receiving the two schedules. The current COG IRS-V study has now included this combination (using the short schedule) in the latest randomized study.

Vinorelbine is well tolerated and has been evaluated in combination with daily oral cyclophosphamide in previously heavily treated patients with relapsed RMS with encouraging results [13,14]. This combination is now under investigation in the current EpSSG study in which patients who achieve CR with conventional chemotherapy and local treatment are randomized to stop therapy or to continue to receive a further 6 months of "maintenance" therapy with these two agents.

Radiotherapy has been a standard component of therapy for the majority of patients in the IRSG studies from the outset. Randomized studies within IRS-I to IRS-III have established that RT is unnecessary for group I (completely resected) patients with embryonal histology. Analyses from the same studies suggest that RT does offer an improved failure-free survival

(FFS) in patients with completely resected alveolar RMS or with undifferentiated sarcoma. Studies from the European groups have attempted to relate the use of RT to response to initial chemotherapy. The most radical approach is being used by the SIOP group which has tried to withhold RT in patients with group III (pT3b) disease if CR is achieved with initial chemotherapy ± conservative second surgery. In the MMT 89 study, which included 503 patients, the systematic use of RT was avoided in patients who achieved complete local tumor control with chemotherapy with or without surgery, Five-year overall survival (OS) and event-free survival (EFS) rates were 71% and 57%, respectively. The differences between EFS and OS reflected local treatment strategy and successful retreatment for some patients after relapse (the salvage gap). The authors concluded that selective avoidance of local therapy is justified in some patients, though further work is required to identify prospectively those for whom this is most applicable [15].

So this approach is warranted for some patients, for example, those with tumors of the orbit, where outcomes from different international groups have previously been formally compared at a joint international workshop (there were no significant differences in overall survival between international groups using different strategies for radiotherapy, despite differences in event-free survival) [16]. However, the role of radiotherapy is clearly important for other subgroups of patients (for example, those with parameningeal, limb, and/ or alveolar disease) and there is a need to try to define risk groups as accurately as possible at the outset to avoid overtreatment, and also to reduce the risk of relapse and the need for salvage therapy.

Doses of RT have, somewhat pragmatically, been tailored to age, with reduced doses in younger children, although there is no defined threshold below which late effects can be avoided and yet tumor control is still achieved. The place for hyperfractionated RT was explored in IRS-IV when randomized against conventional fractionation [17]. Although there was a higher incidence of severe skin reaction and nausea and vomiting in patients receiving hyperfractionated RT, it was generally well tolerated. However, there was no advantage in failure-free survival, and conventional RT continues to be used as standard therapy.

Lessons from studies of nonrhabdomyosarcoma soft tissue sarcomas

Although this chapter refers to two studies that include patients with non-RMS STS [18, 19], the former is the only published study which was specifically designed to answer a randomized question about the value of chemotherapy in this difficult and heterogeneous group of patients. Unfortunately, the power of this study was limited and further work needs to be undertaken to better understand optimal therapy. Perhaps the most important immediate question is to ascertain whether the treatment of children with non-RMS STS, particularly with the diagnoses more frequently seen in adults, should be assessed any differently than for adults with the same condition. If not, combined studies, particularly of new agents, could be productive.

An important recent development in Europe has been the initiation of a new EpSSG study specifically for children with non-RMS STS and this will facilitate the systematic collection of data from the consistent treatment of children with these rare tumors. There is also now regular communication across the Atlantic with respect to the classification and treatment of non-RMS STS. Separate approaches are offered for synovial sarcoma for "adult" type non-RMS STS and for unique pediatric histiotypes, and links with adult trials will also be important. None of these studies yet includes a randomized element and the numbers of patients in some of these rare diagnostic groups, even when collected at European level, still make this a logistical and statistical challenge.

Conclusion

Although considerable progress has been made in improving overall survival in RMS, progress has been incremental and intuitive, based on careful treatment planning, the co-ordination of chemotherapy with surgery and RT, and better prognostic treatment stratification. Relatively little has been learned about improving treatment from randomized studies but previous conclusions about the role of doxorubicin are being revisited and further new agents (irinotecan, vinorelbine) are under evaluation. The challenge for the future requires the development of a greater ability

to selectively reduce treatment for some groups of patients with a high chance of cure and to identify better forms of therapy for those with a very poor prognosis. Patients with metastatic disease, for example, continue to have a very poor survival rate. Wider international collaboration is the key to providing a patient base that will allow timely and valid randomized studies.

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Summary of previous studies

The evidence base for treatment strategies is particularly strong in this tumor type due to the long history of large randomized trials designed and executed by the IRSG and currently the COG. Between 1988 and 2001, 11 IRSG studies were published. There were two studies from the POG and single randomized trials from the SIOP and Italian (AIEOP) groups respectively. Much useful information has been gained from the large SIOP trials but most of these have not been randomized.

IRS-I, published in 1988 [1] had four objectives. First, to evaluate the role of local radiotherapy in IRS group I patients who received vincristine, actinomycin D, and cyclophosphamide (VAC). Second, to determine whether the addition of cyclophosphamide to vincristine and actinomycin was of benefit in group II patients who received local irradiation. Third, to document the complete remission rate achieved by pulsed VAC with local irradiation in patients with group III and IV disease and fourth, to evaluate the role of adding doxorubicin to VAC in group III and IV patients.

Patients under the age of 21 years with rhabdomyosarcoma or undifferentiated sarcoma were eligible; 686 patients were eligible for inclusion. In group I patients, disease-free survival (DFS) at 5 years was 81%, overall survival 93% in those receiving no radiation compared with 79% and 81% respectively for those who were irradiated and, in particular, there was no significant difference with regard to either local or distant relapse.

In group II patients, the disease-free survival again showed no difference between patients who received or did not receive radiation therapy with identical overall survival of 72% and disease-free survival of 72% and 66%, respectively, for those who received or did not receive cyclophosphamide. In group III, which included 380 patients, the complete response rate achieved combining pulsed VAC with local radiotherapy was 67% while it was 72% for those who received pulsed VAC plus doxorubicin and irradiation. There was no difference in the 5-year DFS between those who received doxorubicin and those who did not – 43% versus 39% ($p=0.91$) or 5-year overall survival of 52% each for both treatment arms. In group IV patients, a complete response rate of 50% was achieved overall and although there was a trend to benefit from doxorubicin in these patients with regard to a more rapid complete response rate and lower relapse rate, there was no significant difference in DFS or OS.

IRS-II, reported in 1993 [2], addressed three questions: (1) the value of cyclophosphamide in favorable site/pathology (extremity alveolar lesions excluded) group I patients, (2) the role of pulsed VAC compared to VA in favorable group II patients (extremity alveolar lesions excluded), and (3) the role of doxorubicin in group III and IV patients excluding special pelvic sites. There were 776 evaluable patients in total although 999 eligible patients were included in the analysis. This study demonstrated that VA given for 1 year was equivalent to 2 years of VAC in group I patients not receiving local irradiation therapy with an overall survival of 85%. In group II patients, cyclophosphamide does not add benefit to VA with DFS of 69% in those not receiving cyclophosphamide compared to 74% for those receiving cyclophosphamide. Finally, in group III and IV patients, doxorubicin did not appear to significantly improve outcome, with almost identical CR rates and OS in those achieving CR.

IRS-III [3] was designed to determine the role of doxorubicin in addition to VAC in group II patients, and, secondly, to determine whether the addition of either cisplatin or cisplatin plus etoposide to pulsed VAdrC –VAC in group III and IV patients improves survival outcome. There were in total 1062 eligible patients, For group II patients, 5-year progression-free survival (PFS) was 56% versus 77% in those receiving doxorubicin. For group III patients in the three regimens, PFS was 70%, 62%, and 56% respectively – no significant difference. For group IV patients, PFS was 27%, 27%, and 30% respectively. The more complex chemotherapy did not therefore appear to have any significant advantage. Again, it is notable that

although not achieving statistical significance, with the addition of anthracycline in group II patients, there is a trend towards lower relapse rates.

IRS-IV [4,5] compared three induction and continuation regimens based on the VAC protocol with the substitution of ifosfamide for cyclophosphamide (VAI) or the replacement of actinomycin and cyclophosphamide with ifosfamide and etoposide (VIE). Patients with local or local regional disease were included but any patient felt to be at risk of renal problems was assigned VAC. Also excluded were the good-risk group I patients with testis, orbit or eyelid primaries who received only VA. A total of 894 patients was included. The 3-year failure-free survival for VAC, VAI, and VIE was 74%, 74%, and 76% respectively. It was, therefore, concluded that none of the novel regimens had any advantage over the standard VAC protocol but it is notable that compared to previous IRS trials, a higher dose of cyclophosphamide was used (2.2 g/m^2).

In patients with metastatic disease there was a randomized comparison between two drug pairs [6]. This utilized the novel and somewhat controversial "window" design where untreated patients receive as yet unproven single or combination chemotherapy. In this study, the drug pairs comprised vincristine/melphalan or ifosfamide/etoposide in untreated metastatic rhabdomyosarcoma; 151 patients were randomized. Complete response rates did not differ at week 12: 13% versus 12%, partial response (PR) rate 61% versus 67% and progression of disease 13% versus 12%. There was, however, a significantly worse 3-year EFS with the VM combination: 19% versus 33% ($p=0.04$). This was felt to be potentially due to the influence of melphalan on hemopoietic stem cell function resulting in poor tolerance of subsequent chemotherapy and consequent dose reduction.

Another component of IRS-IV reported by Donaldson [7] compared the effectiveness and toxicity of hyperfractionated versus conventionally delivered radiation therapy in group III patients; 599 patients were entered, 490 were eventually randomized. Conventional radiation consisted of 50.4 Gy in 28 fractions compared with 59.4 Gy in 1.1 Gy doses twice per day with a 6-h interval between doses. There was no significant difference in outcome between the two groups but hyperfractionation was associated with a significantly higher instance of severe skin reaction, nausea and vomiting, and mucositis.

The very early SIOP study run between 1975 and 1983 and published in 1985 [8] was an historically important trial, which determined whether the use of chemotherapy and radiation therapy prior to surgery could minimize treatment sequelae. Patients initially received one course of VAC and those who had a greater than 25% reduction were advised to continue with chemotherapy alone whereas others received extensive surgery or local radiation therapy. Overall outcome between the two arms indicated that in chemosensitive patients, the use of radiation or extensive surgery had no significant benefit providing complete response was achieved with combination of chemotherapy. This trial, despite its limitations, prepared the ground for the subsequent philosophy of trying to avoid radiation and aggressive surgery, a strategy, which has been subsequently refined in later single-arm studies. These studies have enabled identification of subgroups in whom outcome was likely to be compromised by an insufficiently aggressive approach to local control but, in contrast, a population in whom cure could be achieved with chemotherapy alone or in some cases chemotherapy followed by multimodality salvage treatment.

An Italian AIOP trial published in 1988 [9] compared two methods of administration of actinomycin as part of the VAC regimen. This was a very small trial and indicated that the fractionation of actinomycin D in divided doses daily over 5 days was no more effective in achieving response than a single dose.

Finally, two trials run by the Pediatric Oncology Group have been published. In 1998 Pratt *et al.* reported POG8654 [10], which compared VAC with VAC with the addition of dacarbazine (DTIC) in patients with group III or IV disease. This failed to show any significant benefit but included a very mixed group of tumor types in addition to rhabdomyosarcoma.

The second report in 1999 [11] evaluated whether the administration of chemotherapy following surgical resection of nonrhabdomyosarcomatous soft tissue sarcomas improved local or systemic control. In view of the continued controversy around the role of adjuvant therapy in this group of patients, this was of particular interest. Children with group I disease received no radiotherapy but were randomly assigned to receive chemotherapy with VAdrC

or observation, those with group II disease received age-adjusted postoperative radiation therapy and were then randomly assigned to receive or not receive chemotherapy, and those with group III disease underwent second-look surgery 6–12 weeks after completed radiation therapy and if complete remission was documented, these were also randomized to receive or not receive adjuvant chemotherapy. This study failed to show any significant benefit from the chemotherapy but, unfortunately, was compromised by the heterogeneous nature of the different histologies.

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Study 1

Arndt CAS, Stoner JA, Hawkins DS *et al*. Vincristine, actinomycin and cyclophosphamide compared with vincristine, actinomycin and cyclophosphamide alternating with vincristine, topetecan and cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group study D9803. *J Clin Oncol* 2009;**27**:5182–8.

Objectives

To compare the outcome of patients with intermediate-risk rhabdomyosarcoma treated with standard VAC chemotherapy to the outcome of those treated with VAC alternating with vincristine, topetecan, and cyclophosphamide (VTC).

Study design

Intermediate-risk RMS defined as stages 2 and 3 clinical group III embryonal rhabdomyosarcoma and all nonmetastatic alveolar, undifferentiated sarcomas (UDS), and ectomesenchymoma. Tissue submission for central review was required to confirm histology and study eligibility. Eligibility criteria for study inclusion were previously untreated patients younger than 50 years, beginning therapy within 42 days after initial biopsy, serum bilirubin of <1.5 mg/dL, and normal serum creatinine for age. Patients were assigned to a clinical group by each participating institution following surgery on the basis of clinicopathological determination of extent of disease and degree of surgical resection, according to criteria of the IRS postsurgical grouping classification. If primary excision of a tumor was the definitive operation, patients were classified after this procedure provided it was performed within 42 days of the initial procedure and prior to chemotherapy. Lymph node sampling was based on primary site of disease and required for paratesticular RMS in boys older than age 10 years and in those with extremity tumors and recommended for clinically positive nodes prior to study enrollment.

Patients were randomly assigned to either VAC or VAC/VTC. Patients with parameningeal primary tumors with intracranial extension were assigned to VAC and immediate radiation therapy (nonrandomized). The drug doses used in this study were age adjusted and for children ≥3 years of age, the doses were vincristine 1.5 mg/m^2, dactinomycin 0.045 mg/kg, topotecan 0.75 mg/ m^2×5 days, cyclophosphamide 2.2 g/m^2 (when this was combined with dactinomycin) and 250 mg/ m^2×5 days (when combined with topotecan). For younger children, the doses of vincristine, dactinomycin, and cyclophosphamide in the VAC combination were according to body weight.

Patients were evaluated at weeks 12, 24 and end of therapy. Patients who responded poorly to induction chemotherapy were recommended to proceed to preoperative radiotherapy followed by second-look surgery at week 24. Patients received response-adjusted radiation therapy according to stage group and histological subtype at diagnosis and disease status after the second-look surgery, if done, at week 12. Radiation dose ranged from 36 to 50.4 Gy depending on risk grouping. Dactinomycin and topetecan were withheld during radiation therapy.

Statistics

The primary comparison was between the two randomized regimens. Patients were stratified into five groups: embryonal RMS, stage 2 or 3, group III; embryonal RMS, group IV, younger than 10 years; alveolar RMS or UDS, stage 1 or group 1; alveolar RMS or UDS, stage 2 or 3, group II/III; and parameningeal extension stage 2 or 3.

Long-term FFS was expected to be 64% on the basis of IRS-III and IRS-IV. The study was designed with an 80% power (two-sided α of 0.05) to detect an overall increase in the 5-year FFS from 64% with VAC to 75% with VAC/VTC. A total of 158 failures were required, and projected to occur after follow-up of 518 patients. Kaplan–Meier and log-rank tests were used for FFS and OS. The Cox proportional hazards regression modeling was used to estimate hazard ratios and investigate whether the effect of VAC/VTC differed by risk stratum. Median follow-up was 4.3 years (0–8.2 years).

Results

Patients recruited between 1999 and 2005 included 702 patients; 85 were ineligible for analysis, 516 were randomly assigned to either VAC (n=264) or VAC/VTC (n=252). There was high concordance between central path review and institutional diagnosis: 96% for alveolar, 85% embyronal. The percentage of courses in which therapy was administered as recommended as protocol was 89% or greater for each regimen.

Estimated 4-year FFS rates were 73% for VAC and 68% for VAC/VTC (p=0.3). This was similar to that for IRS-IV, at 69%. Within subgroups, there is a slightly higher risk of failure among patients with stage 2–3 or group II–III alveolar who were treated with VAC/VTC compared to VAC alone (p=0.05), with differences within other strata not significant.

Toxicity

There was little difference between toxicities between arms although patients on VAC were more likely to develop febrile neutropenia. There were 17 second malignancies: six on VAC/VTC, nine on randomized VAC and two on nonrandomized VAC.

Conclusions

The study confirmed previous reports of a higher failure risk in higher stage groups and in patients with alveolar compared to embryonal disease. However, the study did not show any improvement in outcome (failure-free survival) for intermediate-risk RMS when topetecan was substituted for dactinomycin in half the cycles.

Study 2

Mascarenhas L, Lyden ER, Breitfield PP *et al.* Randomized phase 11 window trial of two schedules of irinotecan with vincristine in patients with first relapse or progression of rhabdomyosarcoma: a report from the Children's Oncology Group. *J Clin Oncol* 2010;**28**:4658–63.

Objectives

To compare response rates for two schedules of irinotecan combined with vincristine in patients with rhabdomyosarcoma at first relapse or disease progression.

Study design

Eligible patients had biopsy-proven RMS, undifferentiated sarcoma or ectomesenchymoma and were younger than 21 years of age with a first relapse or disease progression and had Eastern Co-operative Oncology Group (ECOG) performance status of 2 or less and life expectancy of at least 2 months. There were strict definitions for adequate organ function and cardiac function. Patients who had received more than one prior chemotherapy treatment regimen, those with prior exposure to anthracyclines, ischemic heart disease, myeloablative chemotherapy, disease impinging on or within the brain and spinal cord and those who were pregnant or lactating were excluded.

Patients with unfavorable prognosis (alveolar histology at initial diagnosis, stage 1 clinical group I embryonal histology diagnosis with distant recurrence, or stages 2, 3 or 4 and clinical group II, III or IV embryonal histology at initial diagnosis) were randomly assigned to one of two schedules of irinotecan combined with vincristine.

- Regimen 1A included irinotecan 20 mg/m^2 per day IV for 5 days at weeks 1, 2, 4, and 5 with vincristine 1.5 mg/m^2 IV on day 1 of weeks 1, 2, 4, and 5.
- Regimen 1B included irinotecan 50 mg/m^2 per day IV for 5 days at weeks 1 and 4 with vincristine as in regimen 1A.

Disease response was assessed using the NCI Response Evaluation Criteria for Solid Tumors (RECIST) at week 6. Those with responsive disease, either complete or partial, continued to receive 44 weeks of multiagent chemotherapy that incorporated the assigned irinotecan-vincristine regimen.

Statistics

The analysis compared response rate, toxicities, failure-free survival, and overall survival of patients on regimens 1A and 1B. The study was powered to detect a 25% improvement in the response rate to regimen 1A compared to 1B (α=0.1, 1–β=0.9, one-sided test favoring regimen 1A since the only difference of clinical importance was an improved response with the more prolonged but inconvenient schedule).

A sample size of 51 patients per arm (102 randomly assigned patients) was required to detect a significant improvement in the response rate. Fisher's exact test was used to compare the difference in proportions for baseline patient characteristics and treatment response

between regimens. Estimation for survival was performed using the Kaplan–Meier method and compared using the log-rank test.

Results

COG-ARST0121 enrolled 139 patients between July 2002 and October 2006; 93 were enrolled and randomly assigned between the prolonged regimen and the short regimen. Patient characteristics including age, histology, primary site, size of largest lesion and whether the recurrence was local, regional nodal or distant were all similar for those treated in 1A and 1B. There was, however, a larger proportion of males on 1B (70% versus 40%). Recurrences were local in 25 patients, regional nodal in seven, distant metastatic in 36, combined local and regional nodal in five, combined local and distant metastatic in 10 and combined local, regional nodal, and distant metastatic in two.

Toxicity

Fifty percent of patients on regimen 1A and 66% on 1B experienced at least grade 3 toxicity in the first 6 weeks of therapy. There was no statistically significant difference in the instance of diarrhea (22% versus 13%) or anemia (39% versus 28%). Neutropenia was less common on regimen 1A (16% versus 34%) but there was no difference in the incidence of febrile neutropenia.

The week 6 response could be assessed in 89 (42 in regimen 1A and 47 in regimen 1B) of the 92 randomly assigned patients. Three patients were nonevaluable: one withdrew consent, one did not complete treatment, and one was not assessable due to metal artifact on the scan. Overall response (CR+PR) rate in this study was 31%.

There was no significant difference in response rates between regimen 1A, 26%, and regimen B, 36% ($p=0.36$). There were no complete responses on regimen 1B compared to four complete responses on regimen 1A. Response rate in patients with alveolar RMS were significantly higher compared to embryonal or other: 48% versus 5% on regimen 1A and 48% versus 20% on regimen 1B ($p=0.01$ and 0.08 respectively). Failure-free survival was similar between both regimens: the 1-year FFS rates on regimens A and B were 37% and 38% respectively, declining to 14% and 15% at 3 years.

Conclusions

The trial revealed no difference in response rate between the two schedules, disproving the preclinical prediction of superior activity with prolonged schedules. The authors speculated that perhaps the addition of vincristine, one of the most active agents on RMS, could have diluted any differential effect.