Use of Investigational Drugs as Initial Therapy for Childhood Solid Tumors*

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Solid tumors are relatively rare in children, but comprise about two-thirds of all malignancies that affect this age group. Most of these tumors respond well to initial treatment, and some (Wilms' tumor, low-stage Hodgkin's disease, low-stage rhabdomyosarcoma, and low-stage neuroblastoma) are readily cured with modern therapy. Still, many tumors that respond initially acquire clinical drug resistance, respond poorly to rechallenge with known active agents, and demonstrate a low level of responsiveness to experimental agents. This creates a major therapeutic dilemma for the pediatric oncologist. Although a critical need exists to identify new active agents for many solid tumors in childhood, current primary therapy is frequently quite active even in tumors which have a very high rate of relapse. Unfortunately conventional testing of anticancer drugs in previously treated patients can lead to ostensibly poor results when, in fact, the agent may have clinically significant activity. Several arguments can be marshaled against current phase II clinical trials. At relapse, patients may have tumors with multiple drug resistance and may tolerate therapy poorly due to previous treatment and the advanced state of their tumors. Finally, the attending physician, the patient, and the family may be reluctant to consider experimental chemotherapy, resulting in too few subjects in phase II trials to ensure adequate evaluation of all promising compounds.

One way to circumvent these difficulties is to test new phase II agents in previously untreated patients at high risk for failure on standard chemotherapy. This strategy is being implemented at St. Jude Children's Research Hospital by a team of investigators that includes pharmacologists who have developed models of human solid tumors in immune-deprived mice, clinical pharmacokineticists, and clinical oncologists. In this paper, we outline the conceptual framework of this investigative effort and the results of our initial efforts with three common pediatric solid tumors – rhabdomyosarcoma, osteosarcoma, and Ewing's sarcoma – emphasizing experience with melphalan in the treatment of patients with newly diagnosed rhabdomyosarcoma [1].

A. Conceptual Basis

Testing new agents in previously untreated patients yields the most reliable estimate of actual drug activity. Tumors are most sensitive to effective therapy at diagnosis, before the development of clinical drug resistance. When relapse occurs, the tumor is likely to have acquired resistance to some, if not all, of the agents used in primary therapy. In addition, the tumor may be clinically cross resistant to

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* Supported in part by grants CA 23099 and CA 21765 from the National Cancer Institute and the American Lebanese Syrian Associated Charities (ALSAC)

new agents being tested in classic phase II trials. Such testing of new experimental agents in previously untreated children with typically advanced cancer is acceptable, both scientifically and ethically, *only* if care is taken in establishing appropriate criteria for the selection of patients and experimental agents.

B. Criteria for Patient Eligibility

The patient must be at high risk of ultimate treatment failure and, consequently, death from tumor. This does not mean that the tumor should be potentially resistant to all available therapy. In fact, in all the solid tumors selected for this approach at our center, combination chemotherapy exists which produces clinical responses in a significant proportion of patients. The key point is that all of the patients were judged to have a greatly increased risk of eventual treatment failure. Exactly how high this risk must be is difficult to ascertain; a minimum estimate would be probable failure and death in 40%–50% of patients. The greater the likelihood for cure with effective primary therapy, the greater the care that must be exercised in deciding who will be eligible for treatment with experimental agents as initial therapy.

C. Selection of Drugs

There must be a strong rationale for the selection of experimental agents. A drug could be selected for "up-front" testing if it demonstrates marked activity in a relevant model; e. g., the human tumor xenograft in immune-deprived mice. Melphalan and, to some extent, ifosfamide were selected for testing in untreated rhabdomyosarcoma following demonstration of very significant activity in xenografts of human rhabdomyosarcoma [2, 3]. An agent (or combination of agents) could also have shown activity in conventional phase II trials. Ifosfamide was selected on this basis for use in rhabdomyosarcoma [4–6] and in osteosarcoma [6, 7], as was the combination of ifosfamide/VP-16 in Ewing's sarcoma [8]. A compelling pharmacologic rationale with supporting laboratory data might be a third criterion for selection of a new agent. Although, to date, we have not based any choice of an agent solely on this reason, the demonstration of similar pharmacokinetics for melphalan in the xenograft model system and in children was a deciding factor in whether this agent would be used in children with previously untreated rhabdomyosarcoma [1].

The following sections present, in greater detail, implementation of this strategy in three common childhood solid tumors. The basic framework for drug testing is a phase II trial in which the experimental agent or drug combination is administered before any other therapy. This "window of opportunity" lasts for 6–9 weeks before initiation of "standard" treatment.

D. Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft tissue sarcoma in children [9]. Although patients with low-stage disease are frequently cured with surgery, combination chemotherapy, and radiation therapy [9], those with advanced tumors fare poorly [10, 11]. In addition, few new agents with significant antitumor activity have been identified by standard phase II testing.

The following categories of patients are eligible for testing with phase II agents before they receive standard chemotherapy: (a) patients with unresectable primary tumors excluding those in favorable sites (orbit, face, and cheek primaries) – IRS group III – and (b) patients with metastatic disease – IRS group IV. The outcome of aggressive multiagent chemotherapy, radiation therapy and surgery in these two categories has changed little over the past 10 years [10, 11], with the possible exception of parameningeal sites. At St. Jude Chil-

dren's Research Hospital, the predicted disease-free survival for the last 96 consecutive patients in these two categories is about 30%.

The selection of new agents to be tested in rhabdomyosarcoma has been based primarily on the xenograft model, as discussed in the following paper by Houghton, and in a recent publication by Horowitz et al. [1]. Briefly, human rhabdomyosarcomas from previously untreated patients were grown as xenografts in immune-deprived mice and then were used to screen a spectrum of anticancer drugs for activity. The ranking of relative activity in the xenografts is essentially the same as in the human phase II trials. Of the agents tested to date, melphalan (L-phenylalanine mustard, L-PAM) emerged as the single most active agent in human rhabdomyosarcoma and ifosfamide the second most active. However, when moved into a conventional phase II trial, melphalan produced responses in only 1 of 15 previously treated patients. The drug would likely have been abandoned had not its plasma disposition, including total systemic clearance and AUC (area under the concentration vs. time curve), been similar in patients and in the xenograft model. This suggested that therapeutically adequate levels of melphalan were being attained in patients. Therefore, a phase II trial of melphalan in previously untreated patients was initiated. As recently published [1], melphalan proved highly active, producing responses in 10 of the first 13 patients with advanced rhabdomyosarcoma. Upon completion of this trial, ifosfamide has now been introduced for testing in previously untreated patients with rhabdomyosarcoma (RMS V Study). The outline of this protocol is shown in Fig. 1. Therapeutic results will be available when sufficient numbers of patients have been evaluated for response.

Undoubtedly, the significant activity of melphalan in rhabdomyosarcoma would have been undetected had we not tested this agent in previously untreated patients. In the initial phase II trial, all of

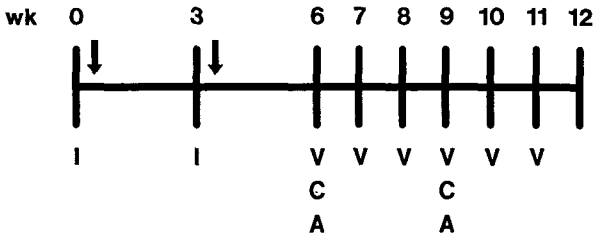

Fig. 1. Schema for ifosfamide trial (induction phase) on RMS V. *I*, ifosfamide; *V*, vincristine; *C* cyclophosphamide; *A*, Doxorubicin. *Arrows* indicate Mesna uroprotection

the patients had received vincristine, doxorubicin, and cyclophosphamide and all but one had received dactinomycin and radiotherapy; hence, the early failure of melphalan was probably the result of tumors with resistance to multiple agents. Indeed, recent work by Houghton et al. [12] indicates that tumors resistant to vincristine are cross resistant to melphalan.

E. Osteosarcoma

First-line adjuvant and neoadjuvant treatment for osteosarcoma, the most common primary bone malignancy in the pediatric population [13], comprises relatively few agents: high-dose methotrexate, doxorubicin, cisplatin, and in some centers the combination of bleomycin, dactinomycin, and cyclophosphamide. In spite of aggressive multiagent protocols, over one-third of patients with nonmetastatic resectable primary tumors will relapse [14]. There has been little progress in the treatment of patients who present with metastatic disease at diagnosis or have unresectable primary tumors, groups that account for about one-third of all patients with osteosarcoma seen at our institution.

We have elected to enroll all patients with high-grade osteosarcoma in a modified phase II trial, because of the difficulty in predicting long-term, disease-free survival in this disease in the individual patient. With the possible exception of cellular DNA content [15] and serum lactate dehydrogenase levels [16, 17], there

are no reliable prognostic indicators for patients with resectable osteosarcoma. Moreover, the clinical outcome of adjuvant therapy in patients treated at this center has not changed appreciably over the past 15 years [16]. This would appear to justify a high-risk classification in every case of high-grade osteosarcoma, and particularly in cases with metastatic lesions or unresectable primaries at diagnosis.

Ifosfamide was selected for up-front testing in the current osteosarcoma study (OS-86), because of results obtained in classic phase II trials conducted at this institution [6] and elsewhere [7]. Although xenograft models for osteosarcoma have recently been established [18], we have not used them to identify new agents. In its initial phase II trial, ifosfamide produced responses (complete plus partial responses) in 4 of 15 patients with relapsed osteosarcoma, including an unmaintained remission of over 4 years in one patient [6]. Although ifosfamide clearly has significant activity in relapsed osteosarcoma, it may increase toxicity when used in multiagent trials; thus, a better assessment of the level of activity in patients needs to be made before this agent is included in phase III protocols. Since ifosfamide caused consistent subclinical renal toxicity [19] as well as some instances of significant increases in serum creatinine [6], it is likely that it would add to the renal toxicity of combination chemotherapy, particularly that including cisplatin and high-dose methotrexate. Increased toxicity would be acceptable if ifosfamide demonstrated significant antitumor activity in more than 25% of previously untreated patients.

Figure 2 outlines the schema of therapy for the OS-86 trial. For the first 6 weeks on study, patients receive only ifosfamide. After complete radiologic and clinical evaluation to determine therapeutic efficacy, patients receive a third cycle of ifosfamide followed by high-dose methotrexate and doxorubicin. Following surgery at week 13, cisplatin is added to the schedule. This trial will clearly define the activity of this new agent in previously untreated patients and will begin to determine the spectrum of toxicities that are likely to occur when this agent is included in a multiagent bona fide phase III study.

F. Ewing's Sarcoma

Ewing's sarcoma is highly responsive to initial therapy. In the St. Jude EW-79 trial, over 90% of patients responded to low-dose oral cyclophosphamide and doxorubicin [20]. However, patients with metastatic disease at diagnosis and those with large primary lesions are known to have a high rate of relapse [21, 22]. Few patients with this tumor who relapse will be salvaged, particularly if relapse occurs

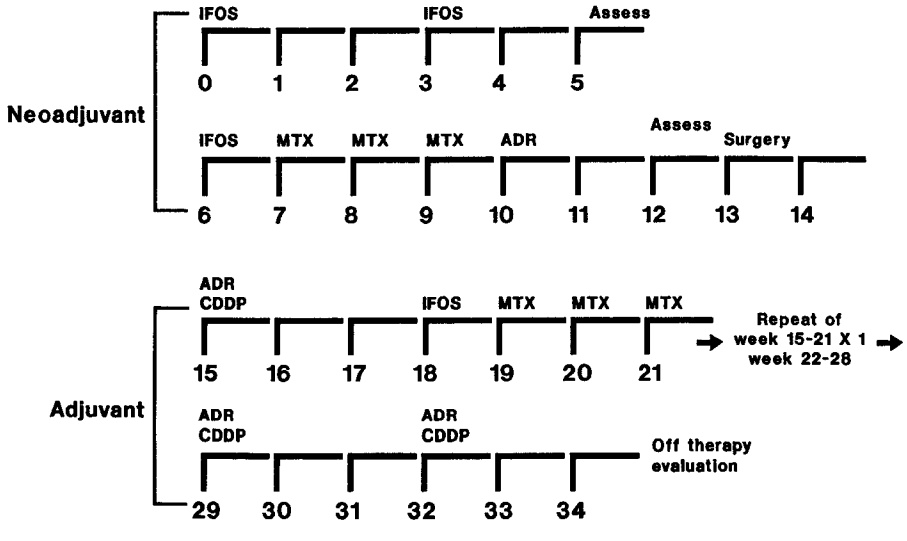

Fig. 2. Schema of chemotherapy for osteosarcoma (OS-86). *Ifos,* Ifosfamide; *MTX*, high-dose methotrexate with leucovorin rescue; *ADR,* doxorubicin; *CDDP*, cisplatin. All *numbers* indicate weeks of therapy

before or soon after cessation of chemotherapy. Unfortunately, only four chemotherapeutic agents are generally considered to have significant activity in Ewing's sarcoma: cyclophosphamide, doxorubicin, dactinomycin, and vincristine. Clearly, newer agents with significant activity against Ewing's sarcoma need to be identified. Recent phase II trials failed to identify new active agents; however, Miser et al. [8] showed that the combination of ifosfamide/VP-16 was very active in recurrent Ewing's sarcoma. Accordingly, an up-front trial of ifosfamide/VP-16 in patients at high risk for treatment failure has been initiated at St. Jude Hospital.

Patients with Ewing's sarcoma and clinical evidence of metastatic disease at diagnosis are at increased risk of treatment failure [21]. Recently, the size of the primary tumor has been shown to be an important prognostic indicator of treatment outcome [22]. At this institution, patients treated with metastatic disease at diagnosis or primary tumors >8 cm in largest dimension have about a 50% probability of disease-free survival, despite a very high initial response rate.

The combination of low-dose oral cyclophosphamide and doxorubicin shows marked activity in almost all patients with Ewing's sarcoma [20]. This has made selection of a new experimental drug for primary therapy quite difficult. The lack of data from human xenograft models and phase II trials that would suggest high levels of activity for any single phase II agent has made the selection of a single drug for this approach not feasible. However, initial reports from Miser et al. [8] showing marked activity of ifosfamide/VP-16 in relapsed Ewing's sarcoma (15 partial responses in the first 16 patients treated) indicated that this combination would be acceptable for trials in previously untreated patients. One could argue that these data are justification for immediate inclusion of ifosfamide/VP-16 in phase III trials in Ewing's sarcoma. Yet, the findings need to be confirmed, particularly in light of a recent follow-up report from Miser's group [23] that several patients have shown no response to this drug combination. In addition, ifosfamide/VP-16 will certainly add toxicity to any four-drug regimen presently used in Ewing's sarco-

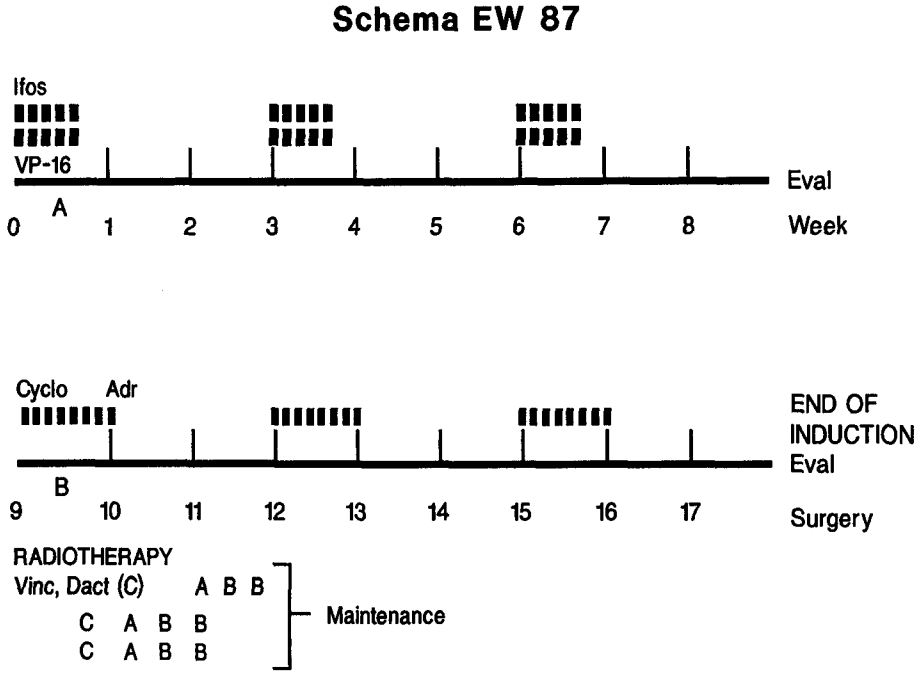

Fig. 3. Schema of chemotherapy for Ewing's sarcoma (EW-87). *Ifos*, ifosfamide; *VP-16*, etoposide; *Cyclo*, cyclophosphamide; *Adr*, doxorubicin; *Vinc*, vincristine; *Dact*, dactinomycin. Both the Ifos/VP-16 pair and the Cyclo/Adr pair are repeated times three at 21-day intervals during induction. *A*, Ifos/VP-16 drug pair; *B*, Cyclo/Adr drug pair; *C*, Vinc/Dact drug pair

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The treatment schema for the present Ewing's sarcoma study for patients at high risk of relapse (EWI 87) is shown in Fig. 3. Three cycles of ifosfamide/VP-16 are given at 21-day intervals. After a complete clinical and radiologic assessment, the patient receives three cycles of low-dose oral cyclophosphamide and doxorubicin. The patient is then evaluated for response, including biopsy or resection of the primary site. Maintenance therapy consists of repetitive cycles of vincristine/dactinomycin, ifosfamide/VP-16, and cyclophosphamide/doxorubicin. High-dose (60 Gy) hyperfractionated radiotherapy is delivered to the primary tumor beginning at week 18.

G. Discussion

Development of new effective drugs is vital to the improvement of cure rates in childhood solid tumors. Conventional phase II studies will continue to be a useful tool for identifying potentially active new agents, but may underestimate the clinical value of many agents that would have significant activity against untreated tumors. For this reason, we have developed a program for testing selected new agents in previously untreated patients with solid tumors who are considered to have high risk of treatment failure. This approach is not unique to our institution. Indeed, earlier experience in similarly designed clinical trials suggests both the validity and inherent problems of up-front drug testing. Teniposide (VM-26), for example, was recently reported to be quite active in adults with small cell carcinoma of the lung [24] when used as primary therapy, despite its lack of activity in classic phase II trials. The Pediatric Oncology Group is also using this approach to identify new agents with activity in advanced-stage neuroblastoma.

Cullen and coworkers [25] tested idarubicin in previously untreated adults with small cell carcinoma of the lung; only 3 (14%) of 21 patients responded. At the completion of the trial, the authors concluded that responses to standard treatment with cyclophosphamide, vincristine, and etoposide following initial exposure to idarubicin seemed inferior to that previously seen in patients who received the same standard therapy without idarubicin. Although patients entered in that trial would clearly meet our criteria for a high-risk group (predicted median survival of approximately 8 months), and the experimental "window of opportunity" was short (16 of the 21 patients received only one or two courses of idarubicin), Cullen and coworkers used a rationale for drug selection that differs from ours. Their decision to begin up-front testing was based on the fact that idarubicin was an anthracycline analogue (doxorubicin is one the more active agents in small cell carcinoma of the lung), it can be given orally, and it is potentially less cardiotoxic than doxorubicin. They presented no data suggesting activity in previously treated patients nor data from relevant models of human small cell carcinoma of the lung. As one requirement for up-front testing of new compounds, Cullen et al. [26] recently suggested that "there should be evidence that the study drug is active in the disease in question," although they would accept activity of an analogue as sufficient evidence.

Kellie et al. [27] tested ifosfamide in previously untreated children with neuroblastoma, noting responses in 8 of 18 patients. Following exposure to ifosfamide, only four patients achieved a good partial or complete response to combination chemotherapy with vincristine, cyclophosphamide, cisplatin, and etoposide (OPEC) or a variant combination. Both a lower response rate and a shorter median survival were noted in these patients compared retrospectively

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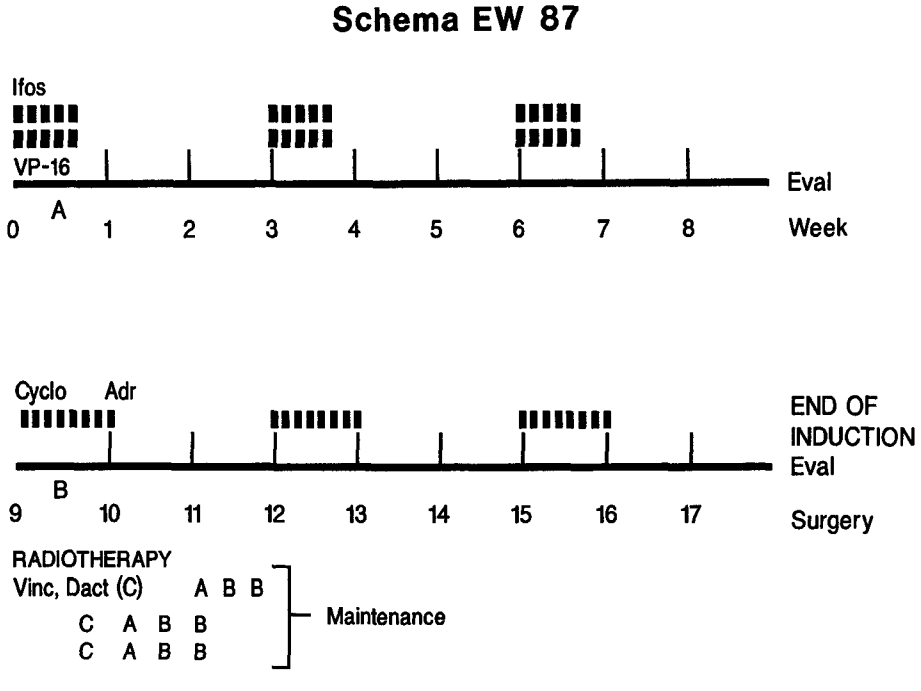

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with similar patients treated with OPEC from the time of diagnosis. The study population was appropriately selected and the phase II trial was sufficiently short. The primary rationale to test ifosfamide was that its analogue, cyclophosphamide, is active in neuroblastoma. In an earlier standard phase II trial of ifosfamide conducted by this group [28], only 2 of 25 patients responded. Thus, in both trials, the phase II agent was selected without clear evidence of activity in a relevant model or in classic phase II trials. Whether poorer responses to the up-front phase II agent will predict (or cause) poorer responses to standard treatment remains to be shown.

The identification of melphalan as a highly active agent in rhabdomyosarcoma (despite failure to define its activity in a standard phase II trial) provides strong support for the investigative approach we have described. However, safeguards must be in place to ensure an ethical study. As Cullen et al. [26] point out, careful clinical evaluation by experienced investigators, strict withdrawal criteria, continual protocol monitoring of response data, and reporting responses to both the phase II agent and standard therapy are essential. In our view, the two most critical factors required for implementation of this approach are: (a) careful selection of patients so that only those at high risk of treatment failure are included and (b) a strong rationale for selection of drug. Currently, we require that a prospective agent show either high levels of activity in the relevant human tumor xenograft or activity in classic phase II trials. The availability of the xenograft models and the collaboration of basic scientists, clinical pharmacokineticists, and clinical investigators makes this investigative effort unique. With appropriate care and diligence, primary testing of new agents in previously untreated patients should provide needed information regarding the actual level of antitumor activity of these agents and combinations. This in turn will speed the identification of clinically useful compounds and guide the future development of chemotherapy for childhood solid tumors.

Acknowledgment. We gratefully acknowledge John Gilbert for editing this manuscript.

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