Although combination chemotherapy has had a major impact on the prognosis of children with rhabdomyosarcomas (1), chemotherapy has not yet acquired an important role in the management of this disease in the adult (2). Drugs which have proven to be highly effective in advanced childhood sarcoma have been incorporated into the programs for treatment of the primary tumor in this young age-group, whereas adjuvant chemotherapy in the adult is still experimental (3-5). These developments reflect the difference in sensitivity to chemotherapy between the sarcomas of adults and children, the latter being much more responsive (6).

The few reported data on response rates of single-agent treatment with Vincristine, Cyclophosphamide, or Actinomycin-D in children and adults with sarcoma, are shown in the first table.

Table 1.
SINGLE-AGENT TREATMENT IN CHILDREN AND ADULTS WITH SARCOMA (6)

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CHILDREN No. of cases</th>
<th>Remission rate (%)</th>
<th>ADULTS No. of cases</th>
<th>Remission rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>20</td>
<td>50</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>42</td>
<td>62</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Actinomycin-D</td>
<td>38</td>
<td>27</td>
<td>6</td>
<td>3/6^x</td>
</tr>
<tr>
<td>DTIC</td>
<td>-</td>
<td>-</td>
<td>60</td>
<td>15</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>-</td>
<td>-</td>
<td>357</td>
<td>27</td>
</tr>
</tbody>
</table>

^x no definition of response

A.T. van Oosterom et al. (eds.), Therapeutic Progress in Ovarian Cancer, Testicular Cancer and the Sarcomas, pp. 425-438. All rights reserved.
The duration of response in adults usually varies between one and four months. A response lasting more than a year is exceptional. The combination of Vincristine, Actinomycin-D and Cyclophosphamide (VAC) had proven to be quite active in childhood rhabdomyosarcoma. In contrast, Jacobs observed only 5/14 (29%) responses in adults with soft-tissue sarcomas treated with this combination (7). This same combination yielded only an 8% response rate in a randomized study performed at the Mayo Clinic (8), although the very low response rate in this study can be attributed to the long interval of 5 weeks between successive cycles.

In 1969 and 1970 the Southwestern Oncology Group (SWOG) studied the activity of DTIC in 60 adults with sarcoma. If patients with osteosarcoma and mesothelioma are excluded, the response rate in this study drops to only 15% (6,9). The evolution of chemotherapy in adult soft-tissue sarcomas during the period between 1970 and 1980, has been centered around the anthracycline antibiotic Adriamycin, and viewed retrospectively must be considered somewhat disappointing. Furthermore, few of the studies have been randomized (10).

Significant advances were initially reported for combination regimens including Adriamycin (9), but it is now becoming more and more evident that these advances have been of limited extent. It is clear that we have actually reached a dead end with the combination of Adriamycin, DTIC, Cyclophosphamide and Vincristine.

Adriamycin is without doubt the most effective drug in our present therapeutic armament for this tumor group (11,12). Response rates with single-agent Adriamycin have ranged from 9 to 70% (6). These differences can be partially explained by the different schedules and doses applied by various investigators. Patients treated with a dose of 60-75 mg/m² tend to respond better than those treated with lower doses, and response rates tend to be higher (25-40%) in studies in which the drug was given in one bolus every 3 weeks (11+13), compared with those in which the drug was
given daily for 3 days (q 3 weeks) (14). The 3-weekly one
day schedule of administration has been applied in both the
non-randomized (12) and randomized (15) studies done by
the SWOG and in a randomized study of the Eastern Coopera-
tive Oncology Group (ECOG) (13).
The 3-day regimen repeated at 3-week intervals had been
used in a previous study performed by the ECOG to compare
Adriamycin randomly with Cycloleucine (14). Response rates
of both drugs were below 20% with the schedules applied.
From the available data it may be concluded that when ad-
ministered as a single-agent, Adriamycin should be given
in a dose of at least 70 mg/m² q 3 weeks. In most of the
studies there appears to be no difference in the response
of the various histological subtypes, although the number
of patients in each subtype group is often small (6). The
median duration of response to Adriamycin was 4-5 months,
and the duration of survival was 15 months for responders
as compared with 8 months for non-responders in the ECOG
study (13).
Studies performed in the early Seventies at the Southern
Research Institute in rodents bearing sarcoma 180, B 16 me-
lanoma, or C3H breast carcinoma showed that the toxicity
of Adriamycin and DTIC given in combination was not additi-
ve, and almost full doses of each drug could be used (16).
Because both drugs had shown activity in soft-tissue sar-
coma in man, Gottlieb et al. initiated in 1971 a non-ran-
domized clinical study (SWOG-445) with these agents in
combination (12,16), which they called the ADIC regimen.
They selected the following schedule: Adriamycin 60 mg/m²
on day 1 and DTIC 250 mg/m² on days 1 through 5. The cy-
cles were repeated every 3 weeks. Doses were increased by
increments of 15 mg/m² for Adriamycin and 50 mg/m²/ day
x5 for DTIC if the white blood cell count of the individu-
al patient had not dropped below 3000/mm³. Many of the pa-
tients could tolerate a dose of 75 mg/m² Adriamycin and
300 mg/m²/day x5 of DTIC. An increased remission rate up
to 47% was observed with this regimen (6,12). Responders
tended to be younger and have had less prior chemotherapy.
There was, again, no difference in response between the various histological subtypes (Table 2).

Table 2.
RESPONSE TO THE COMBINATION OF ADRIAMYCIN AND DTIC, ACCORDING TO HISTOLOGICAL SUBTYPE

<table>
<thead>
<tr>
<th>Histological type</th>
<th>No. of evaluable patients</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated</td>
<td>26</td>
<td>58</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>39</td>
<td>51</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>20</td>
<td>45</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Synovial cell sarcoma</td>
<td>11</td>
<td>45</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>Neurofibrosarcoma</td>
<td>27</td>
<td>48</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>183</strong></td>
<td><strong>47</strong></td>
</tr>
</tbody>
</table>

Besides the increased remission rate, a slight increase in the duration of response was observed for ADIC as compared with both single-agent Adriamycin and single-agent DTIC treatment. The duration of survival increased with ADIC as compared with the duration obtained with Adriamycin alone.

A subsequent SWOG study with VADIC (Vincristine added to Adriamycin and DTIC) was performed in 1972-1973 (12). The addition of Vincristine gave a minimal advantage consisting of a reduction in the number of patients with progressive disease. Certainly the negligible toxicity of Vincristine was a dubious reason for maintaining this drug in subsequent regimens studied by many groups.

The next SWOG study (73-02) added Cyclophosphamide in a dose of 500 mg/m², administered on day 1 of each cycle, which gave the CYVADIC regimen (Table 3), (12).
Table 3.
CYVADIC REGIMENS\(^X\) STUDIED BY THE SOUTHWESTERN ONCOLOGY GROUP

<table>
<thead>
<tr>
<th>Drugs</th>
<th>SWOG 73-02</th>
<th>SWOG 74-02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>500 mg/m(^2), day 1 i.v.</td>
<td>500 mg/m(^2), day 1 i.v.</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.5 mg/m(^2), day 1</td>
<td>1.5 mg/m(^2), day 1(^\text{xx})</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>50 mg/m(^2), day 1</td>
<td>50 mg/m(^2), day 2</td>
</tr>
<tr>
<td>DTIC</td>
<td>250 mg/m(^2), days 1-5</td>
<td>250 mg/m(^2), days 1-5</td>
</tr>
</tbody>
</table>

\(^X\)q 3 weeks, \(^\text{xx}\) weekly for 7 weeks

The original 73-02 study yielded a response rate of 59% in soft-tissue sarcomas (6), whereas the slightly modified CYVADIC regimen, studied in a randomized trial (SWOG 74-02), resulted in a remission rate of 50% and a complete response rate of 15% (15). Thus, the complete plus partial response rate achieved with CYVADIC was only slightly better than the rate obtained with the ADIC regimen (47%). The toxicity reported for the CYVADIC regimen clearly indicates that introduction of other myelosuppressive drugs into this combination will not be feasible (Table 4).

Table 4.
HAEMATOLOGIC TOXICITY ASSOCIATED WITH CYVADIC (EXPRESSED IN PERCENTAGE OF 136 PATIENTS)

<table>
<thead>
<tr>
<th>Nadir granulocyte count(^X)</th>
<th>Nadir platelet count(^\text{xx})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&gt;1000)</td>
<td>(&gt;100)</td>
</tr>
<tr>
<td>500-1000</td>
<td>50-100</td>
</tr>
<tr>
<td>(&lt;500)</td>
<td>(&lt;50)</td>
</tr>
</tbody>
</table>

|                 | 44%  | 29%  | 27%  | 79%  | 16%  | 5%   |

\(^X\)cells/mm\(^3\); \(^\text{xx}\)cells x 10\(^3\)/mm\(^3\)

Toxicity was increased particularly by the addition of Cyclophosphamide to VADIC.

Replacement of DTIC by Actinomycin-D (CYVADACT) yielded a response rate of only 40% (15), which might indicate an antagonism between Adriamycin and Actinomycin-D, a minimal effect of Actinomycin-D in sarcomas, or a more frequent
reduction of the Adriamycin dose because of a more severe
toxic reaction to Actinomycin-D than to DTIC.
It is also of interest to mention a recent randomized
study performed in 27 patients by Rodriguez et al. at the
M.D. Anderson Hospital, in which an intensified CYVADIC
scheme was introduced. Three intensive courses were admi-
nistered with or without the use of a protected environment
and prophylactic antibiotics (19). The starting dose of
Adriamycin and Cyclophosphamide were 60 mg/m² and 600 mg/m²,
respectively. These doses were escalated at each cycle if
no infection occurred in the previous course. Only one in-
fection episode occurred in the protected environment as
against six infections in the control group. The beneficial
effect on the response rate might well have been accounted
for by the Adriamycin by itself. There was, however, no
beneficial effect on the duration of response.
Clearly, it is not feasible to add any myelosuppressive
agent to the CYVADIC regimen without being forced to reduce
the dose of the other drugs, including that of Adriamycin.
Hence, one might observe a reduced effect of such a com-
bination as compared to that of ADIC or even single-agent
Adriamycin. At present, one should consider the ADIC regi-
men as the standard regimen for adults with advanced soft-
tissue sarcoma.
Recently, the EORTC Soft-Tissue and Bone Sarcoma Group
performed a randomized study (62761) in patients with ad-
vanced sarcomas (20) to compare the standard CYVADIC re-
gimen with a cyclic regimen in which Adriamycin plus DTIC
was alternated with Vincristine plus Cyclophosphamide.

Table 5.
CYVADIC REGIMENS STUDIED BY THE EORTC SOFT-TISSUE AND
BONE SARCOMA GROUP (PROTOCOL 62761)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>$S_1^x$</th>
<th>$S_2^{xx}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>500 mg/m², day 1 i.v. 1200 mg/m², day 29 i.v.</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>1,4 mg/m², day 1</td>
<td>1,4 mg/m², day 29</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>50 mg/m², day 1</td>
<td>50 mg/m², day 1</td>
</tr>
<tr>
<td>DTIC</td>
<td>250 mg/m², days 1-5</td>
<td>250 mg/m², day 1-5</td>
</tr>
</tbody>
</table>

$x$: q 4 weeks; $xx$: q 8 weeks.
The only divergence from the original CYVADIC regimen was the duration of the interval between the cycles (4 weeks instead of 3 weeks). The aim of this study was to reevaluate the CYVADIC regimen and to find out whether alternation would result in prolongation of the duration of response. In both arms the dosages of Adriamycin, Cyclophosphamide, and DTIC were reduced by 33% for patients aged 60-75 years. Preliminary results have been reported recently (21). To date, the results in 140 evaluable patients show a response rate of 38.3% for the full-dose CYVADIC regimen; when the dosages were reduced the response rate dropped to 22.2% (Table 6).

Table 6.
EORTC TRIAL 62761: BEST OVERALL RESPONSE TO TREATMENT, ACCORDING TO AGE-GROUP

<table>
<thead>
<tr>
<th>Age-groups (yr)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>NC (%)</th>
<th>Prog (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-59</td>
<td>15 (13.3)</td>
<td>17 (15.0)</td>
<td>41 (36.3)</td>
<td>40 (35.4)</td>
<td>113</td>
</tr>
<tr>
<td>60-75</td>
<td>1 (1.7)</td>
<td>5 (18.5)</td>
<td>6 (22.2)</td>
<td>15 (55.6)</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>16 (11.4)</td>
<td>22 (15.7)</td>
<td>47 (33.6)</td>
<td>55 (39.3)</td>
<td>140</td>
</tr>
</tbody>
</table>

With respect to the dose-response relationship previously observed for Adriamycin, the reduced response rate compared even to that obtained with ADIC could be accounted for by the reduction of the Adriamycin dose per cycle. The longer interval between each cycle may explain the lower response rate observed with the full-dose regimen compared with the results obtained with the CYVADIC regimen studied in SWOG 74-03 (13). The cyclic regimen resulted in a response rate of only 15.9%, whereas the percentage for the CYVADIC regimen was 36.4. These data are shown in Table 7, which includes the elderly group given the adjusted dosage. These findings confirm the conclusion that Vincristine and Cyclophosphamide are poor drugs for the treatment of soft-tissue sarcoma, and are often unable to maintain an effect achieved with the ADIC combination administered 4 weeks earlier.
Table 7.

EORTC TRIAL 62761: BEST OVERALL RESPONSE TO TREATMENT

<table>
<thead>
<tr>
<th>Regimen</th>
<th>CR (%)</th>
<th>FR (%)</th>
<th>NC (%)</th>
<th>Prog (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-drug</td>
<td>13 (16.9)</td>
<td>15 (19.5)</td>
<td>28 (36.3)</td>
<td>21 (27.3)</td>
<td>77</td>
</tr>
<tr>
<td>Cyclic</td>
<td>3 (4.8)</td>
<td>7 (11.1)</td>
<td>27 (42.8)</td>
<td>26 (41.3)</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
<td>16 (11.4)</td>
<td>22 (15.7)</td>
<td>55 (39.3)</td>
<td>47 (33.6)</td>
<td>140</td>
</tr>
</tbody>
</table>

Vincristine and Cyclophosphamide should therefore be excluded in new regimens to be studied. The data obtained in the EORTC study also show that one should not evaluate treatment only at 8 weeks, because remissions may be achieved even after 6 to 8 cycles of treatment. The duration of response in the limited number of patients responding to the cyclic S₂ regimen, appeared to be similar to that of patients responding to the S₁ regimen. It is too early to give data on survival, but there are clear indications that the differences in response rates between the two regimens and between the high- and low-dosage groups, will be reflected in the survival curves. The differences between the survival curves of complete responders, partial responders, patients with no change of disease, and patients with progressive disease are significant and independent of treatment.

When the many non-randomized studies performed during the past decade are reviewed, the percentage of non-pre-treated patients, the extent of disease, and the patients' general condition should be taken into consideration. Pre-treatment with other drugs probably reduces the remission rate significantly. The number of pre-treated patients has in all probability dropped sharply in studies performed after reports on the responses observed in the initial studies with single-agent Adriamycin therapy. This factor might have even influenced the response rate in the ADIC area compared with the preceding studies with Adriamycin as a single-agent.

A response rate of 36% for Methotrexate has recently been reported in a group of patients with soft-tissue sarcomas,
many of them not pre-treated (22). Three different regimens, including various other drugs, were used, but it is difficult to determine from the report which regimen was most effective. More details on this experience in England are reported in the preceding chapter. In addition, evidence supporting the effectiveness of Methotrexate comes from two small series comprising a total of 24 patients treated with high-dose Methotrexate after showing progression on CYVADIC (23,24). A total of 8 responders (33%) were observed in these two studies. At present, there is certainly no evidence that supports the use of high doses of Methotrexate in soft-tissue sarcoma. A study on low doses of Methotrexate in non-pre-treated patients definitely seems warranted. Our main aim should be to find new active drugs. In Chapter 34 the results of many recent Phase-II studies are reported. In the future we should seriously consider performing Phase II studies in non-pre-treated patients or possibly after a trial with single-agent treatment with either Adriamycin or a new anthracycline analog. The EORTC Soft-Tissue and Bone Sarcoma Group has recently adopted the latter procedure. New anthracycline derivatives are under study in an attempt to find an agent with less side effects for the heart and the bone marrow. If such an agent proved to maintain its antitumor effect, we might be able to exploit the antitumor effect better. In cases of progression on single-agent treatment with an anthracycline analog, other new agents can be given a fair chance in Phase II studies performed in these patients with limited pre-treatment. This approach might help us to find more effective agents which could subsequently be incorporated into combination regimens including an anthracycline derivative. The latter policy has been adopted by the EORTC Soft-Tissue and Bone Sarcoma Group for the early Eighties.

The following conclusions can be drawn from this survey:

1) Adult soft-tissue sarcoma is less responsive to chemotherapy than childhood sarcoma.
2) Adriamycin is the most effective agent in advanced adult soft-tissue sarcoma and forms the backbone of all effective chemotherapy regimens.

3) The addition of DTIC, Vincristine, and Cyclophosphamide has only increased the therapeutic effectiveness to a limited extent; at present, one may consider the ADIC regimen as the standard treatment for soft-tissue sarcoma.

4) The dose-response relationship found for Adriamycin may explain the lower response rate in the older age-group in the EORTC study, whose doses had been adjusted.

5) The EORTC cyclic regimen gives a lower response rate than the 4-drug regimen.

6) Response to chemotherapy may occur slowly, and may not become apparent until administration of 6-8 cycles.

7) Phase II studies are extremely important to overcome the present deadlock in the treatment of sarcoma.

8) Phase II studies should be performed in either non-pre-treated patients or patients treated only with an anthracycline.

9) The development of an effective post-surgery adjuvant chemotherapy regimen may help us to circumvent the problem of drug resistance in advanced sarcoma.

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