E.O.R.T.C. News

E.O.R.T.C. Protocol for the Therapy of Metastatic Soft Tissue Sarcoma,*
A Randomized Trial†

H. M. PINEDO,‡ C. P. J. VENDRIK,‡ M. STAQUET,‡ Y. KENIS,§ and R. SYLVESTER||

*E.O.R.T.C. Soft Tissue Sarcoma Cooperative Group, Protocol 62761,
‡Oncology Unit, Department of Internal Medicine, Academisch Ziekenhuis, Utrecht, The Netherlands,
§Service de Médecine et d’Investigation Clinique, Institut Jules Bordet, Bruxelles, Belgium,
||E.O.R.T.C. Data Center and Laboratoire de Statistique Médicale, Université Libre de Bruxelles, Belgium and
|||E.O.R.T.C. Data Center, Bruxelles, Belgium

1. BACKGROUND AND INTRODUCTION

Until recently chemotherapy in metastatic soft tissue sarcoma has given poor results. Since a few years adriamycin (ADM) as a single agent in these tumors has given higher remission rates than obtained with any other drug [1, 2].

Gottlieb’s results [3–6] and those of others [7], with combination therapy in soft tissue sarcoma are encouraging. In broad phase II studies during 1970–1971 adriamycin and 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (NSC-45338) both proved to have definite activity when given as single agents in soft tissue sarcoma [1, 2, 8]. These effects were obtained despite extensive previous therapy with surgery, radiotherapy and the commonly used chemotherapeutic agents vincristine (VCR), actinomycin D (ACD) and cyclophosphamide (CPA). The remission rates for ADM and NSC-45338 (DIC) in these studies were 29 and 15% respectively. His studies also show that ADM is the most active single drug agent and that it can be combined well with other agents. Regression rates of single and combination therapy in soft tissue sarcoma are shown in Table 1. It can be seen that the effects of ADM and DIC are additive [5], while this has been shown in experimental data as well [9]. The two drugs can be given together with little increase in toxicity. Addition of VCR appears to act independently at essentially the same level as DIC. The median duration of remission of combination treatment has been significantly longer (16 months for ADM + DIC).

In a pilot study performed in 1974–1975 within the Soft Tissue Sarcoma Working Party ACD has been introduced instead of VCR. However, toxicity of this 4-drug combination was unacceptable.

Actinomycin D had been introduced in the combination treatment because this drug is effective in single drug treatment of soft tissue sarcoma. Because of the toxicity the schedule has been changed. A single dose treatment with the 4-drug CYVADIC combination described by Gottlieb will be compared with a cycling schedule. With the alternating administration ADM can be given for a longer period of time, while resistance might be built up less rapidly.

2. PURPOSE OF STUDY

The purpose of this trial is to investigate the remission rate and duration of remission and survival of two schedules of 4-drug treatment in soft tissue sarcoma, a single dose schedule and a cycling schedule. The proposed alternating schedule has not been studied before in soft tissue sarcoma, but the four drug combination has been studied previously [4]. The second objective of this study will be to verify these results.

†Supported by grant No. 3 R10 CA 11488–07.
Table 1. Remission rate of single and combination therapy of ADM and DIC* with VCR† and CPA‡

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All sarcomas</th>
<th>Sarcomas—(Ewing + osteo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADM (pooled data, Gottlieb)</td>
<td>36/131 (29%)</td>
<td>16/76 (21%)</td>
</tr>
<tr>
<td>DIC</td>
<td>10/67 (15%)</td>
<td>10/66 (16%)</td>
</tr>
<tr>
<td>ADM + DIC (SWCCG)</td>
<td>85/200 (42%)</td>
<td>71/167 (43%)</td>
</tr>
<tr>
<td>ADM + DIC + VCR (SWCCG)</td>
<td>19/40 (48%)</td>
<td>18/35 (51%)</td>
</tr>
<tr>
<td>ADM + DIC + VCR + CPA (SWCCG)</td>
<td>45/107 (42%)</td>
<td>75/136 (55%)</td>
</tr>
</tbody>
</table>

*Imidazol carboxamide.  
†Vincristine.  
‡Cyclophosphamide.  

3. SELECTION OF PATIENTS

3.1 Conditions of patient eligibility

1. Eligible patients must have confirmed residual or metastatic soft tissue sarcoma.
2. The cell types which are included are summarized in Section 10.
3. All patients should have measurable and evolutive disease. Osseous lesions and pleural effusions are not considered as measurable lesions. Progression must be proved within a period of 2 months before the beginning of the treatment, but if it has been proven in a shorter period of time, the patient can enter on study.
4. All patients previously treated by radiation with progressive and measurable growth outside the field of radiation may be accepted for the present study.
5. The patient must be inoperable without other definitive therapy available.

3.2 Conditions for patient exclusion

1. Patients 14 years old or younger.
2. Patients above 75 years of age.
3. Patients with overt psychoses or marked senility.
4. Performance status according to Karnofsky under 50 (see Table 2).
5. Active second tumor or serious concomitant disease.
6. Acute intercurrent complications such as infection or post surgical complication.
7. Previous treatment with ADM, DTIC, VCR or CPA.
9. Central nervous lesions including metastases.
10. Unfavorable hematologic status: leukocytes < 4000 per mm³, thrombocytes < 100,000 per mm³.

4. DESIGN OF TRIAL

4.1 Patients will be randomized to receive either the $S_1$ single dose schedule or the $S_2$ cycling schedule. Patients will be stratified according to cell type since there are differences in remission rates between the histologic subtypes and also according to age (15–59 years, 60–75 years). No stratification for histologic grading will be done (Table 3).

4.2 Treatment should be administered, if possible, for a minimum of 8 weeks. In responders or in patients with static disease, the dose schedule should be continued for at least 2 years. Patients go off study upon progression and should be followed until death whenever possible.

5. THERAPEUTIC REGIMENS

5.1 For patients between 15 and 59 years of age, the schedule will be

$S_1$: ADM 50 mg/m², Day 1
      DTIC 250 mg/m²/day, Days 1–5
      CPA: 500 mg/m², Day 1
      VCR: 1.5 mg/m² (top dose 2 mg), Day 1
This course is repeated every 4 weeks.

$S_2$: ADM: 50 mg/m², Day 1 plus
      DTIC 250 mg/m²/day, Days 1–5;
      CPA: 1200 mg/m², Day 1 plus
      VCR 1.5 mg/m² (top dose 2 mg), Day 1
      Cycled dose: every 4 weeks, alternating (ADM + DTIC) and (CPA + VCR).

5.2 For patients between 60 and 75 years of age, the schedule will be

$S_1$: ADM: 35 mg/m², Day 1
      DTIC: 170 mg/m²/day, Days 1–5
      CPA: 330 mg/m², Day 1
      VCR: 1.0 mg/m², Day 1
      This course is repeated every 4 weeks.

$S_2$: ADM: 35 mg/m², Day 1 plus
      DTIC, 170 mg/m²/day, Days 1–5
      CPA: 800 mg/m², Day 1 plus
      VCR: 1.0 mg/m², Day 1
      Cycled dose: every 4 weeks, alternating (ADM + DTIC) and (CPA + VCR).
Table 2. Dose modifications in case of leukopenia and/or thrombocytopenia

<table>
<thead>
<tr>
<th>Thrombocytes</th>
<th>≥ 100,000</th>
<th>75,000–100,000</th>
<th>≤ 75,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>100%</td>
<td>50%</td>
<td>—</td>
</tr>
<tr>
<td>≥ 4000</td>
<td>2000–4000</td>
<td>50%</td>
<td>—</td>
</tr>
<tr>
<td>≤ 2000</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 3. Drug schedule

<table>
<thead>
<tr>
<th>Age</th>
<th>15–59</th>
<th>60–75</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adriamycin, Day 1</td>
<td>50 mg/m²</td>
<td>35 mg/m²</td>
</tr>
<tr>
<td>DTIC, Days 1–5</td>
<td>250 mg/m²/day</td>
<td>170 mg/m²/day</td>
</tr>
<tr>
<td>Cyclophosphamide, Day 1</td>
<td>500 mg/m²</td>
<td>330 mg/m²</td>
</tr>
<tr>
<td>Vincristine, Day 1</td>
<td>1-5 mg/m² (top dose 2 mg)</td>
<td>1-0 mg/m²</td>
</tr>
</tbody>
</table>

This course is repeated every 3 weeks.

| S2:       |       |       |
| Adriamycin, Day 1 plus | 50 mg/m² | 35 mg/m² |
| DTIC, Days 1–5 | 250 mg/m²/day | 170 mg/m²/day |
| Cyclophosphamide, Day 1 plus | 1200 mg/m² | 800 mg/m² |
| Vincristine, Day 1 | 1-5 mg/m² (top dose 2 mg) | 1-0 mg/m² |

Cycled Dose: every 3 weeks, alternating (ADM + DTIC) and (CPA + VCR).

Table 4. Dose modifications of ADM in hepatic dysfunction

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>BSP-retention</th>
<th>% of normal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.0 mg/100 ml</td>
<td>&lt; 12%</td>
<td>100%</td>
</tr>
<tr>
<td>2–3 mg/100 ml</td>
<td>12–18%</td>
<td>50%</td>
</tr>
<tr>
<td>&gt; 3 mg/100 ml</td>
<td>&gt; 18%</td>
<td>25%</td>
</tr>
</tbody>
</table>

5.3 Duration of therapy
ADM will be administered to a total dosage of 550 mg/m². After reaching this dosage, therapy will be continued with DTIC, VCR and CPA at the same doses. No dose escalation is permitted. In patients still showing disease progression after a treatment period of 6 weeks, therapy has to be discontinued. In responders or in patients with static disease the dose schedule will be continued for at least two years. Treatment for patients going off study due to progression will be determined individually by each institution. However, it is recommended that patients failing in S₁ will be crossed over to S₂. It is suggested to treat patients failing on S₁ by doubling the S₁ doses (if facilities for isolation of patients are available).

5.4 Drug formulation and procurements
5.4.1 Supplied. ADM: vials containing 10 mg; DTIC: vials containing 100 and 200 mg; VCR: vials containing 1 mg; CPA: vials containing 100, 200, 500 or 1000 mg as a powder.

5.4.2 Storage. ADM: refrigerator 4°C; DTIC: deep freeze –20°C; VCR: refrigerator 4°C; CPA: refrigerator, keep dry.

5.4.3 Methods of administration. All four drugs should be introduced i.v. (pushdose).

5.5 Supportive therapy
No radiotherapy should be given to patients in the trial, except for palliative treatment of lesions of the skeleton.

5.6 Nausea and vomiting
Phenothiazine should be administered before giving medicaments.

6. TOXICITY AND DOSE MODIFICATIONS

6.1 Dose modifications of adriamycin should take place with hepatic dysfunction according to Table 4. This dose
should also be applied with development of liver dysfunction after start of treatment. Dose modifications of Adriamycin should not be applied with renal dysfunction.

6.2 If at 4 weeks the leukocytes are between 2000 and 4000 and/or the thrombocytes between 75,000 and 100,000 the dose will be adjusted according to Table 2. If at 4 weeks leukopenia and/or thrombocytopenia persist below these levels, treatment will be postponed a maximum of 3 weeks. If a cycle has to be postponed more than 3 weeks, the patient should be dropped from the trial. At the moment (within 4–6 weeks from the beginning of the last cycle) that the leukocytes and thrombocytes have recovered to levels above 2000 and 75,000 respectively, treatment can be re-continued at 50% of the initial dose. In this case the dosage of subsequent cycles will be maintained at 50% of the initial dose even if leukocytes and thrombocytes recover to normal levels within 3 weeks.

7. PRETREATMENT STUDIES

7.1 History
   a. Age
   b. Sex
   c. Date and nature of first symptoms
   d. Date of initial diagnosis and how made
   e. Prior treatment (dates, methods, nature and duration of response).

7.2 Physical examination
   a. Ambulatory status using Karnofsky’s criteria
   b. Height, weight and surface area
   c. Description and measurements of soft part metastases with a suitable caliper
   d. Photographs of the soft tissue lesions.
   (optional),

7.3 Laboratory studies
   a. Complete blood count
   b. Serum creatinine, Na, K, Ca
   c. Serum uric acid
   d. Bilirubin, alkaline phosphatase, transaminases, serum proteins and electrophoresis
   e. Urinalysis.

7.4 X-thorax

7.5 Bone
   Skeletal X-ray survey including following bones: skull lateral and AP views, pelvis AP view, lumbar, dorsal, cervical spine lateral and AP views.

7.6 Isotopic scintigraphy
   Liver scan; skeletal scan: skull, spine and pelvis.

7.7 Electrocardiogram

8. FOLLOW-UP STUDIES

8.1 Every week during the first 8 weeks and then every 3 weeks thereafter: 7.3a.

8.2 Every 4 weeks: 7.2a, 7.2b, 7.2c, 7.2d.

8.3 Every 8 weeks: 7.3b, 7.3c, 7.3d, 7.3e, 7.4.

8.4 Every 6 months: 7.5, 7.6, unless indicated earlier either on a medical indication or for determination of a complete remission.

8.5 In case of objective tumor response: pre-treatment studies except 7.1.

8.6 In case of toxicity: follow-up of the toxicity until complete recovery.

8.7 Every side-effect of therapy has to be recorded: anorexia, nausea, vomiting, mouth ulcerations, alopecia, haemorrhagic cystitis, hepatic dysfunction.

8.8 Complementary studies may be performed provided they do not interfere with or bias the results of the studies required by the protocol. Immunological studies are optional.

9. DEFINITION OF RESPONSE

Only objective tumor response criteria are used in these studies. These are the following:

9.1 A complete remission is defined as the disappearance of all symptoms and signs of soft tissue sarcoma for a minimum of 4 weeks.

9.2 A partial remission is defined as a significant decrease in size in at least 50% of all lesions for a minimum of 4 weeks while the remainder are static. In the case of accurately measurable lesions, such a decrease is defined as a reduction by 50% of the product of the two largest tumor diameters. For lesions that do not lend themselves to accurate measurement, the reduction should be at least three-fourths of the estimated volume. Changes in body chemistry and improvement in hemodoiisis cannot be construed as criteria of objective remission.
9.3 No change is recorded for a patient when no new lesions appear and no lesions increase in size; decreases in lesion size, if any, are not sufficient to indicate a partial remission.

9.4 Progression occurs when any lesion increases in size or any new lesions appear, regardless of what the response of the other lesions may have been.

10. REGISTRATION AND RANDOMIZATION OF PATIENTS

A patient is registered and randomized after the local pathology review by telephoning to the E.O.R.T.C. Data Center (tel: Brussels 538.65.33) from 9.00 a.m. to 5.00 p.m., Monday through Friday. The date of registration is the date of making this telephone call. At this time the following information is requested:

1. Protocol number (62761).
2. Patient’s age (15–59 or 60–75 yr).
3. Cell type (see below).
4. Patient’s name.
5. Institution’s name.
6. Physician’s name.
7. Caller’s name.

The treatment assigned by randomization will then be given.

If registration by telephone is not possible, patients may also be registered by telex: 22773, or by mail:

E.O.R.T.C. Data Center,
Institut Jules Bordet,
1, rue Héger-Bordet,
1000 Bruxelles, Belgium,

by including the information requested above. Stratification will take place on the patient’s age (15–59 or 60–75 yr) and on the following cell types:

1. Angiosarcoma (haemangiendotheliomasarcoma + haemangiofibrocytoma)
2. Fibrosarcoma
3. Leiomyosarcoma
4. Liposarcoma
5. Neurofibrosarcoma
6. Rhabdomyosarcoma
7. Synovial cell sarcoma
8. Undifferentiated sarcoma
9. Mesothelioma
10. Unclassified or miscellaneous.

Thus, Kaposi’s sarcoma, chondrosarcoma, and osteosarcoma, will be excluded. No stratification will be done on extent of disease or anatomic staging.

11. CENTRAL PATHOLOGY REVIEW

There will be a central pathology review with grading of the histology by the Department of Pathology, University Hospital, Utrecht, The Netherlands. The following material and information is requested:

11.1 Clinical data: age, sex, localization of tumor, number of samples taken for histopathological exam, original macro and micro report.

11.2 Six unstained sections of each sample (or paraffin blocks, by preference tumor tissue in fixation fluid).

11.3 The central Pathology Review would be very grateful to receive tumor tissue, fixed or embedded, for electronmicroscopy. It can be processed and studied by the University Hospital in Utrecht.

11.4 If additional biopsies during the course of the study are done or if an autopsy is performed, the Central Pathology Review would be very interested to study this material as well.

12. SUBMISSION OF FORMS

All forms are to be sent in duplicate to the E.O.R.T.C. Data Center, Institut Jules Bordet, 1, rue Héger-Bordet, 1000 Bruxelles, Belgium.

The schedule for submission of forms is as follows:

1. On-study form (Form II)

Send within one week of the patient’s entry on study (randomization).

2. Chemotherapy form (Form V)

Send after completion of each 4 week cycle of chemotherapy.

3. Flow sheet (Form VII)

The first flow sheet should be filled out prior to the first cycle of chemotherapy and sent with the on-study form. It should also be filled out at 8 weeks, 4 months, and then every 3 months thereafter.

4. Measurement form (Form VIII)

The schedule is the same as for the flow sheet. The first measurement form should be filled out prior to the first cycle of chemotherapy
and sent with the on-study form. It should also be filled out at 8 weeks, 4 months, and then every 3 months thereafter. The location of the lesion is identified by the grid on page 2 of the measurement form. The location of any lesion is identified by a letter (horizontal axis) followed by a 2 digit number (vertical axis). Initially the coordinates relating to the center of the lesion should be used. When following a lesion, the same coordinates must always be used to identify the lesion even if the lesion changes in size and shape. In the case of multiple lesions in one area, the largest lesion should be indicated on the form.

5. **Summary form (Form IX)**

To be sent in whenever the patient goes off study for any reason.

Patients who go off study while still alive should be followed until death whenever possible and the Data Center notified of the date of death, cause of death, and localization of disease if the cause of death is malignant disease, upon the death of the patient.

**13. STATISTICAL CONSIDERATIONS**

Three hundred patients will be entered on study and randomized to receive either the single \( S_1 \) or cyclical \( S_2 \) dose schedule. While a remission rate of approximately 50% is expected on each arm, 150 patients on each arm is sufficient to detect a difference of 15% in the two response rates. \( (\alpha = 0.05, \beta = 0.20) \). If the remission rate is approximately 50% then 75 responding patients on each arm is sufficient to detect a ratio of 1:5:1 in the mean (or median) length of the time to progression of the two treatments if all responding patients are followed until progression \( (\alpha = 0.05, \beta = 0.20) \)

This assumes that the time to progression follows an exponential distribution.

The expected duration of the trial depends on the number of (responding) patients entered each year and the distribution of the time to recurrence. If 100 evaluable patients are entered each year and 50% respond, then it will take 3 years to enter the required number of patients. However, to do an analysis at the error rates given above, the length of the trial will depend on the length of the longest time to progression. If the median length of remission is one year on \( S_1 \), then in order to detect a median length of remission of 1.5 years on \( S_2 \), the shortest duration of the trial will occur if patients are entered for 4-7 years. After this time a definitive analysis can be made.

**14. ADMINISTRATIVE RESPONSIBILITIES**

This study is a joint effort between the E.O.R.T.C. Soft Tissue Sarcoma Cooperative Group:

Nederlands Kanker Instituut, Amsterdam: Dr. R. Somers.
Rotterdamsch Radiotherapeutisch Instituut, Rotterdam: Dr. R. Treurniet, Dr. J. H. Mulder.
Academisch Ziekenhuis, Leiden: Dr. A. T. van Oosterom.
Academisch Ziekenhuis, Utrecht: Dr. H. M. Pinedo.
Radboud Ziekenhuis, Nijmegen: Dr. Th. Wagener.
Ziekenhuis Westeinde, 's-Gravenhage: Dr. G. Booy.
Institut de Cancérologie et d’Immuno-génétique, Hôpital Paul-Brousse, Villejuif, France 94800: Prof. C. Jasmin.
Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy: Dr. G. Bonadonna.
Innere Klinik und Poliklinik (Tumorfor- schung) der Ruhruniversität Essen, Germany: Prof. Dr. C. G. Schmidt.
Zentrum für Innere Medizin, Robert Bosch-Krankenhaus, Stuttgart, Germany: Prof. Dr. W. Wilmanns.
Christie Hospital, Cancer Research Campaign, Manchester, United Kingdom: Prof. D. Crowther.
Institut Jules Bordet, 1000 Bruxelles, Belgium: Dr. Y. Kenis and Dr. M. Staquet. Swiss Group for Clinical Cancer Research, 62 rue de Carouge, 1205 Genève: Dr. H. J. Senn.
University Hospital, 9000 Ghent, Belgium: Dr. A. De Schryver.

**Study Coordinator**

Dr. H. M. Pinedo, Oncology Unit, Department of Internal Medicine, Academisch Ziekenhuis, Utrecht, The Netherlands.
Telephone: 030-379111 or 372202.

**Central Pathology Review**

Professor G. Bras and Professor J. V. Unnik, Department of Pathology, University Hospital, Utrecht, The Netherlands.
Telephone: 030-379111.
REFERENCES


