Adjuvant and neoadjuvant treatment in STS

NAIYARAT PRASONGSOOK, MD, MS.
MEDICAL ONCOLOGY UNIT,
PHRAMONGKUTKLAO HOSPITAL
Disclosures

- I have no disclosures
OUTLINE

- Introduction
- Rational of adjuvant chemotherapy
- Adjuvant chemotherapy
  - Clinical studies
- Neoadjuvant chemotherapy
  - Clinical studies
- Guidelines
- Conclusions
Introduction

- Standard treatment for most G2/3: surgery and radiation

- For patients with high risk features:
  - Disease recurrence and mortality $\geq 50\%$

- Data supporting chemotherapy for localized disease is not universally accepted

- However, systemic therapy for advanced disease is safe and effective
Soft tissue sarcoma

Frequency by location

- 50% occur in extremities
- 25% occur in the abdomen, pelvis, or chest
  - 15% of these are retroperitoneal
- 10% occur in head and neck
Soft tissue sarcoma

Sites of metastasis

- **Lung**: most common
  - But rare with GIST, desmoid tumor, DFSP
- **Liver**: GIST, Leiomyosarcoma, Angiosarcoma
- **Fat**: Myxoid liposarcoma
- **Brain**: Angiosarcoma, Alveolar soft part sarcoma
- **Lymph nodes**: Epithelioid sarcoma, SDH-deficient GIST, Clear cell sarcoma, Angiosarcoma

DFSP: Dermatofibrosarcoma protuberrans

SDH: Succinate dehydrogenase
Soft tissue sarcoma

- Decrease local recurrence rate
- Eradicate microscopic metastasis
- Improve survival

Large + high grade + localized

RFS, OS are poor

Objective of adjuvant chemotherapy

RFS: Release free survival

OS: Overall survival
important factors

Making decision on adjuvant chemotherapy

The appropriate patient

The tumor with sufficient risk of recurrence/metastasis

The most effective chemotherapy agent(s)
Prognostic factors

**PATIENT FACTOR**
- Good performance status ($p < 0.0001$)
- Young age ($p < 0.0045$)
- Organ function

**TUMOR FACTOR**
- High grade
- Aggressive histology
- Short DFI
- Large primary (>5 cm)
- Deep, subfascial tumor
- < R0 resection

Bonvalot et al, Lancet Oncology 2016
Soft-tissue Sarcomas
Subtype Sensitivity to Systemic Agents

**Very sensitive** histologies:
- PNET/Ewing’s, Rhabdomyosarcoma, DSRCT, GIST, Angiosarcoma, Myxoid/round cell sarcoma
- Desmoid Tumors, PVNS, DFSP

**Intermediately sensitive** histologies:
- Fibrosarcoma, Leiomyosarcoma, Unclassified Pleomorphic Sarcoma, Extraskeletal Osteosarcoma
- Alveolar soft-parts sarcoma, solitary fibrous tumor, extraskeletal myxoid chondrosarcoma, PEComa

**Minimally sensitive** histologies:
- Hemangioendothelioma, Epithelioid sarcoma, DD liposarcoma, MPNST

**Resistant** histologies:
- Clear-cell sarcoma, GI leiomyosarcoma
**Advanced STS**

**SINGLE AGENT DOXORUBICIN EFFICACY**
- 45 mg/m² = ORR 18%
- 60 mg/m² = ORR 20%
- 75 mg/m² = ORR 37%
- Various = ORR 5-25%


**SINGLE AGENT IFOSFAMIDE EFFICACY**
- 6 gm/m² = ORR 10%
- 8 gm/m² = ORR 17%
- 10 gm/m² = ORR 21%
- 14 (infusion) = ORR 29%
- 14 (bolus) = ORR 57%

Patel, et al. JCO 1977
Routine component of treatment for sarcoma in CHILDREN (i.e. Rhabdomyosarcoma, Ewing sarcoma)

However, this role for common adult subtypes of soft tissue sarcoma (i.e. Liposarcoma, Synovial sarcoma, and Leiomyosarcoma) remains controversial due to the complexity of the group of diagnoses involved
  • Even though, there were over 20 RCTs and 2 meta-analysis
ADJUVANT TRIALS

Soft tissue sarcoma
LARGE CLINICAL STUDIES FOR ADJUVANT CHEMOTHERAPY IN ADULT STS

- Sarcoma Meta-Analysis Collaboration (SMAC)
- Updated Meta-analysis
- Pooled analysis of the EORTC trials

Randomized Adjuvant Chemotherapy for STS

Sarcoma Meta-Analysis (n=1,568)

- STS with resection ± RT
- Large sample size
- Doxo (50-90 mg/m²) + other chemotherapy (844 pts)
- 67% High grade
- RFS (10%) benefit from chemotherapy
- Trend toward OS benefit from chemotherapy

Randomized Adjuvant Chemotherapy for STS

Sarcoma Meta-Analysis (n=1,568)

Limitations:

- Broad dose range for doxo and NO ifosfamide
- Accrual >17 years (1973-1990)
- Included 5% low grade (28% unknown)
- 51% unknown histology subtype (chemoresistant histology?)
- 18% patients with tumor <5 cm
- No subset significance by anatomic site, grade, size, histology
- 47% had RT

Patients who benefit the most of chemotherapy:

- Man 30-60 years old
- Extremity non-leioS
- 5-10 cm
- Grade?

There were no consistent evidence of a difference in any endpoint;
- age, gender, stage, site, grade, histology, extent of resection, tumor size, exposure to RT
- However, the strongest evidence of a beneficial effect on survival was shown in the subset of patients with extremity and truncal sarcomas
- 7% Absolute benefit in OS at 10 years for adj. chemotherapy arm

SMAC (1997)

Randomized Adjuvant Chemotherapy for STS

Updated Meta-analysis (n=1,953)

- STS with resection ± RT
- Large sample size
- Doxo (50-90 mg/m²) ± Ifos (5-9 gm/m²)
- OS (11%) and RFS (12%) benefit from chemotherapy (Doxo + Ifos)

Randomized Adjuvant Chemotherapy for STS

Updated Meta-analysis (n=1,953)

Limitations:

- Broad dose range for doxo and ifos
- 4 new studies added ifos
- Accrual >23 years (1973-1996)
- Included intermediate and low grade
- Include any STS histology subtype (chemoresistant? GIST?)
- No subset analysis by anatomy site, grade, size, histology
- Unreported disease-specific survival

Updated meta-analysis from SMAC (2008)

- The absolute risk reduction for doxorubicin + Ifosfamide was 11% (30 vs 41% risk of death)
- Benefit could not be shown for doxo alone (OR 0.84, 95% CI 0.68-1.03)
- The fundamental importance of IFOSFAMIDE in the adjuvant treatment of sarcomas overall
- However, it did not include data from the single largest negative trial

<table>
<thead>
<tr>
<th>Experiment</th>
<th>SMAC (Sarcoma Meta-Analysis Collaboration) (1997) (n = 1,568)</th>
<th>Updated meta-analysis (2008) (18 RCTs, n = 1,953)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment</td>
<td>Post op chemo alone (doxorubicin-containing regimen, &lt;5% adding Ifosfamide) vs Surgery alone</td>
<td>- 5 of 18 studies: Doxorubicin + Ifosfamide Others: Doxo alone, or in combination with other agents</td>
</tr>
<tr>
<td>Local recurrence free interval</td>
<td>HR 0.73 (95% CI 0.56-0.94)</td>
<td>OR 0.73 (95% CI 0.56 - 0.94)</td>
</tr>
<tr>
<td>Distant recurrence free interval</td>
<td>HR 0.7 (95% CI 0.57 - 0.85)</td>
<td>OR 0.67 (95% CI 0.56 - 0.82)</td>
</tr>
<tr>
<td>Overall recurrence free interval</td>
<td>HR 0.75 (95% CI 0.64-0.87)</td>
<td>-</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>HR for death 0.89 (95% CI 0.76-1.03)</td>
<td>- Doxo + Ifos: OR for death 0.56 (95% CI 0.36 - 0.85) - Doxo alone: OR 0.84 (95% CI 0.68 - 1.03)</td>
</tr>
</tbody>
</table>

A pooled analysis of individual patient data from 2 largest adjuvant trials of Doxo + Ifosfamide (n = 819)
- compare to surgery alone

Adjuvant chemotherapy **WAS NOT** associated with a significant survival benefit
- Except, in subset of patients undergoing R1 resection

Multivariate analysis
- Tumor size, histology subtype, and grade **WERE NOT** associated with any PFS or OS from adjuvant chemotherapy

# Soft-tissue Sarcomas

**Absolute Risk Reduction from Adjuvant Chemotherapy**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Local Recurrence</th>
<th>Distant Recurrence</th>
<th>Any Recurrence</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>3% (1-7%)</td>
<td>9% (4-14%)</td>
<td>9% (4-14%)</td>
<td>5% (6-21%)</td>
</tr>
<tr>
<td>Doxorubicin + Ifosfamide</td>
<td>5% (1-12%)</td>
<td>10% (1-19%)</td>
<td>12% (3-21%)</td>
<td>11% (3-19%)</td>
</tr>
<tr>
<td>Doxorubicin OR Doxorubicin + Ifosfamide</td>
<td>4% (0-7%)</td>
<td>9% (5-14%)</td>
<td>10% (5-15%)</td>
<td>6% (2-11%)</td>
</tr>
</tbody>
</table>

**Absolute Risk Reduction (95% CI)**

Pervaiz, Cancer 113:573-581
The role of adjuvant chemotherapy remains uncertain and controversial.

In spite of positive results in updated meta-analysis from SMAC, it is difficult to recommend adj chemo for doxo-based (it appears to be small, no more than 5% absolute increase in survival at 5 to 10 years).

NCCN/ESMO guideline:
- Option for high risk patients
- 5-6 cycles of doxo (75 mg/m² per cycle in split bolus doses or continuous infusion over 3 days) + Ifosfamide (9-10 gm/m² in split doses over 3 hours per day for 3-4 days), with mesna.

Taking into consideration:
- PS, comorbid (esp. age), site of disease, histology subtype (eg. younger patients with synovial sarcoma or the round cell version of myxoid liposarcoma)
SUMMARY FOR ADJUVANT CHEMOTHERAPY FOR STS

- Risk vs benefit

- Discussion in the context of expected treatment-related toxicities
  - potential sterility in younger people
  - cardiomyopathy
  - renal damage
  - second cancers
  - overall impairment of QOL
NEOADJUVANT THERAPY

Soft tissue sarcoma
Soft tissue sarcoma

- Large + high grade + localized

Objective of Neoadjuvant chemotherapy

- Alleviate tumor-related pain and suffering
- Down-stage unresectable tumor to enable resection
- Determine individual tumor chemosensitivity
A randomised phase II study on neo-adjuvant chemotherapy for ‘high-risk’ adult soft-tissue sarcoma

E. Gortzak\textsuperscript{a}, A. Azzarelli\textsuperscript{b}, J. Buesa\textsuperscript{c}, V.H.C. Bramwell\textsuperscript{d}, F. van Coevorden\textsuperscript{a,*}, A.N. van Geel\textsuperscript{e}, A. Ezzat\textsuperscript{f,1}, A. Santoro\textsuperscript{b}, J.W. Oosterhuis\textsuperscript{e}, M. van Glabbeke\textsuperscript{g}, A. Kirkpatrick\textsuperscript{g}, J. Verweij\textsuperscript{e}, the E.O.R.T.C. Soft Tissue Bone Sarcoma Group and the National Cancer Institute of Canada Clinical Trials Group/Canadian Sarcoma Group

\textsuperscript{a}The Netherlands Cancer Institute/ Antoni van Leeuwenhoekhuis, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
\textsuperscript{b}Istituto Nazionale per lo studio e la cura dei tumori, Milano, Italy
\textsuperscript{c}Hospital General de Asturias, Oviedo, Spain
\textsuperscript{d}London Regional Cancer Centre, London, Ontario, Canada
\textsuperscript{e}Rotterdam Cancer Institute (Daniel den Hoed kliniek) and University Hospital, Rotterdam, The Netherlands
\textsuperscript{f}King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia
\textsuperscript{g}European Organisation for Research and Treatment of Cancer, Data Centre, Brussels, Belgium

Received 8 December 2000; accepted 14 December 2000

- 134 evaluable patients
- Randomisation
  - 3 courses of CT + surgery
  - Surgery alone
A randomised phase II study on neo-adjuvant chemotherapy for ‘high-risk’ adult soft-tissue sarcoma

<table>
<thead>
<tr>
<th>Stratification according to risk factor</th>
<th>No preoperative chemotherapy n (%)</th>
<th>Preoperative chemotherapy n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 cm, group II/III</td>
<td>18 (24)</td>
<td>18 (24)</td>
</tr>
<tr>
<td>&gt;8 cm, group I</td>
<td>6 (8)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>&gt;8 cm, group II/III</td>
<td>31 (41)</td>
<td>33 (44)</td>
</tr>
<tr>
<td>Inadequate surgery, group I/II</td>
<td>13 (17)</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>7 (9)</td>
<td>5 (7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution according to localisation</th>
<th>No preoperative chemotherapy n (%)</th>
<th>Preoperative chemotherapy n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbs</td>
<td>61 (81)</td>
<td>62 (83)</td>
</tr>
<tr>
<td>Head/neck</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Trunk</td>
<td>7 (9)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>3 (4)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>No preoperative chemotherapy n (%)</th>
<th>Preoperative chemotherapy n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible</td>
<td>67 (89)</td>
<td>67 (89)</td>
</tr>
<tr>
<td>Ineligible</td>
<td>8 (11)</td>
<td>8 (11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for ineligibility</th>
<th>No preoperative chemotherapy n (%)</th>
<th>Preoperative chemotherapy n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroperitoneal localisation</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>T. category</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Age</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Other histology</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Grade unknown</td>
<td>–</td>
<td>1</td>
</tr>
</tbody>
</table>

Total | 75 (100) | 75 (100) |
A randomised phase II study on neo-adjuvant chemotherapy for ‘high-risk’ adult soft-tissue sarcoma

Response to chemotherapy ($n=49$)

<table>
<thead>
<tr>
<th>Response</th>
<th>$n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>26 (53)</td>
</tr>
<tr>
<td>Progression</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
</tr>
</tbody>
</table>

At a median follow-up of 7.3 years:

– 5 year disease-free survival is 52% for the no chemotherapy and 56% for the chemotherapy arm ($P=0.3548$).

– 5 year overall survival for both arms is 64 and 65%, respectively (standard error 7%) ($P=0.2204$).

Eur J Cancer 2001; 37(9): 1096-103
Improved overall survival by adding regional hyperthermia to neo-adjuvant chemotherapy (NAC) in patients with localized high-risk soft tissue sarcoma (HR-STS):

Long-term outcomes of the EORTC 62961/ESHO randomized multicenter phase III study (NCT00003052)


Co-ordinated by:
Dept. Medical Oncology. University Hospital of the LMU Munich – Campus Grosshadern.
Munich, Germany
Regional Hyperthermia: Clinical application

ESHO quality assurance guidelines for regional hyperthermia

*Bruggmoser et al. Strahlenther Onkol 2012*

Neo-Adjuvant Chemotherapy (NAC): ifosfamide (6g/m²)+doxorubicin (50 mg/m²)+etoposide (250 mg/m²)

Regional Hyperthermia (2 RHT/per NAC cycle).
Local PFS

HR 0.65; 95%CI, 0.49-0.86; p=0.002

DFS

HR 0.73; 95%CI, 0.54-0.98; p=0.04

Median F/U 11.3 years

EIA: etoposide/ifos/doxo
RHT: regional hyperthermia

Among patients with localized high-risk STS

- Addition of regional hyperthermia to me-adjuvant chemotherapy;
  - Increase survival
  - Increase local PFS

Summary: EORTC 62916/ ESHO


NCCN Guidelines Version 2.2019

- These results need to be confirmed in large cohort studies
- The use of RHT with preoperative chemotherapy is not recommended in the guidelines
FULL-DOSE NEOADJUVANT ANTHRACYCLINE+IFOSFAMIDE CHEMOTHERAPY IS ASSOCIATED WITH A RFS AND OS BENEFIT IN LOCALIZED HIGH-RISK ADULT STS OF THE EXTREMITIES AND TRUNK WALL: INTERIM ANALYSIS OF A PROSPECTIVE RANDOMIZED TRIAL.

Gronchi A; Ferrari S; Quagliuolo V; Martin Broto J; Lopez Pousa A; Grignani G; Ferraresi V; Basso U; Blay JY; Tendero O; Valverde C; Rutkowski P; Merlo FD; Fontana V; Marchesi E; Ledesma P; Dei Tos AP; Bagué S; Coindre JM; Morosi C; Stacchiotti S; Donati DM, Palassini E; Palmerini E; De Sanctis R; Picci P; Bruzzi P and Casali PG
ESMO 2016/ ASCO2018: Significant Survival Gains From Neoadjuvant Chemotherapy for High-Risk Soft Tissue Sarcoma

- Multicenter study, 287 enrolled patients with high risk (deep seated, high grade, or ≥5cm) soft tissue sarcoma of the trunk or extremities

- Randomized 1:1 (preoperative chemotherapy)
  - Epirubicin (120mg/m2) + Ifosfamide (9g/m2) x 3 cycles vs
  - Five histologically tailored regimens;
    - Gemcitabine + Docetaxel (undiff pleomorphic sarcoma)
    - Trabectedin (high grade myxoid liposarcoma)
    - High dose prolonged-infusion ifosfamide (synovial sarcoma)
    - Etoposide + Ifosfamide (MPNT)
    - Gemcitabine + dacarbazine (leiomyosarcoma)

Gronchi et al, Lancet Oncol 2017
**Histology-tailored Neoadjuvant STS**

- Median follow up of 12.3 months
- Patients with induction Epirubicin + Ifosfamide showed significantly higher probability of:
  - RFS at 46 months compared to patients with histology-driven regiment
    - 62% for standard chemo vs 38% for histotype-specific therapy; (HR 1.95, 95%CI 1.12-3.19; p-value = 0.004)
  - OS (HR 0.89 vs 0.64, p-value=0.033)

Gronchi et al, Lancet Oncol 2017
Standard versus histotype-tailored chemotherapy in the five different histology subtypes

<table>
<thead>
<tr>
<th>Histology Type</th>
<th>Events/patients</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated pleomorphic sarcoma</td>
<td>28/97</td>
<td>2.17 (0.98–4.80)</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>17/70</td>
<td>1.85 (0.65–5.22)</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumour</td>
<td>12/27</td>
<td>2.38 (0.69–8.19)</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>7/28</td>
<td>2.28 (0.27–12.66)</td>
</tr>
<tr>
<td>High-grade myxoid liposarcoma</td>
<td>8/64</td>
<td>1.03 (0.24–4.39)</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td><strong>70/286</strong></td>
<td><strong>1.95 (1.12–3.19)</strong></td>
</tr>
</tbody>
</table>

Gronchi et al, Lancet Oncol 2017
Conclusions

Neoadjuvant Doxorubicin + Ifosfamide

- Expedites administration of adjuvant therapy
- Data support anthracycline + ifosfamide as the optimal regimen
- Useful for organ-sparing approaches
- May minimize XRT and surgical fields
- Rapidly alleviates pain in chemosensitive tumors
There is no consensus on the current role of adjuvant Chemotherapy

Adjuvant Chemotherapy can be proposed as an option to the high-risk individual patients for a shared decision making with the patients [II, C]

- High-grade
- > 5cm tumor

Neoadjuvant chemotherapy

- Anthracyclines plus ifosfamide for at least 3 cycles can be viewed as an option;
- The high-risk individual patient, for shared decision making [II, C]

Stage IIIA-IIIIB: (T >5 cm, G2/3)

- Surgery\(^k,t\) to obtain oncologically appropriate margins
  - or
  - Preoperative RT\(^n\) (category 1)
    - or
    - Preoperative chemoradiation\(^n,u\) (category 2B)
    - or
    - Preoperative chemotherapy\(^u,v\) (category 2B)

  → Surgery\(^w\) to obtain oncologically appropriate margins

  → RT\(^n\) (category 1) or
    - RT\(^n\) + adjuvant chemotherapy\(^u\) (category 2B)

  → Consider adjuvant chemotherapy\(^n,u\) (category 2B)

  → RT\(^n\) or
    - RT\(^n\) + adjuvant chemotherapy\(^u\) (category 2B)
Future directions: adjuvant / neoadjuvant

- Non-overlapping neoadjuvant + adjuvant regimens
  - Histology-tailored systemic regimens + doxo/ifos
- Longer durations of therapy
- Addition of olaratumab to doxo/ifos


- Maintenance therapy (pazopanib, trabectedin, eribulin, olaratumab, low dose chemotherapy)
- Is survival the best endpoint for neoadjuvant/ adjuvant systemic therapy?