Ten year follow up of a randomized study of Viscum album Fermentatum Pini vs Etoposide in osteosarcoma in complete surgical remission after second relapse

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Disclosure: Iscador AG supported this study
Incidence of primitive bone sarcoma:
2 - 3 / 1 M people

Proportion of osteosarcoma: 45 %

Median age at first diagnosis: 15 years

5-year Overall Survival (OS):
- without antineoplastic therapy: 10 %
- after surgery / chemotherapy: 70 – 80 %
  - Doxorubicine, Methotrexate, Cisplatin, Ifosfamide

5-year Post Relapse Disease Free Survival (PRDFS): 6-27%
Istituto Orthopedico Rizzoli (IOR) experience

1) 620 patients with localized osteosarcoma of an extremity treated between 1985-1998
(Bacci G., Acta Oncol 2005, 44(7) 748-55)

- 235 of 620 patients relapsed
- Average time interval between
  - diagnosis and 1\(^{\circ}\) relapse: 25.4 months
  - 1\(^{\circ}\) and 2\(^{\circ}\) relapse: 12.7 months
  - 2\(^{\circ}\) and 3\(^{\circ}\) relapse: 11.8 months
  - 3\(^{\circ}\) and 4\(^{\circ}\) relapse: 15.2 months
  - 4\(^{\circ}\) and 5\(^{\circ}\) relapse: 4.0 months

Only 14/120 (11.6\%) pts who had a second relapse had a prolonged survival
2) Survival after second and subsequent recurrences in osteosarcoma: a retrospective multicenter analysis  Tirtei E et al 2017 Tumori May1 tj:5000636

60 patients with osteosarcoma after second relapse (2003-2013)

5 yrs Overall survival 22%

5 years Overall Survival after Complete Surgical Remission after 2° relapse was 33,4%

Lungs metastases vs other metastatic site: 5 yrs OS 33,6% vs 5%

84% had a post second relapse interval <12 ms.
16%> 12 ms PRDF
Actual treatment of relapsed patients

- **Early first relapse** (≤ 24 months from diagnosis)
  - Surgery (when feasible plus chemotherapy HDIFO, Gem/docetaxel)

- **Late first relapse** (> 24 months from diagnosis)
  - Limited disease: only surgery
  - Extended disease: HDIFO, Gem/docetaxel from 2012

- **Second relapse**
  - Surgery whenever possible
  - Chemotherapy (HDIFO, Gem-Docetaxel from 2012)
  - Further experimental drugs

2007: in high-risk patients free from disease after surgery: w/s or oral etoposide, Interferon.
Rationale for oral etoposide in osteosarcoma

- Topoisomerase II inhibitor
- Employed in several tumors, p.o. or i.v.
  - lymphomas, lung cancer, ovarian cancer, Ewing's sarcoma
- Off-label as "adjuvant" post relapse in bone sarcoma
- Well tolerated
- Only one trial published (Kebudi et al., Pediatr Blood Cancer 2004; 42:320-4)
  - Remissions in 14% of 21 pediatric sarcoma patients (age 3-16 years)
Immunotherapy in Osteosarcoma: the past

1) Interferon Alfa: utilized in '60 at Karolinka Institute in pre Chemotherapy era.

2) EURAMOS 1: MAP+/•Pegilated Interferon in HG osteosarcoma Gresponder
Viscum (Mistletoe)

- Mistletoe (Viscum) is a semiparasitic plant that has been used for centuries in popular medicine (Greek, Druids) and it is one of the most prescribed drugs among cancer patients in Europe: prescribed in 60% of German speaking language countries. Not available commercially in the United States and are not approved as a treatment for people with cancer. Available in Italy as well. Over 1200 papers on mistletoe/Viscum.

- The use of mistletoe as a treatment for people with cancer has been investigated with improved survival and/or quality of life but nearly all of the studies had major weaknesses that raise doubts about the reliability of the findings. Its metabolite lectins, viscotoxin polysaccharides have immuno stimulant, cytotoxic activities in preclinical studies.

- Viscum Album grows on different trees and different type of Viscum (Viscum P from Pine, Viscum M from Mali etc). It is usually administrated subcutaneously 2 or 3 times /week, but iv, intratumoral administration have been described.

- Iscador is Viscum Album Fermentatum according to a procedure described by Steiner R.
Rationale for *Viscum album* fermentatum Pini

- **Immunomodulating activity**
- Increase of NK cells, T-lymphocytes, macrophages
  - Apoptotic activity (in vitro)
- **Lukasklinik Arlesheim/Switzerland**
  - Positive outcomes after surgery in 13 patients with bone sarcoma
- **IOR: Individual therapy attempts**
  - 5 osteosarcoma pts. after 2° relapse
  - *V. album* fermentatum Pini treatment over 12 months
  - Average DFS 18 months
  - Very well tolerated
Study Design

Pts Disease Free after Second relapse

RANDOMIZATION

18 Patients:
Etoposide 50 mg/m²/d po for 21 d every 28 d for 6 cycles

18 Patients:
Viscum album ferm. Pini 1 vial/sc x 3/wk for 12 months

Study visits at baseline and months 3, 6, 9

Exit visit at month 12
Clinical Endpoints

- Post Relapse Disease free Survival (PRDFS)
  - Primary efficacy parameter: 12-months PRDFS rate
  - Clinical hypothesis: increase from 12% to 40%
  - Treatment arms are independently from each other compared to expected value of 12%

- Quality of Life (QoL)
  - EORTC QLQ-C30 (adults) or PedsQL (juveniles – not shown here)

- Safety / tolerability of etoposide and Viscum album
  - Adverse events, adverse drug reactions

- Immune response to treatment
Study Patients

- Inclusion Criteria
  1. Osteosarcoma / spindle cell sarcoma of bone after second relapse, histologically confirmed
  2. Actually free from metastases or local relapse
  3. Age ≥10 years
  4. ECOG Performance Status 0-2
  5. Adequate bone marrow function, bilirubin, creatinine
  6. No other malignancy prior study entry and during follow up
  7. Last antineoplastic treatment received ≥ 30 days prior to study entry

- Exclusion Criteria
  1. Missing staging criteria showing disease-free condition
  2. Concomitant treatment with immunomodulating drugs
  3. Treatment with etoposide or *Viscum album* prior to study entry
Treatment Regimes

- Etoposide
  - Alkaloid derived from *Juniperus virginia* or *Podophyllum peltatum*
  - 6 cycles of 50 mg/m²/day p.o. for 21 days every 28 days

- *Viscum album* fermentatum Pini (Iscador P)
  - Fermented aqueous extract of *Viscum album ssp. austriacum* grown on pine trees (Iscador® P)
  - 1 vial injected s.c., 3/week for 12 months
  - Dose escalation from 0.01 to 20mg or best tolerated dose
Amended Changes From Original Plan

- Slow recruitment of 3 instead of 12 patients/year
- Decision on early termination of recruitment
- Sample size reduction from 18 patients to 10 patients per treatment arm
- Pre-planned adaptive interim analysis including the first 20 patients is redefined as final analysis
<table>
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<th>Patient Characteristics</th>
<th>Viscum n=9</th>
<th>Etoposide n=11</th>
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<tbody>
<tr>
<td>Male:Female</td>
<td>4:5</td>
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<tr>
<td>Age [years]</td>
<td>28 (18-48)</td>
<td>39 (11-66)</td>
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<td>Interval from primary disease [years]</td>
<td>4.0 (1.5-10.5)</td>
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<td>median DFS 1° interval [months]</td>
<td>19,1 (2-40)</td>
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<td>DFS 2° interval [months]</td>
<td>21.1 (3-82)</td>
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<td>Time from 2° relapse to baseline [weeks]</td>
<td>13.9 (0.9-76.6)</td>
<td>7.6 (1.9-24.6)</td>
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</table>
Quality of Life – EORTC QLQ-C30

- Selected Scales – Mean Change from Baseline

- Global Health Status / QoL
- Insomnia
- Fatigue
- Pain
- Insomnia
Quality of Life – EORTC QLQ-C30

- All Scales – Change from Baseline
RESULTS 31.12.2017

From 2007 to 2011: pts enrolled ITT 20
Evaluable for response 19

9 patients enrolled in Viscum Arm
11 patients enrolled in Etoposide arm

Median follow up 84 months (1-122)
Median age 33.9(11-65)
F:M=11:9

1 year Post Relapse DFS of Viscum 55,6% compared to historical 12% rate: (P = 0.0041)
1 year PRDFS of Etoposide 27,6%.
Post Relapse Disease Free Survival

- **PRDFS Rate after 12 months**
  - Binomial estimate [percentage ± 95% confidence interval]

**Intention to treat analysis**
- Viscum: 5 of 9 patients, $p_{12\%} = 0.00412$
- Etoposide: 3 of 11 patients, $p_{12\%} = 0.27239$

**Complete case analysis**
- Viscum: 5 of 9 patients, $p_{12\%} = 0.00412$
- Etoposide: 2 of 10 patients (1 drop-out), $p_{12\%} = 0.68345$
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Post Relapse Disease Free Survival

- Post-Trial Follow Up

Hazard Ratio
HR=0.287
CI=(0.087-0.944)
p=0.0399
10 years OS forecast rate 66.7% Viscum vs 36.4% Etoposide

Hazard Ratio
HR=0.396
CI=(0.102-1.535)
p=0.1802

5-year OS
VA-E=66.7%
(0.282-0.878)
Etop=36.4%
(0.112-0.627)
OR=0.29
CI=(0.40-35.49)
p=0.189
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<td>Median OS</td>
<td>Viscum 104 (17-122)</td>
<td>vs Etoposide 42.5 ms (3-110)</td>
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Immune response to Viscum

Lymphocytes count (total Lym, CD3, CD4, CD8, CD16, B) at T0, T3, T6, T9, T12 months in both arms
Conclusions (1)

Limit of small number patients (rare disease)
Etoposide: no significant PRDFS benefit at 1 yr, more side effects
Viscum better PRDFS
OS was not statistically different in both arms due to salvage therapy (surgery) after 3rd relapse.
Conclusions (2)

Evaluate Viscum as maintenance treatment in high risk osteosarcoma patients in Complete Remission

Compare in randomized trial to other more expensive drugs

Interferon
Mifamurtide
Thanks to

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