



ELSEVIER



European Journal of Integrative Medicine ■ (■■■■) ■■■-■■■

European Journal of
**INTEGRATIVE
MEDICINE**www.elsevier.com/eujim

Original article

A randomized study with adjuvant mistletoe versus oral Etoposide on post relapse disease-free survival in osteosarcoma patients

Alessandra Longhi^{a,*}, Erminia Mariani^b, Jürgen J. Kuehn^c^aChemotherapy Division, Istituto Ortopedico Rizzoli, Via Pupilli 1, 40136 Bologna, Italy^bImmunology and Genetics Laboratory, Istituto Ortopedico Rizzoli, Bologna, Italy^cLukas Clinic, Arlesheim, Switzerland

Received 28 December 2008; received in revised form 29 January 2009; accepted 2 February 2009

Abstract

Background: Osteosarcoma is a highly malignant bone tumor affecting mainly adolescents. While it can be cured in approximately 60% of cases with the recommended neoadjuvant chemotherapy, few experimental target drugs are currently available through phases I and II trials for relapsed and inoperable patients. We know from historical controls that the risk to relapse increases after the second relapse. Relapse-free survival then decreases to <20% at 12 months. Oral Etoposide is often used in clinical practice but outside any protocol or evidence of improved survival.

Methods and Materials: *Viscum album fermentatum Pini* (*Viscum*) is a highly popular phytocompound across central Europe with immunomodulatory activity. Encouraged by the preliminary findings of a pilot study that showed a prolonged disease-free survival (DFS) of more than 12 months in four of our five osteosarcoma patients after their second relapse, we started a two-arm randomized study comparing *Viscum album fermentatum Pini* s.c. to oral Etoposide for patients free from disease after their second metastatic relapse. Our aim is to compare the disease-free survival to a historical group of patients at 12 months.

Results: To date, the median follow-up is 9.5 months while the study is in progress. The median DFS is currently 3 months for Etoposide and 8.5 months for *Viscum*. Patients on *Viscum* report a higher quality of life due to lower toxicity, compared to Etoposide.

Conclusion: In-depth study of the immunomodulatory mechanisms of *Viscum* in osteosarcoma patients is required. *Viscum* shows promise as adjuvant treatment in prolonging DFS after a second relapse, while Etoposide does not seem to prolong the DFS in patients after their second relapse. A larger multi-center trial is required to determine efficacy of therapy in osteosarcoma patients. Preliminary data are reported.

© 2009 Elsevier GmbH. All rights reserved.

Keywords: Mistletoe; *Viscum album*; Etoposide; Osteosarcoma; Disease-free survival

Introduction

Osteosarcoma is an aggressive disease, for which neoadjuvant chemotherapy with the four most effective drugs (Doxorubicin, Methotrexate,

*Corresponding author. Tel.: +39 051 6366374;
fax: +39 051 6366277.

E-mail address: alessandra.longhi@ior.it (A. Longhi).

Cisplatin, Ifosfamide) has increased the disease-free survival (DFS) from 10% to 60% at 5 years. Spindle cell sarcoma of the bone (malignant fibrous histiocytoma (MFH), fibrosarcoma, leiomyosarcoma) is usually treated in the same manner and with similar results.

For those patients who relapse, mainly with lung metastases, surgery is still the most effective treatment. Most of the patients relapse a second time and mainly in the lung (40% [1]). In a study from Italian Sarcoma Group (ISG)/Scandinavian Sarcoma Group (SSG) [2], the 3-year DFS after the second relapse in patients who received surgery and chemotherapy for the second relapse was 12% (80% of those patients who relapsed, relapsed again within 1 year). In a recent trial [3] our group evaluated 235 osteosarcoma patients who relapsed after neoadjuvant chemotherapy: 120 (51%) out of the 235 patients had a second relapse with a median interval between second and third relapse of 11.6 months. Of these 120 patients only 14 (11.6%) achieved prolonged remission (mean 33 months, range 2–117 months). Among the other 106 patients, 66 died and 40 went into remission after surgery, but had a third relapse after a median of 11.8 months.

Presently we use four cycles of high-dose Ifosfamide (HDIFO 15 g/m² every 21 days) after the first relapse if the interval from diagnosis to relapse is shorter than 24 months, with surgery whenever possible, or only surgery when the interval is longer than 24 months. After the second relapse we treat patients with surgery whenever possible, followed sometimes by oral Etoposide 50 mg/m² for 21 days every 28 days for six cycles with the aim to prolong the DFS.

Etoposide is a topoisomerase II inhibitor used mainly intravenously in the treatment of several tumors (i.e. lymphomas, lung cancer, ovarian cancer, Ewing's sarcoma) in combination as well as in monotherapy. Some osteosarcoma protocols employ Etoposide i.v. in neoadjuvant schemes usually for poor responders in postoperative treatment with intensification purpose (i.e. the European and American Osteosarcoma Study Group (EURAMOS)). Oral Etoposide is well tolerated and has been more extensively studied in other malignancies. Only one small study on oral Etoposide as monotherapy in osteosarcoma patients has been published [4]. Reported a 15% relapse rate (RR) in sarcoma-relapsed pediatric patients treated with oral Etoposide 50 mg/m² day for 14 days.

Sandri et al. [5] report a successful use of oral Etoposide at 50 mg/m² in children with recurrent ependimomas with 40% RR. Toxicity of oral Etoposide is mild: nausea, leucopenia, alopecia. Hematologic toxicity is one of the main limiting toxicities in second- or third-line chemotherapy in these heavily pretreated patients. Etoposide cannot be given for a longer period due to the risk of secondary hematologic malignancy.

In our institute, we use oral Etoposide 50 mg/m² day for 21 or 14 days, every 28 days for six cycles.

New effective drugs are awaited for the treatment of relapsed osteosarcoma. But so far we have only few options with negligible results. Against the background of above-mentioned facts, the aim of this study is to compare the effectiveness of oral Etoposide with a natural, herbal product, *Viscum album fermentatum* Pini. *Viscum album fermentatum* Pini is a semiparasitic plant derived from *Viscum album* and, as herbal product, is widely used in cancer patients (>60% of tumor patients in Germany and Switzerland).

Viscum album ferm. (Mistletoe, Iscador[®]) is a green shrub and exists in more than one thousand species. *Viscum album* is divided into various subspecies (ssp.), for example, *Viscum album* ssp. *abietis*, *Viscum album* ssp. *austriacum*, etc. with each having its particular host (apple tree, oak, pine). *Viscum album* research has shown that its effects are similar to those of other biological response modifiers in targeting the immune system [6–12]. An up-to-date review on research concerning mistletoe was published by Kienle et al. [13]. It summarizes some promising results in *in vitro*, *in vivo*, and clinical trials.

Main components of the whole plant extract are mistletoe lectins I, II, and III, 6 viscotoxins, and polysaccharides. After water extraction, a fermentation process takes place with *Lactobacillus plantarum*, leading to reduced levels of mistletoe lectins and increased levels of viscotoxins.

Lectins have shown cytostatic activity *in vitro* while viscotoxins have been reported to have cytotoxic activity, and polysaccharides have shown immunomodulatory activity, i.e. an increase in natural killer cell activity [14,15]. The total plant extract is an immunostimulant (increase of natural killer cells, T-lymphocytes, macrophages) and has apoptotic activity (*in vitro*). *Viscum album* ferm. is very well tolerated with low toxicity (local erythema only in 15% of patients). Iscador[®] is one of several

commercial *Viscum album* preparations and on the market since 1917. Most of the research on *Viscum album* focuses on Iscador[®]. No trial exists so far using Iscador[®] in sarcoma patients.

Iscador[®]P (*Viscum album* ssp. *austriacum* (pini)) has low levels of lectins, but increased levels of viscotoxins. As subcutaneous injection it is locally and systemically well tolerated and does not increase body temperature. *Viscum* preparations have also been administered intravenously [16] but subcutaneous injection is more common.

A randomized study compared *Viscum album* ssp. *album* (mali) (Iscador[®] M) versus interferon-alpha versus interferon gamma as adjuvant therapy in high-risk melanoma patients: *Viscum* and both interferons showed the same DFS. However, both did not show a beneficial effect compared to using no adjuvant therapy [17]. A Cochrane review in 2008 of *Viscum album* ferm. reports some benefits on the quality of life in cancer patients but only a limited number of randomized studies of good quality were available [18].

This study compares the DFS in patients at high risk for a further relapse after surgery for a second relapse with a conventional chemotherapy drug (Etoposide) and a non-conventional drug (*Viscum album* ferm.) in use for 80 years in complementary anthroposophic medicine. We compared the DFS of the two study arms with the DFS of a historical cohort of patients.

Another reason to perform the trial was that little published data are available so far concerning the effectiveness of oral Etoposide in sarcoma patients, although it is commonly used in clinical practice.

Material and methods

The protocol design is shown in Fig. 1.

Inclusion criteria

We included patients with histologically confirmed diagnosis of osteosarcoma or spindle cell

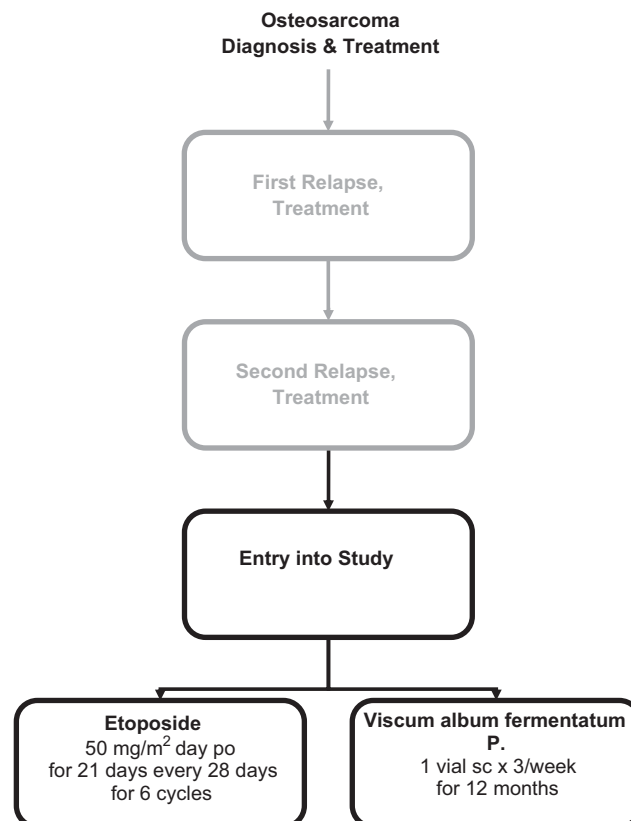


Fig. 1. Study plan.

sarcoma of the bone (MFH, leiomyosarcoma, dedifferentiated chondrosarcoma, fibrosarcoma) after a second relapse, free from metastases and local relapse after surgery for second relapse, age >10 years, ECOG Performance Status <3 (0–2) (Eastern Cooperative Oncology Group [19]), adequate bone marrow function defined as peripheral absolute neutrophils >1500, platelets >100.000, bilirubin <2, creatinine <1.5 × normal value, no other malignancy prior to study entry and during follow-up, last antineoplastic treatment received at least 30 days prior to study entry, signed informed consent.

Exclusion criteria

Patients were excluded from the study if they suffered from bone sarcomas of another histological type (i.e. Ewing's sarcoma), if staging criteria were missing, if they were younger than 10 years, if they have been treated with Etoposide or Viscum album extract prior to study entry, if they received concomitant treatment with drugs having either immunostimulatory or immunosuppressive properties, and if they were pregnant.

Pretreatment investigations

Pretreatment investigations included medical history and physical examination, complete blood count and white blood cell differential count, alkaline phosphatase, evaluation of hepatic and renal functions (creatinine, ALT, AST, GGT, LDH), CT scan of the chest prior to randomization, total bone scan prior to randomization, X-ray, CT, or MRI of the site of primary tumor, ultrasound or CT scan of abdomen, and any other investigations as clinically appropriate.

Evaluation during treatment

In both groups patients visited at baseline and each subsequent month until the third month of treatment, followed by visits every 3 months.

Examinations included physical examination, physical status, body weight, WHO criteria for toxicity of treatment, blood examination, and assessment of quality of life.

Further assessment included the evaluation of total lymphocytes, T, natural killer cells, CD4, CD8, IL2, IL4, IL12, IL15, IFN gamma, and IP10 to

evaluate the balance of Th1/Th2 immune response every 3 months.

Quality of life was assessed by EORTC QLQ-C30 test (European Organisation for Research and Treatment of Cancer, Quality of Life Group, www.eortc.org) at baseline and every 3 months.

Treatment

Patients in the Etoposide group received the following treatment scheme: Etoposide orally 50 mg/m² per day for 21 days, followed by 1-week rest. This schedule is repeated at day 28 over six cycles. If G3/G4 hematological toxicity occurs, the cycle should be shortened to 14 days instead of 21 days. If neutrophils <500, G-CSF can be administered until the count reaches 1000. If patients experience G3/G4 toxicity over two cycles, the total dose of Etoposide is to be reduced to 50%. If patients experience G3/G4 toxicity during the next cycle despite dose reduction, they are withdrawn from treatment.

Patients in the Viscum group were treated according to the following scheme: Iscador[®]P abdominal subcutaneous injections 3 × week. Starting dose 2 × series 0 (0.01–1 mg), followed by 2 × series I (0.1–10 mg) (two boxes = 14 vials); continued treatment throughout the treatment period with series II (1–20 mg). Local reactions at the injection site (redness, slight swelling, itching) with more than 5 cm diameter should be followed by dose reduction, which means injection of half an ampoule (discarding the rest).

Primary endpoint

The primary endpoint of the study is the comparison of DFS after the second relapse at 1 year in both arms. We know from retrospective studies that DFS without treatment is around 12% [2,3]. The aim of this study is to answer the question whether one of the two treatments or both can increase the percentage of 12% DFS to at least 28%, with an expected DFS of 40% at 1 year after surgery for the second relapse.

Secondary endpoints

The secondary endpoint of the study is the comparison of quality of life in both arms measured by the EORTC QLQ-C30 in patients older than 18 years and the POQOL in patients younger than

18 years, respectively (Pediatric Oncology Quality of Life Scale). A further secondary endpoint is the tolerability of Viscum album (Iscador[®]P) subcutaneously.

Statistical evaluation

We want to evaluate as primary endpoint DFS after the second relapse of the two groups. We know from other studies that the average DFS after the second relapse is approximately 12% [2,3]. The expected number of patients recruited per year is 12 ± 2 . The sample size has been calculated based on the hypothesis that one or both drugs can improve the historically documented effect of DFS (12%) to approximately 30–40%. Statistical evaluation demonstrates that we need 18 patients for each arm to get a significance $p = 0.05$ and $b = 0.81$. Based on our experience, we anticipate no dropouts. We will perform an interim analysis for each arm after the first 10 patients. The study will be closed if we do not find a 1 year DFS in at least 2 out of 10 patients in one of the two arms.

Results

Before the start of the protocol, we conducted a pilot study with five patients who had the same eligibility criteria (see above), and who received Viscum album ferm. Pini in four patients and Viscum album ferm. Quercus in one patient. The results are shown in Table 1 and Fig. 2a. The results were satisfactory: patients tolerated the treatment well and had a median DFS of 18 months (6–27).

The protocol was started after Ethical Committee approval in June 2007. By December 2008, 10 patients had been enrolled. Four patients were randomly assigned to the Etoposide arm and six to the Viscum arm. Histology confirmed osteosarcoma in all patients; all patients had undergone surgery because of a second relapse of the disease in the lung. Two patients had undergone surgery in the hip because of a local relapse of the proximal femur as primary localization.

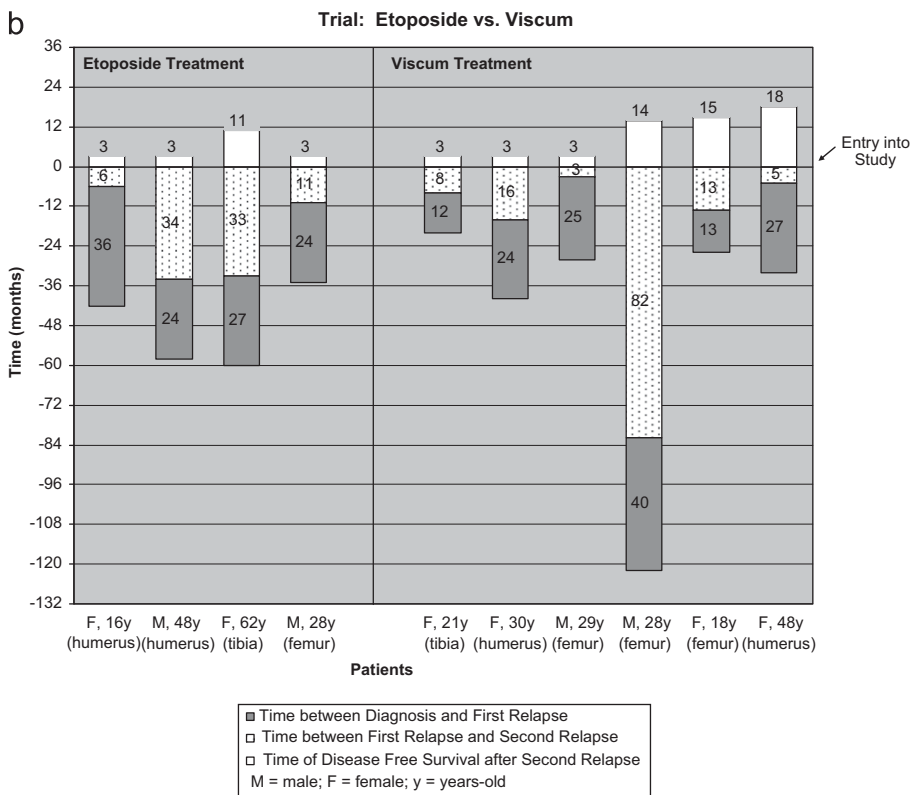
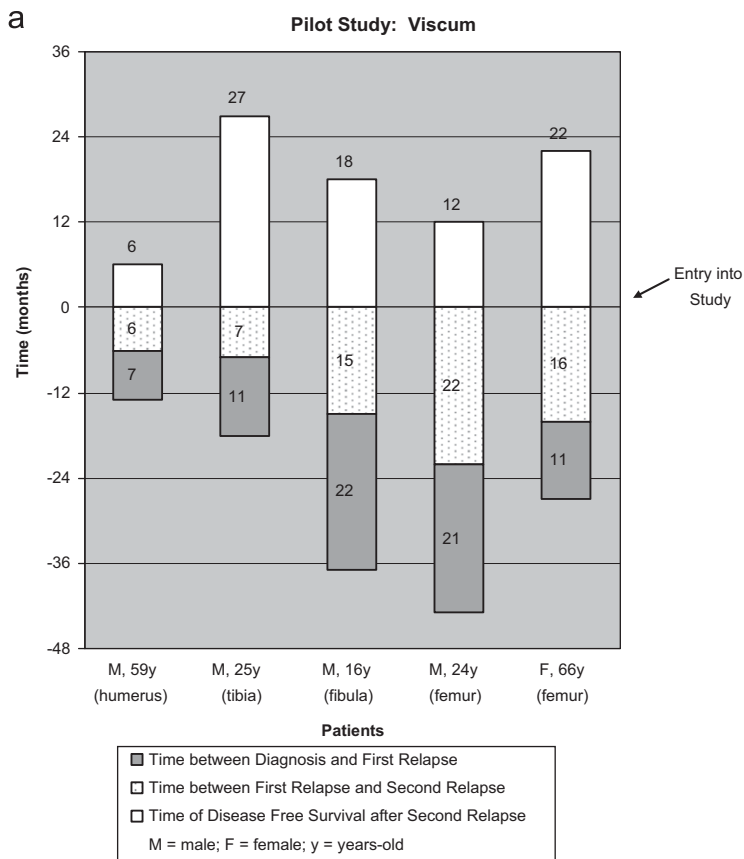
Median age of the patients at study entry was 28.5 years (range 16–62). Median follow-up was 9.5 months (5–14); the ratio of men to women was 4:6.

Table 1

Overview of age, sex, diagnosis, location of carcinoma, time between first and second relapse, therapy, time between first and second relapse, and disease-free survival.

	Age, sex	Location	Time between diagnosis and first relapse (months)	Treatment	Time between first and second relapse (months)	Disease-free survival (months)	Relapse
<i>Pilot study</i>							
Viscum	66, F	Femur	11	HDIFO	16	22	Yes
	24, M	Femur	21	HDIFO	22	12	Yes
	16, M	Fibula	22	HDIFO	15	18	Yes
	25, M	Tibia	11	VP16	7	27	No
	59, M	Humerus	7	None	6	6	Yes (dead)
<i>Trial</i>							
Viscum	48, F	Humerus	27	HDIFO	5	18	No
	18, F	Femur	13	HDIFO	13	15	No
	28, M	Femur	40	HDIFO	82	14	No
	29, M	Femur	25	HDIFO	3	3	Yes
	30, F	Humerus	24	None	16	3	No
	21, F	Tibia	12	HDIFO	8	3	No
Etoposide	28, M	Femur	24	HDIFO	11	3	Yes (dead)
	62, F	Tibia	27	IFN	33	11	No
	48, M	Humerus	24	None	34	3	Yes
	16, F	Humerus	36	HDIFO	6	3	Yes (dead)

HDIFO = high-dose Ifosfamide, IFN = interferon, VP16 = Etoposide.



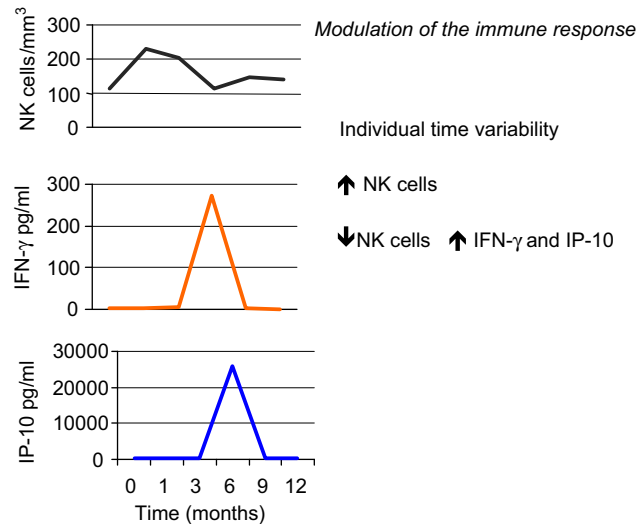


Fig. 3. Preliminary results of natural killer cells (NK cells) and cytokines in four patients treated with *Viscum album fermentatum*. (IFN- γ = interferon gamma; IP-10 = IP-10 chemokine).

The median DFS in the *Viscum* group was 8.5 months (3–18), two patients have received so far only 3 months of treatment, one out of six patients relapsed locally in the area of previous surgery (pelvis). No toxicity was reported except negligible local erythema after s.c. injection.

The median DFS in the Etoposide arm was 3 months (3–11); three out of four patients already relapsed after 3 months (two relapsed in the lung, one had a local relapse at the pelvis) (see Table 1, Fig. 2b).

Toxicity with Etoposide was as follows: G2, G3 hematologic toxicity; granulocyte-colony stimulating factor (G-CSF) was necessary in three patients. Two patients needed dose reduction (14 days instead of 21 days per cycle) due to hematologic toxicity, only one patient needed blood transfusion for anemia G4 (one episode). Three patients remain in treatment (two in the *Viscum* arm and one in the Etoposide arm). The outcome is still open.

Table 1 shows the treatments that patients had received before their second relapse, as well as the previous DFS between diagnosis of osteosarcoma (time of surgery) and first relapse, and the DFS between first and second relapse.

It is important to notice that the median follow-up time is 9.5 months (3–18), and the median DFS

of all groups is 3 months (3–18). The DFS for the Etoposide arm is 3 months (3–11) while the DFS for the *Viscum* arm is 8.5 months (3–18), respectively.

Another important finding is the short DFS with Etoposide even in patients who had previously longer DFS after diagnosis and after the first relapse.

In the *Viscum* arm there was an increase of total T-lymphocytes and of natural killer cells compared to the Etoposide group, but the number is too small to reach statistical significance.

As shown in Fig. 3, we observe the same pattern of response in all four patients: an increase of natural killer cells between the third and sixth months and a subsequent decrease of natural killer cells was registered then, while cytokines increase at 6 months exactly when natural killer cells decrease. We do not know the meaning of this immunomodulatory effect so far.

The analysis of the quality-of-life tests showed a positive trend for *Viscum album fermentatum*. due also to lower toxicity compared to Etoposide.

Conclusions

The treatment of relapsed osteosarcoma patients is problematic especially after a second or further

Fig. 2. (a) Pilot Study: overview of previous relapses and disease-free survival on *Viscum album fermentatum* after the second relapse. (b) Comparative trial: overview of previous relapses and disease-free survival on Etoposide versus *Viscum album fermentatum* after the second relapse.

relapse because there is no effective adjuvant treatment besides surgery. In addition to this, heavily pretreated patients often do not want to receive another aggressive treatment with heavy side effects.

The relationship between cancer and the immune system is well known [20] and a new trend of immunotherapy as adjuvant treatment is also emerging in the treatment of osteosarcoma. Interferon-alpha (IFN) was used in osteosarcoma in the 1960s at the Karolinska Institute before the chemotherapy era, and 10 years overall survival results are similar to those attained with chemotherapy alone [21]. Muramyl tripeptide (MTP) is a BCG-derived drug with immunomodulating activity tested at Memorial Sloan Kettering Cancer Center together with chemotherapy that resulted in improved DFS and prolonged overall survival [22].

IFN and MTP are quite expensive and so far not reimbursed for osteosarcoma by the Italian health system. *Viscum album* *ferm.* has a long history of being used for 80 years, its toxicity is well known and its cost (85€ per month) is much more affordable than the other two drugs.

Of course the results of our study are very preliminary (only four patients were recruited in the Etoposide arm) and a longer follow-up and more patients are needed, but so far the results indicate a positive trend for *Viscum* compared to Etoposide and compared to historical control. In addition, the analysis of immune response was favorable for patients who received *Viscum*. In fact there was an increase in total lymphocytes and natural killer cell counts in almost all patients, the peak being at 3 and 6 months of *Viscum* treatment.

Therapy with *Viscum album fermentatum* Pini seems to be a promising adjuvant treatment in prolonging DFS of patients free from disease after their second relapse. The outcome is at least not worse than in the historical control group. Etoposide does not seem to prolong DFS in our study.

Conflict of interest: None.

References

- [1] Briccoli A. Resection of recurrent pulmonary metastases in patients with osteosarcoma. *Cancer* 2005;104(8):1721–5.
- [2] Fagioli F. High dose chemotherapy in the treatment of relapsed osteosarcoma: an Italian sarcoma group study. *J Clin Oncol* 2002;20(8):2150–6.
- [3] Bacci G, Briccoli A, Longhi A, Ferrari S, Mercuri M, Fagioli F, et al. Treatment and outcome of recurrent osteosarcoma: experience at Rizzoli Institute in 235 patients initially treated with neoadjuvant chemotherapy. *Acta Oncol* 2005;44:748–55.
- [4] Kebudi R. Oral Etoposide in pediatric sarcoma patients. *Pediatr Blood Cancer* 2004;42(4):320–4.
- [5] Sandri A, Massimino M, Mastrodicasa L, Sardi N, Bertin D, Basso ME, et al. Treatment with oral etoposide for childhood recurrent ependymomas. *J Pediatr Hematol Oncol* 2005;27(9):486–90.
- [6] Hugo F, Dittmar T, Treutler EK, Zänker KS, Kuehn JJ. The viscum album extract Iscador P does not cause an autocrine interleukin-6 loop in B-non-Hodgkin's lymphoma cell lines. *Onkologie* 2005;28:415–20.
- [7] Mueller E, Anderer FA. A viscum album oligosaccharide activating human natural cytotoxicity is an interferon gamma inducer. *Cancer Immunol Immunother* 1990;32:221–7.
- [8] Braun JM, Ko HL, Schierholtz JM, Beuth J. Standardized mistletoe extract augments immune response and down regulates local and metastatic tumor growth in murine models. *Anticancer Res* 2002;22(6C):4187–90.
- [9] Schaffrath B, Mengs U, Schwarz T, Hilgers RD, Beuth J, Möckel B, et al. Anticancer activity of rViscumin (recombinant mistletoe lectin) in tumor colonization models with immunocompetent mice. *Anticancer Res* 2001;21(6A):3981–7.
- [10] Kuttan G, Menon LG, Antony S, Kuttan R. Anticarcinogenic and antimetastatic activity of Iscador. *Anticancer Drugs* 1997;8(Suppl. 1):S15–6.
- [11] Hajto T, Hostanska K, Gabius HU. Modulatory potency of the beta-galactoside-specific lectin from mistletoe extract (Iscador) on the host defense system in vivo in rabbits and patients. *Cancer Res* 1990;50:3322–6.
- [12] Chernyshov VP, Heusser P, Omelchenko LI, Chernychova LI, Vodyanik MA, Vykhovanets EV, et al. Immunomodulatory and clinical effects of *Viscum album* (Iscador M and Iscador P) in children with recurrent respiratory infections as a result of the Chernobyl nuclear accident. *Am J Ther* 2000;7(3):195–203.
- [13] Kienle GS, Berrino F, Bussing A, Portalupi E, Rosenzweig S, Kiene H. Mistletoe in cancer—a systematic review on controlled clinical trials. *Eur J Med Res* 2003;8(3):109–19.
- [14] Mockel B, Schwarz T, Zinke H, Eck J, Langer M, Lentzen H, et al. Effects of mistletoe lectin I on human blood cell lines and peripheral blood cells. Cytotoxicity, apoptosis and induction of cytokines. *Arzneim-Forsch/Drug Res* 1997;47(10):1145–51.
- [15] Van Huyen J, Bayry J, Delignat S, Gaston AT, Michel O, Bruneval P, et al. Induction of apoptosis of endothelial cells by *Viscum album*, a role for anti-tumoral properties of mistletoe lectins. *Mol Med* 2002;8(10):600–6.
- [16] Schöffski P, Riggert S, Fumoleau P, Campone M, Bolte O, Marreaud S, et al. Phase I trial of intravenous aviscumine (rViscumin) in patients with solid tumors: a study of the European Organization for Research and Treatment of Cancer New Drug Development Group. *Ann Oncol* 2004;15(12):1816–24.
- [17] Kleeberg UR, Suci S, Bröcker EB, Ruitter DJ, Chartier C, Liénard D, et al. Final results of the EORTC 18871/DKG 80-1 randomised phase III trial. rIFN-alpha2b versus rIFN-gamma versus ISCADOR M versus observation after

- surgery in melanoma patients with either high-risk primary (thickness > 3 mm) or regional lymph node metastasis. *Eur J Cancer* 2004;40(3):390–402.
- [18] Horneber MA, Bueschel G, Huber R, Linde K, Rostock M. Mistletoe therapy in oncology. *Cochrane Database Syst Rev* 2008(2):CD003297.
- [19] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of The Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–55.
- [20] Blair GE, Cook GP. Cancer and immune system. An overview. *Oncogene*. 2008;27:5868.
- [21] Muller CR, Smeland S, Bauer HC, Sater G, Strander H. Interferon-alpha as the only adjuvant treatment in high-grade osteosarcoma: long term results of the Karolinska Hosp series. *Acta Oncol* 2005;44(5):475–80.
- [22] Meyers PA, Schwartz CL, Krailo MD. Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival. A report from the Children's Oncology Group. *J Clin Oncol* 2008;26(4):633–8.