Novel Models of Myxoid Liposarcoma Xenografts Mimicking the Biological and Pharmacologic Features of Human Tumors

Roberta Frapolli1, Elena Tamborini2, Emanuela Virdis2, Ezia Bello1, Eva Tarantino2, Sergio Marchini1, Federica Grosso4, Roberta Sanfilippo4, Alessandro Gronchi3, Juan Carlos Tercero5, Gabriella Peloso6, Paolo Casali4, Silvana Pilotti2, and Maurizio D’Incalci1

Abstract

Purpose: Myxoid liposarcoma is a common subtype of liposarcoma. It is associated in more than 90% of cases with the chromosomal translocation t(12;16)(q13;p11) leading to the fusion FUS-CHOP gene that is responsible for the oncogenic transformation of preadipocytes. Recently the marine natural product trabectedin has shown highly selective activity for myxoid liposarcoma, even in the most aggressive round-cell subtype.

Experimental Design: Fragments of 17 sarcomas were transplanted s.c. in female athymic NCr-nu/nu mice. Xenografts were established and characterized by morphology, fluorescence in situ hybridization analysis for the translocation and reverse transcriptase-PCR analysis for fusion transcripts. Trabectedin was injected i.v.

Results: Seven of 17 tumors grew as continuous xenografts, five of them being myxoid liposarcoma of the round-cell subtype. The chromosomal rearrangement and fusion transcripts in different passages were the same as in the human tumors from which they were derived. The responsiveness to trabectedin in type II myxoid liposarcoma xenografts was as high as in patients. The pathologic response was associated with the presence of the FUS-CHOP fusion gene, indicating that the drug does not totally eradicate the disease. Type III myxoid liposarcoma xenografts seemed much less sensitive to trabectedin, confirming previous clinical observations.

Conclusions: This study reports for the first time the characterization of human myxoid liposarcoma xenografts that adequately mimic the biological and pharmacologic features of the human tumor. These models offer a useful tool for investigating the mechanism of selectivity of trabectedin, testing new combinations with this drug and evaluating novel therapies for myxoid liposarcoma.

Myxoid liposarcoma is the second most common subtype of liposarcoma. It accounts for one third of liposarcomas which, in turn, account for approximately 10% of all mesenchymal malignancies.

Microscopically, myxoid liposarcoma is made up of uniform round/oval primitive nonlipogenic cells and variable numbers of uni/multivacuolated lipoblasts intermixed with a well-developed plexiform capillary network and embedded in a myxoid matrix composed of hyaluronic acid. Depending on the proportion of the cellular component to the stroma and the prevalence of immature and mature cellular features, myxoid liposarcoma is divided into a usual or pure subtype, and a round cell or cellular subtype. Usual myxoid liposarcoma is the most differentiated form and shows low cellularity, evidence of lipoblast differentiation, and a conspicuous vascular network, whereas the round-cell subtype presents the opposite extreme of the differentiation gamut and shows high cellularity made up of primitive nonlipogenic cells, little or no intervening myxoid stroma, and a capillary vascular pattern that is not easy to visualize. Diagnosis of the round-cell subtype requires >5% hypercellular area (1). Irrespective of the grade of differentiation and consistent with the notion that these histologic variants belong to
Translational Relevance

This study describes the development of human myxoid liposarcoma xenografts that are morphologically and biologically very similar to the human tumor they derive from. All the xenografts that grew successfully in different passages belonged to the round-cell subtype and maintained the chromosomal translocation t(12;16)(q13;p11) with the expression of the FUS-CHOP transcript that is responsible for the oncogenic transformation. The breakpoint characteristic of type I, II, or III FUS-CHOP was identical to that in patients.

Because trabectedin has been recently reported to be very effective in a high percentage of myxoid liposarcoma patients we investigated the effects of this drug in myxoid liposarcoma xenografts. The response was histologically comparable with that in patients, with much greater activity in type II than in type III myxoid liposarcoma. These new models offer a useful tool for clarifying the mechanism of selectivity of trabectedin and for identifying novel drugs and combinations to be tested rationally in clinical practice.

the same tumor category, the subtypes share the same cytogenetic abnormalities, represented by t(12;16)(p13; p11). This translocation is present in >90% of myxoid li-
togenetic abnormalities, represented by t(12;16)(p13; p11) with the expression of the FUS-CHOP transcript that is responsible for the oncogenic transformation. The breakpoint characteristic of type I, II, or III FUS-CHOP was identical to that in patients.

Because trabectedin has been recently reported to be very effective in a high percentage of myxoid liposarcoma patients we investigated the effects of this drug in myxoid liposarcoma xenografts. The response was histologically comparable with that in patients, with much greater activity in type II than in type III myxoid liposarcoma. These new models offer a useful tool for clarifying the mechanism of selectivity of trabectedin and for identifying novel drugs and combinations to be tested rationally in clinical practice.

Materials and Methods

Animals
Female athymic NCr-mu/nu mice, seven weeks old, were obtained from Harlan Laboratories. They were maintained under specific pathogen-free conditions, housed in individually ventilated cages, and handled using aseptic procedures. Procedures involving animals and their care were conducted in conformity with the institutional guidelines that are in compliance with national (Legislative Decree 116 of January 27, 1992 Authorization n.169/94-A issued December 19, 1994 by the Ministry of Health) and international laws and policies (EEC Council Directive 86/609, OJ L 358. 1, December 12, 1987; Standards for the Care and Use of Laboratory Animals, United States National Research Council, Statement of Compliance A5023-01, November 6, 1998).

Diagnostic assessment of human and murine xenografts

Histologic characterization. The histologic criteria applied to define myxoid liposarcoma histotype and its usual and round-cell subtypes were as described in the WHO classification (1). To obtain a diagnostic confirmation, we did cytogenetic analysis [fluorescence in situ hybridization (FISH)] and/or molecular analysis [reverse transcriptase-PCR (RT-PCR)] on all the tumor specimens, both human and murine xenografts.
## Table 1. Clinical characteristics of sarcoma patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/Sex</th>
<th>Primary tumor site (year)</th>
<th>Histologic subtype at onset (year)</th>
<th>FISH analysis</th>
<th>FUS/CHOP transcript.</th>
<th>Specimen type</th>
<th>Previous treatment</th>
<th>Time</th>
<th>Histology</th>
<th>FISH RT-PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>51/F</td>
<td>Right arm (2005)</td>
<td>MFS</td>
<td>Neg</td>
<td>Not present</td>
<td>Surgical</td>
<td>No</td>
<td>2005</td>
<td>MFS</td>
<td>Neg</td>
</tr>
<tr>
<td>002</td>
<td>48/M</td>
<td>Left thigh (2001)</td>
<td>RC &gt;20%</td>
<td>Pos</td>
<td>Type II</td>
<td>Surgical</td>
<td>RT and CT</td>
<td>2005</td>
<td>RC &gt;20%</td>
<td>Pos Type II</td>
</tr>
<tr>
<td>003</td>
<td>80/M</td>
<td>Right thigh (1992)</td>
<td>MFS</td>
<td>Neg</td>
<td>Not present</td>
<td>Surgical</td>
<td>RT and CT</td>
<td>2005</td>
<td>MFS</td>
<td>Neg</td>
</tr>
<tr>
<td>004</td>
<td>58/M</td>
<td>Retroperitoneum (2003)</td>
<td>RC = 30%</td>
<td>Pos</td>
<td>Type III</td>
<td>Tru-cut</td>
<td>RT and CT</td>
<td>2005</td>
<td>RC = 30%</td>
<td>Pos Type III</td>
</tr>
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<td>005</td>
<td>44/F</td>
<td>Retroperitoneum (2002)</td>
<td>LMS</td>
<td>Not done</td>
<td>Not done</td>
<td>Surgical</td>
<td>RT and CT</td>
<td>2005</td>
<td>LMS</td>
<td>Not done</td>
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<tr>
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<td>53/M</td>
<td>Left leg (2004)</td>
<td>RC &gt;20%</td>
<td>Pos</td>
<td>Type III</td>
<td>Tru-cut</td>
<td>CT</td>
<td>2006</td>
<td>Usual</td>
<td>Pos Type III</td>
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<tr>
<td>007</td>
<td>47/M</td>
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<td>Usual</td>
<td>Pos</td>
<td>Type II</td>
<td>Surgical</td>
<td>CT</td>
<td>2006</td>
<td>Usual</td>
<td>Pos Type II</td>
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<tr>
<td>008</td>
<td>24/F</td>
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<td>MFS</td>
<td>Neg</td>
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<td>2006</td>
<td>MFS</td>
<td>Neg</td>
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<tr>
<td>009</td>
<td>64/M</td>
<td>Left thigh (2006)</td>
<td>RC &gt;90%</td>
<td>Pos</td>
<td>Type III</td>
<td>Surgical</td>
<td>No</td>
<td>2006</td>
<td>RC &gt;90%</td>
<td>Pos Type III</td>
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<tr>
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<td>34/F</td>
<td>Left thigh (2006)</td>
<td>Usual</td>
<td>Pos</td>
<td>Type II</td>
<td>Surgical</td>
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<td>45/M</td>
<td>Right thigh (2002)</td>
<td>RC &gt;90%</td>
<td>Pos</td>
<td>Type II</td>
<td>Surgical</td>
<td>RT and CT</td>
<td>2006</td>
<td>RC &gt;90%</td>
<td>Pos Type II</td>
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<td>65/M</td>
<td>Right axilla (2004)</td>
<td>DD</td>
<td>Neg</td>
<td>Neg</td>
<td>Tru-cut</td>
<td>CT</td>
<td>2006</td>
<td>DD</td>
<td>Neg</td>
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<td>33/F</td>
<td>Left thigh (2006)</td>
<td>RC about 70%</td>
<td>Pos</td>
<td>Type II</td>
<td>Surgical</td>
<td>No</td>
<td>2006</td>
<td>RC about 70%</td>
<td>Pos Type II</td>
</tr>
<tr>
<td>015</td>
<td>56/M</td>
<td>Left thigh (1992)</td>
<td>RC about 20%</td>
<td>Pos</td>
<td>Type II</td>
<td>Surgical</td>
<td>CT</td>
<td>2007</td>
<td>RC about 20%</td>
<td>Pos Type II</td>
</tr>
<tr>
<td>016</td>
<td>61/F</td>
<td>Right thigh (2007)</td>
<td>RC = 80%</td>
<td>Pos</td>
<td>Type II</td>
<td>Surgical</td>
<td>No</td>
<td>2007</td>
<td>RC = 80%</td>
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<tr>
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<td>31/M</td>
<td>Left leg (2007)</td>
<td>RC &gt;5%*</td>
<td>Pos</td>
<td>Type I</td>
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<td>2007</td>
<td>RC &gt;5%*</td>
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</tr>
</tbody>
</table>

Abbreviations: MFS, myxofibrosarcoma; LMS leiomyosarcoma; DD, dedifferentiated liposarcoma; RC, round cell; CT, chemotherapy; RT, radiotherapy.

*In this case only a biopsy was available and the percentage of the round cell component was not assessed.
Cytogenetic analysis (FISH). The characteristic translocation t(12:16) involving the FUS and CHOP genes was evaluated on a selected area of sections from formalin-fixed paraffin-embedded samples, as previously reported (7). The cases resulting negative for this chromosomal rearrangement were also tested for the alternative translocation t(12:22) involving the EWS and CHOP genes (7) before ruling out the diagnosis of myxoid liposarcoma. Morphologic overlap between myxofibrosarcoma and dedifferentiated liposarcoma may in fact result in misdiagnosis.

Molecular analysis of fusion transcripts. When frozen material was available RT-PCR was done to characterize fusion transcript types. Total RNAs were extracted by the Trizol method (Life Technologies), reverse transcribed into cDNA, and amplified using specific primers detecting the FUS-CHOP fusion transcript, as already described (7). All the PCR products were sequenced by an automated sequencer (3100 Genetic Analyzer, Applied Biosystem) following standard protocols and aligned with the GenBank sequences NT_010393 (FUS gene) and NT_029419 (CHOP gene).

PTEN sequencing. cDNA was specifically amplified for exons 2 to 9 of PTEN using previously published primers and conditions (20). Exon 2 mutations were confirmed on genomic DNA using the following primers: forward 5′-GTGGCTTAGAAATCTTTTC-3′ and reverse 5′-GTTTGATTGCTGCATATTTCAG-3′, in the following conditions: 40 cycles at 96°C for 8 minutes; 95°C for 30 seconds, 60°C for 30 seconds, 72°C for 1 minute, and an extension of 72°C for 5 minutes.

Patients and tumors
Samples from 17 patients treated at the Fondazione IRCCS Istituto Nazionale Tumori, Milan, whose fragments were grafted into nude mice, were revised by a pathologist. At the same time, FISH and RT-PCR analyses were done. Based on this combined diagnostic approach, three tumors were classified as usual myxoid liposarcoma (cases 002, 004, 006, 009, 012, 014, 015, 016, and 017), three as myxofibrosarcoma (cases 001, 003 and 008), one as leiomyosarcoma (case 005), and one as a dedifferentiated liposarcoma (case 013; Table 1A).

Establishment of tumor xenograft
Nude mice under isoflorane anesthesia were grafted bilaterally s.c. with representative human tumor fragments of about 4 × 4 mm derived from the samples described above. Fresh material was obtained from a surgical specimen (n = 13) or from a dedicated Tru-cut (n = 4) and cytogenetically/molecularly characterized (Table 1B). Tumors were implanted in mice at different times of disease progression, and during the period some patients were treated as detailed in the column “previous treatment.”

Two to five animals were used for each specimen depending on tissue availability. The xenografts were further transplanted from mouse to mouse, and a portion of each neoplastic tissue was used for histologic and cytogenetic/molecular studies. A xenograft model was considered established after the tumor tissue had been passaged three or more times in mice.

Genetic profiles
PCRs were done using the short tandem repeats (STR) multiplex kits AmpFlSTR Identifier PCR amplification kit (Applied Biosystem), which coamplifies 15 STR loci (D8S1179, D21S11, D7S820, CSF1PO, D3S1358, TH01, D13S317, D16S539, D2S1338, D19S433, VWA, TPO, D18S51, D5S818, and FGA) and amelogenin, the gender marker, with 1.5 to 2 ng of DNA samples. The amplification protocols and the thermal cycling conditions were according to the manufacturer’s instructions. A positive and a negative control were coanalyzed in each amplification reaction. Electrophoresis was carried out on an ABI Prism 310 Genetic Analyzer (Applied Biosystems) using the GeneMapper software following the manufacturer’s recommendations. Positive control and allelic ladder were also analyzed. Alleles were designated according to the guidelines of the International Society of Forensic Genetics (21).
The obtained profiles had a frequency $\leq 1 \times 10^{-17}$ using Italian gene frequencies; each cell line belonged to just one person, so it was unique. The profiles are not reported for privacy reasons, but the electropherograms are available upon request (gabriella.peloso@unipv.it).

**Drug treatment**

Female athymic nude mice were engrafted s.c. with tumor fragments. The growing tumor masses were measured with a Vernier caliper, and the tumor weights (1 mm$^3 = 1$ mg) were calculated with the formula: length $\times$ (width)$^2$/2. When the tumor weight reached about 130 to 140 mg (early stage) treatment started. Trabectedin (generously provided by PharmaMar, Madrid, Spain) was given i.v. at the dose of 0.1 mg/kg, every four days for three times (q4d×3) as previously reported (22). Each group comprised seven mice.

Drug efficacy was calculated as $T/C\%$, where $T$ and $C$ are the mean tumor weights of treated and control groups, respectively.

To simulate the clinical situation and to evaluate the histopathologic response better, ML015 xenografts were treated with trabectedin 0.1 mg/kg every seven days for six times (q7d×6). Treatment started when tumor weight was about 900 mg (late stage).

**Results**

We implanted a total of 17 sarcomas s.c. into nude mice (Table 1A and B). In 10 cases tumors grew over two passages but only in 7 were continuous xenografts established. Table 2 reports the xenograft identification and their histologic and molecular features (column A). The success of tumor take was not related to chemotherapy or radiotherapy before biopsy. Tumors appeared between two and nine months after transplantation. The latency decreased slightly after the first passage but still remained variable. Tumors grew very slowly with doubling time variable from 10 to >70 days (column B, left). After each
passage, we compared the histology and the molecular features of the growing tumors with the original sarcoma. Tumor fragments from established xenografts were frozen and subsequently retransplanted in mice, making these models potentially available for the use in other laboratories.

**Histology and molecular characterization of the established xenograft models: comparison with the corresponding human tumors**

The morphologic features of the tumors grown in mice were very similar to those observed in the tru-cut biopsies or surgical specimens from patients and were consistent with those recorded at the initial diagnosis on surgical specimens including the ML006 xenograft classified as round cell >20% but for which the material transplanted (tru-cut) corresponded to the usual subtype component. In all the myxoid liposarcoma xenografts (ML004, ML006, ML014, ML015, and ML017) the round-cell component was retained in all passages. Figure 1A shows one representative case (ML014), illustrating the morphology of the human tumor and the xenografts at different passages. Molecular analysis (Fig. 1B) and FISH (Fig. 1C) at all the passages always confirmed the chromosomal rearrangement and fusion transcript type detected in the human tumors.

Interestingly, xenograft ML017, from a patient whose biotic tissue had been found to have a PTEN mutation (Negri et al, personal communication), retained the same alteration throughout all the passages analyzed (Fig. 2).

From the myxoid liposarcoma xenograft we obtained primary culture that grew very slowly and after few passages they lost the FUS-CHOP transcript and started to grow faster.

**Drug sensitivity**

Considering the recent evidence that myxoid liposarcomas are highly sensitive to the marine natural product trabectedin (7, 8), we investigated the response of myxoid liposarcoma xenografts to this drug. The first experiments were done in two different models, ML006 and ML014, which were selected because they are characterized by type III and type II FUS-CHOP transcripts, respectively. As it can be seen in Fig. 3A, control mice with ML006 myxoid liposarcoma reached a tumor weight of about 1.2 g on day 109 after tumor inoculum. Trabectedin slowed the tumor growth, with a best T/C of 41% on day 70. Histologic examination before and after treatment showed no response (Fig. 3B, left).

Figure 3C shows the effect of trabectedin in ML014-bearing mice. The drug completely stopped tumor growth and this effect was long lasting: about seven months after the end of treatment, when control mice had a tumor weighting 1.8 g, treated mice were still in response with the mean tumor weight about 150 mg, not different from that at the moment of randomization (130 mg). The best T/C was 8% on day 265. H&E sections showed a partial response in posttreatment samples (Fig. 3D, left). In both tumor models, FISH and molecular analysis confirmed the presence and the subtype of the FUS-CHOP transcripts in pre- and post-trabectedin tumor (Fig. 3B and D, right).
Fig. 3. Trabectedin treatment in xenografts. A, antitumor activity of trabectedin in ML006 xenografts. Mice were transplanted s.c. with ML006 fragments and treatment started after 36 days (mean tumor weight 140 mg). Trabectedin was injected i.v. q4d×3 at 0.1 mg/kg. Bars, ± SE. B, H&E sections of the mouse tumor (ML006) before and after treatment did not show any morphologic change. The cytogenetic/molecular analysis in this case showed a type III FUS-CHOP transcript. C, antitumor activity of trabectedin in ML014 xenografts. Mice were transplanted s.c. with ML014 fragments and treatment started after 109 days (mean tumor weight 130 mg). Trabectedin was injected i.v. q4d×3 at 0.1 mg/kg. Bars, ± SE. D, pretreatment H&E sections of the mouse tumor (ML014) featuring a round cell subtype of myxoid liposarcoma and posttreatment tumor, with consistent cellular depletion and, in this case, the myxoid liposarcoma cytogenetic/molecular hallmarks type II FUS-CHOP fusion transcript. C+, positive control; C−, negative control; PR, proband samples.
Table 2 (B, right) reports the best T/C registered for all models tested. As can be seen, the sensitivity of both type II myxoid liposarcomas was higher compared with the type III tumors. The myxofibrosarcoma MF003 did not respond to trabectedin, whereas the dedifferentiated liposarcoma DD013 was very sensitive to the drug.

Because the xenograft ML015 was obtained from a patient who had been treated with trabectedin for six cycles, achieving a significant response, we compared the pathologic and molecular response in the patient and in the correspondent xenograft after six doses. Figure 4A shows H&E sections of the pretreatment and posttreatment mouse tumors and the cytogenetic/molecular analyses indicating the chromosomal rearrangement leading to the type II FUS-CHOP transcript. Figure 4B shows the corresponding pretreatment and posttreatment human tumors. Morphologic and cytogenetic/molecular features are superimposable both before (mouse and human, left) and after trabectedin treatment (mouse and human, right). The pathologic evaluation of tumor regression (human and mouse) was scored as grade 2, according to the published criteria (7, 8).

Discussion

The present study describes, for the first time, the characterization of a series of human myxoid liposarcoma xenografts. These models closely mimic the biological and pharmacologic features of the human myxoid liposarcoma tumors from which they derive. Morphologically, the tumor grown in each mouse, for each passage and for each xenograft, closely mirrored the subtype of the corresponding human tumor. The morphologic diagnosis was confirmed in all cases by FISH and RT-PCR revealing the FUS-CHOP rearrangement. C+, positive control; C−, negative control; PR, proband samples.

Excluding the xenografts not confirmed as myxoid liposarcoma (cases 001, 003, 005, 008, and 013), the establishment of myxoid liposarcoma xenografts turned out to be closely related to the round-cell subtype. Five of the nine round-cell (55.5%) but none of the three usual subtypes grafted into the animals gave rise to the xenograft. Previous chemotherapy or radiotherapy did not seem to influence the success of the implant. This may be ascribable to the retention of molecular/cytogenetic hallmarks in posttreatment human specimens even in those cases with the highest response rate (8). Furthermore, two of the five myxoid liposarcoma xenografts harbored the type III transcript (ML004 and ML006; Table 2), which is less frequent than types II and I (6, 7), contains a large portion of the FUS transcription factor (6), and also seems to be correlated with worse overall survival (6) even if a demonstrable prognostic effect is still lacking (5, 7).
Finally, the case with a type I transcript (ML017; Table 2) presented, in the human specimen and the xenograft, a mutated PTEN oncosuppressor gene, known to correlate with activation of the phosphoinositide 3-kinase/AKT pathway. In addition to the more aggressive subtype, i.e., the round cell, three of five of these cases (60%) had hallmarks related to aggressive clinical behavior, suggesting that establishment of the xenograft is likely to be related to the more biologically active tumor subtype.

Recent clinical evidence has been published that the marine natural product trabectedin is particularly effective in myxoid liposarcoma (7, 8), and studies in an immortalized myxoid liposarcoma cell line indicate that the high sensitivity of this tumor might be related to the ability of the drug to act as a differentiating agent by blocking the transactivating ability of the fusion gene product (18).

The present study indicates that myxoid liposarcoma xenografts are sensitive to trabectedin. In fact, in the ML015 case treated with the drug, the response was similar to that in previously reported series of treated patients (7), in which there was a variable depletion of the tumor cells and the vascular component. Notably, ML015 showed the same histologic response as in the patient from which the tumor was originally obtained (Fig. 4). This strongly suggests that this preclinical model could serve as a good starting point for future pharmacologic studies (12).

Investigations are now in progress to explore whether longer treatment with trabectedin alone or combined with other compounds leads to complete eradication of the disease or, at least, reaches the high regression score seen in patient specimens, corresponding to >90% loss of the tumor component. The fact that trabectedin seems very effective in myxoid liposarcoma xenografts as in clinical settings will provide suitable experimental models to explore the mode of action of the drug, to investigate its potential activity alone or in combinations with other anticancer agents, and possibly to clarify differences related to the different FUS/CHOP transcript.

The main drawback of these models is the very low growth rate with an estimated doubling time of 20 to >70 days, implying long observation times for any pharmacologic experiment. This is unexpected in view of the selection in xenografts of the more aggressive subtype, which in the mouse seems to reproduce outcome characteristics more similar to the usual subtype than to the round-cell one.

In summary the new xenografts reported offer a powerful new tool to investigate the biology of myxoid liposarcoma and to develop more selective and effective therapies, particularly for the advanced round-cell subtype requiring pharmacologic treatment, because the localized usual myxoid subtype is mostly successfully managed by surgery with or without radiotherapy.

Disclosure of Potential Conflicts of Interest

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