

Combination of Gemcitabine and Irinotecan for Recurrent Metastatic Osteogenic Sarcoma

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The natural history of osteogenic sarcoma is well known. Eighty percent of patients who present with local limb disease have microscopic subclinical metastases at the time of diagnosis. Therefore, whenever a diagnosis of primary osteogenic sarcoma is made, patients are routinely given neoadjuvant chemotherapy, followed by limb salvage surgery whenever possible and then postoperative adjuvant chemotherapy. All patients need very close follow-up with computed tomography (CT) scans, magnetic resonance imaging (MRI), and bone scans to detect disease recurrence. In this case report, our patient developed recurrent disease after receiving the established regimens for osteogenic sarcoma. Therefore, we decided to use the novel combination of irinotecan and gemcitabine.

Case Report

A 49-year-old white male with no significant past medical history presented in April 1999 to his orthopedist with complaints of left knee pain for the preceding year, which had become much worse during the 2 months prior to presentation, especially on knee flexion when climbing stairs. He denied any shortness of breath, weight loss, fevers, or trauma to his left leg.

X-ray of the left knee showed a 6-cm eccentric lesion involving the distal femur with periosteal reaction and soft tissue mass. A subsequent MRI of the left knee and thigh showed an osteolytic lesion with erosion of the cortex and a 6-cm soft tissue mass on the posterior lateral aspect of the left knee. A biopsy of this area was then performed and the pathology revealed high-grade osteogenic sarcoma. The patient had CT scans of the chest, abdomen, and pelvis, as well as a bone scan performed with no evidence of metastatic disease. He was then started on neoadjuvant

chemotherapy; the protocol consisted of intravenous (IV) doxorubicin 75 mg/m² infused over 96 hours and cisplatin 125 mg/m² given on day 1, alternating with doxorubicin 50 mg/m² given over 96 hours and ifosfamide 2 g/m² given by IV over 1 hour on days 1–4.

An MRI of the left knee performed after 4 cycles of chemotherapy showed significant decrease in the size of the soft tissue mass. In May 1999, the patient underwent limb salvage surgery. Pathology showed residual high-grade osteogenic sarcoma with only 58% postchemotherapy necrosis. Surgical margins were negative for malignancy. Two weeks after surgery he was restarted on the same regimen of chemotherapy, and received an additional 4 cycles through February 2000. The patient did well until August 2001, when a routine follow-up CT scan revealed multiple bilateral lung nodules. In addition, a bone scan showed multiple lesions in his lumbar spine, also consistent with metastatic disease. In September 2001, the patient was started on salvage chemotherapy with high-dose methotrexate 12 g IV followed by leucovorin rescue after 24 hours, repeated every 4 weeks. The patient was on this regimen until January 2002 and had stable lung disease by CT scans. In April 2002, he underwent elective thoracotomy for possible resection of the nodules. Unfortunately, he was found to have innumerable lung nodules, most of which could not be resected. The biopsy of the removed lung nodules showed high-grade osteogenic sarcoma.

Postoperatively, the patient's dose of methotrexate was increased to 16 g, with leucovorin rescue beginning at 24 hours. This treatment was complicated by acute renal failure. Chemotherapy was discontinued and the patient's creatinine level gradually returned to normal. In August 2002, he presented with severe left lower rib pain. A chest CT showed progression of lung disease and new left lower rib lesions. He was started on palliative radiation. An abdominal CT scan done in the same month revealed multiple liver metastases, with the largest lesion

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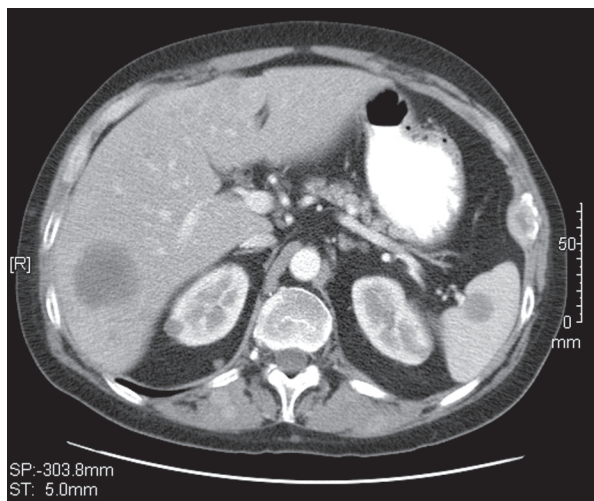


Figure 1. CT scan of the abdomen, with large liver and spleen lesions, before combination chemotherapy with gemcitabine and irinotecan.

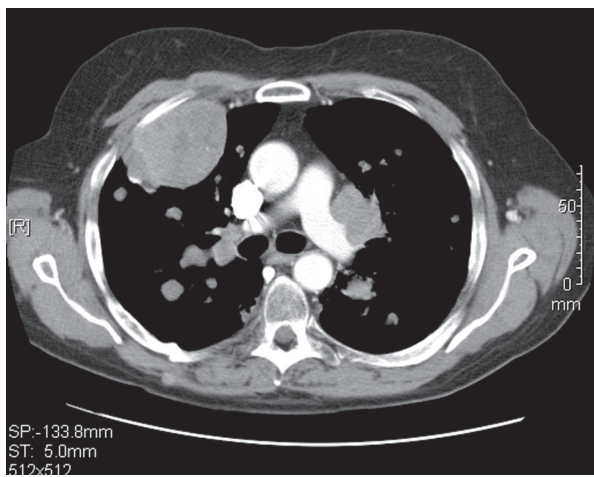


Figure 2. CT scan of the chest, with large right lung mass adherent to the pleura, before combination chemotherapy with gemcitabine and irinotecan.

measuring 3 cm × 4 cm. Following the completion of radiation in September 2002, he was started on etoposide 100 mg/m² IV over 3 days, and he received 4 monthly treatments through December 2002. By the end of December 2002, he developed severe back pain and noted multiple subcutaneous lesions on his scalp. Spinal MRI showed new metastatic lesions at T4 and T10, for which he was given radiation therapy. A scalp lesion was removed in January 2003 and was consistent with metastatic disease. At that time, an abdominal CT scan showed multiple liver lesions, along with bilateral kidney and spleen involve-

ment. A CT scan of the chest also showed progression of the lung disease, with the right lung lesion now measuring 7 cm × 4 cm adherent to the pleura. The patient started having shortness of breath with minimal physical activity. In February 2003, he was started on doxorubicin 15 mg/m², given every 3 weeks. The patient received 4 cycles of this regimen, but he developed worsening shortness of breath; he was found to have progression of disease on follow-up CT scans (Figures 1 and 2), and his scalp lesions increased in number and size.

In August 2003, the patient was started on combination chemotherapy with gemcitabine and irinotecan. The regimen consisted of gemcitabine 1,000 mg/m², with irinotecan 100 mg/m² on days 1 and 8, every 3 weeks. The patient had a dramatic response to this regimen after only 2 treatments, with marked decrease in his scalp lesions and significant improvement in his pulmonary status. A CT scan of the chest, abdomen, and pelvis in October 2003 showed improvement in the number and size of pulmonary metastatic lesions, a decrease in the size of his liver lesions, and stable bony metastatic disease. The patient tolerated the chemotherapy very well. A repeat CT scan in January 2004 showed further decrease in the size of the pulmonary lesions. His liver disease improved by at least 50%, and he again had stable bony disease. His scalp lesions had completely disappeared. The patient felt well and went back to working full time. The latest CT scan, done in May 2004, showed continued improvement in his pulmonary nodules, more than 50% decrease in the size of his spleen metastatic lesions, further decrease in the size of his liver lesions, and stable bony disease (Figures 3 and 4).

Discussion

Treatment options for recurrent metastatic osteogenic sarcoma are still very limited. If a patient fails the standard regimen,¹ consisting of doxorubicin plus cisplatin alternating with doxorubicin and ifosfamide, there is no established salvage regimen with promising data available.

Merimsky et al² reported 6 cases of recurrent osteogenic sarcoma treated with gemcitabine as a single agent 1 g/m² weekly for 7 weeks, then 1 week of rest, then on days 1, 8, and 15 every 28 days. The median time to progression was more than 27 weeks, and some patients achieved stable disease for up to 1 year, but no radiographic response to treatment was reported.

Okuno et al³ reported 2 patients with osteogenic sarcoma treated with 1,250 mg/m² of gemcitabine once a week for 3 weeks every 28 days. The median time to progression was 2.1 months, and again no radiographic responses were seen. The authors did not recommend this regimen due to its low efficacy, but there was an accept-

able level of toxicity.

Blaney et al⁴ reported the use of irinotecan as a single agent for refractory advanced solid tumors in a pediatric group. He administered 39 mg/m² daily IV infusion over 60 minutes for 5 days every 21 days in a heavily pretreated group. Stable disease after 4–20 cycles was observed in 7 patients with a variety of sarcomas, including osteogenic sarcoma. There was acceptable toxicity, but no radiographic responses were observed.

Leu et al⁵ reported 5 cases of osteogenic sarcoma treated with sequential gemcitabine 675 mg/m² on days 1 and 8 followed by docetaxel 100 mg/m² on day 8. Two patients experienced partial responses and 2 had stable disease; progression-free survival ranged from 21 weeks to 30+ weeks. In addition, sequential use of gemcitabine and docetaxel showed significant synergism in the SAOS-2 osteosarcoma cell line.

The combination of irinotecan 100 mg/m² as a 90-minute IV infusion, followed by gemcitabine 1 g/m² as a 60-minute IV infusion on days 1 and 8 every 21 days, showed promising results as first-line chemotherapy in locally advanced or metastatic pancreatic cancer, with an acceptable toxicity profile.⁶

In addition, Bahadori et al⁷ reported that an isobologram analysis revealed that the combination of these drugs exerted synergy over a wide range of concentrations in the MCF-7 (breast cancer) and SCOG (small-cell lung cancer) cell lines.

The combination of gemcitabine and irinotecan has shown acceptable toxicity and synergistic activity against many refractory solid tumors. Our case report demonstrates an excellent clinical and radiographic response in a heavily pretreated patient with recurrent osteogenic sarcoma. We could not find another report in the literature using this combination for treatment of osteogenic sarcoma. Due to the absence of a radiographic response to gemcitabine² and irinotecan⁴ used as single agents, we think that synergism between the 2 drugs makes their combination effective.

Conclusion

The combination of gemcitabine and irinotecan has acceptable toxicity and promising efficacy in the treatment of advanced recurrent osteogenic sarcoma. Therefore, this regimen warrants further investigation in clinical trials for patients with this disease.

References

- Zalupski M, Rankin C, Ryan J, Lucas D. Adjuvant therapy of osteosarcoma — a phase II trial: Southwest Oncology Group Study 9139. *Cancer*. 2004;100(4):818-825.
- Merimsky O, Meller I, Flusser G, et al. Gemcitabine in soft tissue or bone sarcoma resistant to standard chemotherapy: a phase II study. *Cancer Chemother*

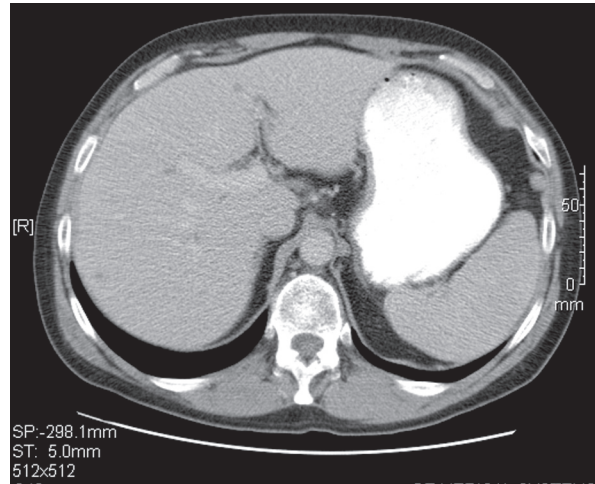


Figure 3. CT scan of the abdomen showing response to the combination of gemcitabine and irinotecan.

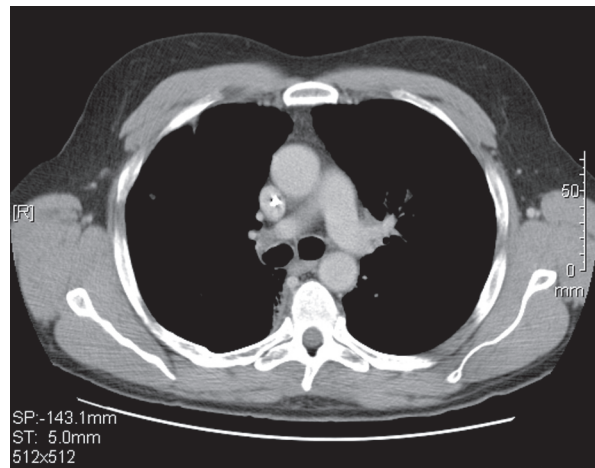


Figure 4. CT scan of the chest showing response to the combination of gemcitabine and irinotecan.

Pharmacol. 2000;45(2):177-181.

- Okuno S, Edmonson J, Mahoney M, Buckner JC, Frytak S, Galanis E. Phase II trial of gemcitabine in advanced sarcomas. ECOG-E1797. *Cancer*. 2002;94(12):3225-3229.
- Blaney S, Berg SL, Pratt C, Weitman S. A phase I study of irinotecan in pediatric patients: a pediatric oncology group study. *Clin Cancer Res*. 2001;7(1):32-37.
- Leu KM, Ostruszka LJ, Shewach D, et al. Laboratory and clinical evidence of synergistic cytotoxicity of sequential treatment with gemcitabine followed by docetaxel in the treatment of osteosarcoma. *J Clin Oncol*. 2004;22(9):1706-1712.
- Ga Alfonso P, Sancho J, Mendez M, et al. Weekly irinotecan and gemcitabine as first line treatment in stage III or IV pancreatic cancer. A Goti cooperative group study. *Proc Am Soc Clin Oncol*. 2003;22:361. Abstract 1449.
- Bahadori HR, Rocha Lima CM, Green MR, Safa AR. Synergistic effects of gemcitabine and irinotecan (CPT-11) on breast and small cell lung cancer cell lines. *Anticancer Res*. 1999;19(6B):5423-5428.

Review

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The 3 most common bone sarcomas in adulthood are osteosarcoma, chondrosarcoma, and malignant fibrous histiocytoma. Osteosarcoma occurs predominantly in children, adolescents, and young adults. It is the most common primary malignant bone tumor (excluding myeloma), comprising 20% of all primary skeletal malignancies. Peak incidence (60% of cases) is during the second decade of life. It accounts for approximately 5% of the cancers in childhood. Chondrosarcoma is approximately half as common as osteosarcoma and accounts for 10–20% of primary malignant bone tumors. Patients' ages range from 7 to 73 years, but most tumors are diagnosed in patients between 30 and 60 years of age. Malignant fibrous histiocytoma of bone represents 2–6% of primary malignant bone tumors, and occurs between the ages of 30 and 70 years.¹ Approximately 50–60% of osteosarcomas are located in the distal femur or proximal tibia, while the third most common site is the proximal humerus. In 75% of patients, the disease occurs in the metaphysis of long bones. In children and adolescents, 80% of these tumors arise from the bones around the knee, whereas in patients above 25 years of age, 40% of lesions are located in flat bones. Chondrosarcoma most commonly involves the femur and the pelvis, with a notable preference for the secondary ossification centers. Primary fibrosarcomas and malignant fibrous histiocytomas arise most commonly in long bones, usually the shafts of the femur or tibia.¹

Prior to the introduction of adjuvant therapy, the natural history of localized, resectable osteosarcoma was characterized by high local and metastatic rates of recurrence: most patients developed metastases within 6 months of diagnosis, and more than 80% developed local or distant recurrence within 2 years of diagnosis.²

Among patients with localized disease, multiple factors influence the long-term prognosis. Tumors of the axial skeleton have greater risk of progression and death than limb tumors. Patients with osteosarcoma of craniofacial and other flat bones have good survival with complete removal of the involved bone, and may even have an improved outcome when treated with chemotherapy. Tumor resectability usually depends on tumor site and depth. Patients with osteosarcoma as a second malignant neoplasm (not radiation-induced osteosarcoma) share the same prognosis as newly diagnosed patients if they are treated aggressively with surgery and combination chemotherapy. The histologic response to preoperative che-

motherapy is the best predictor of long-term disease-free survival among patients with resectable tumors. Patients with greater than 95% necrosis in the tumor mass after induction chemotherapy have a better prognosis than those with smaller amounts of necrosis.³

Metastatic or unresectable osteosarcoma at diagnosis, although advanced and forecasting a grim prognosis, is not necessarily incurable. In the past, the progression-free survival rate for patients with metastatic or unresectable osteosarcoma was less than 20%. However, among patients with pulmonary metastatic disease, in some situations a better than 40% 5-year survival is achievable.¹ Aggressive treatment, including surgical removal of primary and/or metastatic disease at the time of diagnosis or after intensive polychemotherapy, is necessary. In contrast, patients with bony metastases have a poor prognosis.

Locally advanced bone sarcoma usually involves all the compartments of the limb or involves a major adjacent structure such as the neurovascular bundle or areas like the chest wall or vertebrae. Local recurrence of bone sarcoma represents failure of primary surgery with or without chemotherapy. Such tumors tend to be very symptomatic: severe pain, sepsis, tumor fungation, hemorrhage, thrombosis, pathological fractures, radiation-induced necrosis, and severe functional impairment. Diffusely metastatic bone sarcoma is usually an incurable condition that requires palliation. Metastatic disease may be the first presentation of osteosarcoma or, more often, a late evolutionary phase of a formerly localized tumor that had failed to respond to induction chemotherapy, limb sparing surgery, and adjuvant chemotherapy. The lung and bone are common organs for metastatic spread; less frequent are the liver and brain. In such cases with diffuse spread, the disease is usually incurable by further chemotherapy or surgery. Exceptions are solitary metastatic lesions in certain organs that can be completely resected.⁴

Numerous drug combinations, reviewed in Merimsky et al,⁴ have been assessed in treated and untreated metastatic disease. The most effective of these have contained cisplatin, doxorubicin, and high-dose methotrexate plus leucovorin either as a 2- or 3-drug regimen. Numerous small phase II studies have reported response rates of 25–35%. The most important studies on palliative chemotherapy in metastatic osteosarcoma include cyclophosphamide, doxorubicin, and dacarbazine (29 patients, response rate 24%); cisplatin, vincristine, and high-dose methotrexate (29 patients, response rate 28%); dacarbazine plus doxorubicin (20 patients, response rate 35%; 19 patients, response rate 26%); and cyclophosphamide, doxorubicin, and dactinomycin (Cosmegen, Merck; 20 patients, response rate 25%).⁵ Meaningful options for second-line chemotherapy are limited. If there has been a long disease-free interval, it

is a common practice to prescribe the same agents that have been used for induction and postoperative therapy, namely doxorubicin, cisplatin, and ifosfamide, provided that the left ventricular ejection fraction and renal function are preserved. The recent introduction of dexrazoxane as a cardioprotective agent enables the administration of doxorubicin in total doses higher than 400–450 mg/m², as long as the cardiac function is normal.

High-dose methotrexate (8–10 g/m²) and folinic acid rescue are commonly used for metastatic osteosarcoma, provided that renal function and bone marrow reserves are adequate and there is no cardiac contraindication for massive hydration. This approach is associated with substantial morbidity: methotrexate is not well tolerated by adults due to renal toxicity, delayed clearance of the drug from the body, neurological toxicity, and the need for relatively prolonged hospitalization (5–7 days for each methotrexate course).

Ifosfamide may be given as a single agent or in combination with etoposide, together with mesna uroprotection. While given as a monotherapy, the dose of ifosfamide ranges between 9 g/m² and 12 g/m² administered by continuous IV infusion at a rate of 1.8–3 g/m² per day. In combination with etoposide (100 mg/m² per day for 3–5 days), the dose of ifosfamide is 1.8 g/m² per day given for 5 days. The response rate is low and of short duration. It should be noted that high-dose ifosfamide therapy may be nephrotoxic. In an important study in patients with advanced osteosarcoma with ifosfamide, Harris et al⁶ found that the likelihood of response was 30% among previously untreated patients but only 10% among those who had recurrent or refractory disease after prior chemotherapy.

When these approaches fail to provide ongoing control, decision-making becomes more difficult. Many of these patients, especially younger ones, may still have considerable life expectancy and good performance status and are eager to be treated, but realistic treatment options are very limited.

The paucity of chemotherapeutic agents in the standard arsenal used for treating osteosarcoma leads to a constant search for new agents or new combinations.

Gemcitabine is one of the newly introduced agents into the arsenal of drugs against osteosarcoma. Pharmacologically, gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. The cytotoxic effect of gemcitabine is attributed to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate

nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potential). After the gemcitabine nucleotide is incorporated into DNA, only 1 additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination).⁷ Clinically, the important efficacy of gemcitabine against aggressive malignancies such as lung and pancreatic carcinomas arouses our interest and curiosity for its possible effect in other devastating tumors. Gemcitabine has been studied in a long list of tumors, including breast, ovarian, bladder, prostatic, head and neck, and musculoskeletal cancers.

The first case report on a possible activity of gemcitabine monotherapy in a patient with chemotherapy-refractory osteosarcoma was published by our group in 1998.⁸ A 26-year-old woman with doxorubicin-refractory osteosarcoma enjoyed pain relief and marked reduction in narcotics consumption, together with improvement in quality of life and improved performance status, using crutches for walking instead of a wheelchair, hair regrowth, improved appetite, and a feeling of well-being. This report was followed by a small series in which the true objective response rate of osteosarcoma to gemcitabine was 0%, but disease stabilization and clinical benefit response were observed in 5 out of 7 patients after having failed on previous treatments. Time to progression varied from 13 to 96 weeks.⁹

An innovative approach to deliver gemcitabine has been reported by a group from Japan.¹⁰ In an animal model, intra-nasal application of gemcitabine to osteosarcoma-bearing rats resulted in inhibition of the growth of lung metastases.

Gemcitabine-based combinations have been suggested as palliative chemotherapy for advanced soft tissue or bone sarcomas. Zak et al, in the current report of a single but important case, found that the combination of gemcitabine and irinotecan showed acceptable toxicity and synergistic activity and an excellent clinical and radiographic response in a heavily pretreated patient with recurrent osteogenic sarcoma. It is likely that the combination is responsible for the tumor response, since gemcitabine alone can yield stabilization at best. This combination should be investigated in a phase II study in an appropriate patient population. Other gemcitabine-based combinations have also been applied for bone or soft tissue sarcomas. A gemcitabine-taxotere combination

was given to a variety of patients with refractory sarcomas, including 2 patients with osteosarcoma, yielding a overall response rate of 43%.¹¹ The 2 bone sarcomas achieved partial response and stabilization of the disease. Gemcitabine-rapamycin has been given to a patient with metastatic leiomyosarcoma,¹² leading to a response of long duration in several sites. Gemcitabine-dacarbazine combination has been studied in phase I in patients with advanced soft tissue sarcomas, and the efficacy will be evaluated subsequently.¹³

The real aim of chemotherapy after failure on standard regimens is palliation and disease stabilization, rather than reduction in size. From the patient's point of view, living with a stabilized and dormant sarcoma with no symptoms is much better than living with progressive disease and increasing suffering. There are many ways to handle an incurable advanced or metastatic bone sarcoma: amputation surgery, limb sparing procedures, conventional or experimental chemotherapy, resection of metastases in specific sites, and good supportive care. As long as there is something to offer, patients have hope for improvement in their conditions. It is this hope that keeps them alive.

References

1. Malawer MM, Link MP, Donaldson SS. Sarcomas of bone. In: VT DeVita, SI Hellman, SA Rosenberg, eds. *Cancer: Principles & Practice of Oncology*. 5th ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1997;1731-1852.
2. Eilber F, Giuliano A, Eckardt J, Patterson K, Moseley S, Goodnight J. Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. *J Clin Oncol*. 1987;5:21-26.
3. Davis AM, Bell RS, Goodwin PJ. Prognostic factors in osteosarcoma: a critical review. *J Clin Oncol* 1994;12:423-431.
4. Merimsky O, Kollender Y, Inbar M, Meller I, Bickels J. Palliative treatment for advanced or metastatic osteosarcoma. *Isr Med Assoc J*. 2004;6(1):34-38.
5. Benjamin RS, Baker LH, O'Bryan RM, Moon TE, Gottlieb JA. Chemotherapy of metastatic osteosarcoma—studies by the M. D. Anderson Hospital and the Southwest Oncology Group. *Cancer Treat Rep*. 1978;62(2):237-238.
6. Harris MB, Cantor AB, Goorin AM, et al. Treatment of osteosarcoma with ifosfamide: comparison of response in pediatric patients with recurrent disease versus patients previously untreated: a Pediatric Oncology Group study. *Med Pediatr Oncol*. 1995;24:87-92.
7. Gemzar (gemcitabine HCl) for injection: FDA revised label. Available at: <http://www.fda.gov/cder/foi/label/1998/20509lbl.pdf>. Accessed Feb. 24, 2005.
8. Merimsky O, Meller I, Kollender Y, Inbar M. Palliative effect of gemcitabine in osteosarcoma resistant to standard chemotherapy. *Eur J Cancer*. 1998;34(8):1296-1297.
9. Merimsky O, Meller I, Flusser G. Gemcitabine in soft tissue or bone sarcoma resistant to standard chemotherapy, phase 2 study. *Cancer Chemother Pharmacol*. 2000;45:177-181.
10. Jia SF, Worth LL, Turan M, Duan XP, Kleinerman ES. Eradication of osteosarcoma lung metastasis using intranasal gemcitabine. *Anticancer Drugs*. 2002;13(2):155-161.
11. Leu KM, Ostruszka LJ, Shewach D, et al. Laboratory and clinical evidence of synergistic cytotoxicity of sequential treatment with gemcitabine followed by docetaxel in the treatment of sarcoma. *J Clin Oncol*. 2004;22(9):1706-1712.
12. Merimsky O. Targeting metastatic leiomyosarcoma by rapamycin plus gemcitabine: an intriguing clinical observation. *Int J Mol Med*. 2004;14(5):931-935.
13. Buesa JM, Losa R, Fernandez A, et al. Phase I clinical trial of fixed-dose rate infusional gemcitabine and dacarbazine in the treatment of advanced soft tissue sarcoma, with assessment of gemcitabine triphosphate accumulation. *Cancer*. 2004;101(10):2261-2269.
104. Fiedler W, Mesters R, Tinnefeld H, et al. A phase 2 clinical study of SU5416 in patients with refractory acute myeloid leukemia. *Blood*. 2003;102:2763-2767.
105. O'Farrell AM, Foran JM, Fiedler W, et al. An innovative phase I clinical study demonstrates inhibition of FLT3 phosphorylation by SU11248 in acute myeloid leukemia patients. *Clin Cancer Res*. 2003;9:5465-5476.
106. Beebe JS, Jani JP, Knauth E, et al. Pharmacological characterization of CP-547,632, a novel vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for cancer therapy. *Cancer Res*. 2003;63:7301-7309.

(continued from page 296)

trans-retinoic acid, and ionizing radiation of human leukemia cells. *Leukemia*. 2003;17:1794-1805.

101. Liu XS, Shi Y, Han EKH, et al. Downregulation of Akt1 inhibits anchorage-independent cell growth and induces apoptosis in cancer cells. *Neoplasia*. 2001;3:278-286.

102. Estey EH, Thall PF. New designs for phase 2 clinical trials. *Blood*. 2003;102:442-448.

103. Estey EH, Fisher T, Giles F, et al. A randomized phase II trial of the tyrosine kinase inhibitor PKC412 in patients (pts) with acute myeloid leukemia (AML)/high-risk myelodysplastic syndromes (MDS) characterized by wild-type (WT) or mutated FLT3. *Blood*. 2003;102:614A-615A.