



Dorothy Fox. *Cattle Call*. Watercolor, 22" × 30".

The potential benefits of chemotherapy and radiotherapy combinations warrant consideration in treating high-grade sarcomas.

Outpatient Chemotherapy Plus Radiotherapy in Sarcomas: Improving Cancer Control With Radiosensitizing Agents

Pete Anderson, MD, PhD, Dolly Aguilera, MD, Margaret Pearson, CNP, and Shaio Woo, MD

Background: Cancer control by radiotherapy (RT) can be improved with concurrent chemotherapy. Outpatient strategies for sarcomas that combine chemotherapy and RT are possible since supportive care and RT techniques have improved.

Methods: The current status of non-anthracycline chemotherapy in combination with radiation for high-risk sarcoma is reviewed.

Results: Ifosfamide with mesna and newer activated ifosfamide agents (ZIO-201 and glufosfamide) have high potential to improve sarcoma cancer control. In Ewing's sarcoma and osteosarcoma, high-dose ifosfamide with mesna (2.8 g/m²/day of each × 5 days; mesna day 6) can be safely given to outpatients using continuous infusion. Reducing ifosfamide nephrotoxicity and central nervous system side effects are discussed. Other outpatient radiosensitization regimens include gemcitabine (600–1000 mg/m²/dose IV over 1 hour weekly × 2–3 doses), temozolomide (75 mg/m²/daily × 3–6 weeks), or temozolomide (100 mg/m²/dose daily × 5) + irinotecan (10 mg/m²/dose daily × 5 × 2 weeks). In osteosarcoma with osteoblastic metastases on bone scan, samarium (1 mCi/kg; day 3 of RT) and gemcitabine (600 mg/m² IV over 1 hour day 9 of RT) is a radiosensitization strategy. Future drugs for radiosensitization include beta-D-glucose targeted activated ifosfamide (glufosfamide) and sapacitabine, an oral nucleoside with in vitro activity against solid tumors including sarcomas.

Conclusions: The potential to treat major causes of sarcoma treatment failure (local recurrence and distant metastases) with concurrent chemotherapy during radiation should be considered in high-grade sarcomas.

From the Departments of Pediatrics (PA, DA, MP) and Radiation Oncology (SW) at The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

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Address correspondence to Pete Anderson, MD, PhD, The University of Texas M. D. Anderson Cancer Center; Children's Cancer Hospital, Unit 87, 1515 Holcombe Boulevard, Houston, TX 77030. E-mail: pmanders@mdanderson.org

Abbreviations used in this paper: RT = radiotherapy, DSRCT = desmoplastic small round cell tumor, IPM = isophosphoramidate mustard.

Introduction

The use of chemotherapy during radiation has been used in cancer control of many different malignancies. In almost every comparison of radiation therapy (RT) vs RT plus chemotherapy, cancer control has been better with the combined modality therapy. "The equation [increased local tumor control + decreased distant metastasis] = [increased survival] is the paradigm" has been the goal of concurrent chemotherapy and radia-

Table 1. — Oxazaphosphorines: Ifosfamide/Mesna, ZIO-201, Glufosfamide, Cyclophosphamide

Drug	Dose	Route/Schedule	Comments
Ifosfamide (standard)	1.8 g/m ²	IV daily × 5	Standard dose ifosfamide with mesna 1:1
Ifosfamide (high dose)	2.8 g/m ²	IV daily × 5	Ifosfamide with mesna 1:1; day 6 mesna only
ZIO-201 (IPM)	1.5 g/m ²	IV q 3 weeks	IV infusion; mesna not needed; investigational equivalent to 15–30 g/m ² ifosfamide
Glufosfamide (Beta-D-glucosyl-IPM)	4.5 g/m ²	IV q 3 weeks	IV infusion over 6 hours; mesna not needed; investigational “targeted” activated IPM
Cyclophosphamide	1–2.2 g/m ² 25 mg/m ²	IV q 3 weeks or oral daily dosing; give in morning	Mesna with higher IV doses

IV = intravenous
IPM = isophosphoramidate mustard

tion.¹ Issues involving quality of life are also important to the patient when receiving chemotherapy plus RT for high-grade sarcomas. Most families prefer outpatient regimens that allow patients literally to sleep in their own bed. Also, chemotherapy regimens should permit normal nutritional intake and activity. We have found that improvements in supportive care, including better antiemetics for both acute and delayed nausea, use of portable pumps for outpatient infusions, and better hematologic support, have made outpatient chemotherapy a routine treatment.

Radiation is widely used in sarcoma cancer control. RT can make surgery possible, can reduce the likelihood of positive margins, and can be given after surgery if there are close or positive margins. Radiation with surgery has been proven to improve local control for high-grade sarcomas (decrease local recurrence) in several randomized trials compared with surgery alone. The local control rate is the same whether the radiation is given neoadjuvantly or adjuvantly. However, even with optimal treatment (margin-negative surgery and RT) the local recurrence rate for high-grade sarcomas is about 5% to 8%. In addition, RT has no impact on distant recurrence-free survival (DRFS) and thus disease-specific survival (DSS). As such, many investigators have been interested in chemoradiation strategies to not only further improve local control but also give a systemic treatment to improve DRFS and thus DSS.²⁻⁵ RT may also be used as the primary means of sarcoma local control, control of metastases, and palliation of pain. With more precise radiation techniques, including protons (as described in this issue by Patel and DeLaney and also by others⁶⁻⁹) and intensity-modulated radiotherapy (IMRT), radiation can cause less damage to normal tissues than in the past. Particle irradiation (eg, protons) might possibly suppress metastatic potential.¹⁰ RT should be regarded not only as an accepted and widely used modality for sarcomas, but also as one with potential to become even better using chemotherapy for radiosensitization.

Determining which chemotherapy regimen to use during RT is influenced by the ability of a chemotherapy/RT regimen to increase apoptosis vs indication for

systemic activity against distant disease. Despite years of experience, it remains controversial just how much benefit adjuvant anthracycline-based chemotherapy has for soft tissue sarcomas in adults.¹¹ Chemotherapy has a major role in pediatric high-grade sarcomas including osteosarcoma, Ewing’s sarcoma, rhabdomyosarcoma, and desmoplastic small round cell tumor (DSRCT). Non-anthracycline chemotherapy regimens useful during sarcoma RT are the subject of this review.

Promising new agents with the possibility of more specific tumor targeting and improved therapeutic index such as activated ifosfamide drugs (eg, ZIO-201 and glufosfamide)¹²⁻¹⁶ and sapacitabine^{17,18} are also discussed within the context of ifosfamide and gemcitabine regimens, respectively. Finally, some principles and details regarding chemotherapy administration and supportive care during chemotherapy plus RT are reviewed for oncologists, nurses, pharmacists, and families to better understand the art of the possible in a sarcoma center with the goal to achieve better cancer control using coordinated chemotherapy radiosensitization plus RT treatment regimens.

Oxazaphosphorines (Ifosfamide/Mesna, ZIO-201, Glufosfamide, Cyclophosphamide)

Ifosfamide is a useful drug in the treatment of sarcomas (Table 1).¹⁹⁻²¹ Both cyclophosphamide and ifosfamide are oxazaphosphorine prodrugs activated by the P450 system into the active alkylator moiety. Concurrent use of ifosfamide during RT has been the standard of care for patients with Ewing’s sarcoma for more than 10 years and should be considered in other high-grade sarcoma patients who may possibly benefit from ifosfamide for control of distant metastases. The pharmacology, biodistribution, and toxicity of ifosfamide have been extensively reviewed.²²⁻²⁵ Although adverse effects of ifosfamide might include hemorrhagic cystitis, encephalopathy, nephrotoxicity, and cytopenias, these are generally either preventable or manageable. The biotransformation of ifosfamide into the active isophosphoramidate moiety, as well as the generation of toxic and inactive metabolites, is complex (Fig 1).

Acrolein is the metabolite associated with urothelial damage and hemorrhagic cystitis after cyclophosphamide or ifosfamide administration.^{26,27} Either intravenous “hydration” or bladder irrigation can lower the concentration of acrolein in the bladder to reduce the incidence of hemorrhagic cystitis. Mesna, a sulfhydryl agent, detoxifies the acrolein metabolite without compromise of antitumor efficacy. Mesna has effectively allowed the successful development of ifosfamide and high-dose administration.²² If adequate mesna is provided, intravenous hydration is probably unnecessary.

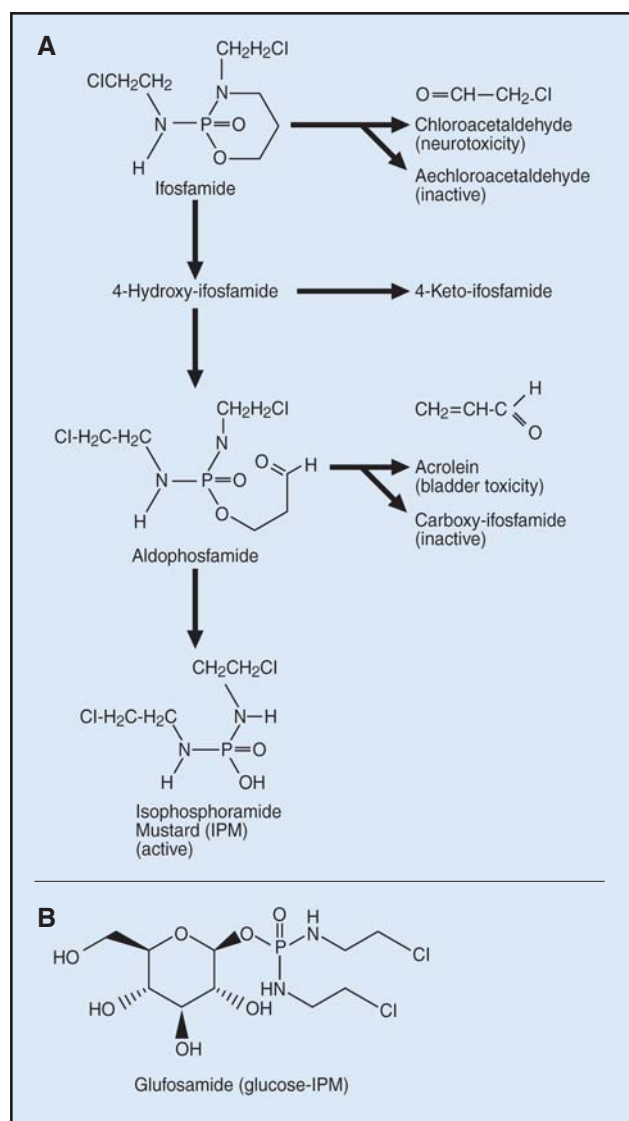


Fig 1. — Oxazaphosphorine structures and biotransformation pathways. (A) Ifosfamide, a prodrug, is metabolized into toxic metabolites (chloroacetaldehyde which is similar to chloral hydrate and is neurotoxic; acrolein that causes bladder toxicity), inactive metabolites (dechloroethyl-ifosfamide), 4-keto-ifosfamide, carboxy-ifosfamide) and the active alkylator moiety, isophosphoramidate mustard (IPM; ZIO-201). (B) Glufosamide is activated IPM with linkage to beta-D-glucose to target IPM to tumors cells with increased uptake of glucose. Adapted from Germann N, Urien S, Rodgers AH, et al. Comparative preclinical toxicology and pharmacology of isophosphoramidate mustard, the active metabolite of ifosfamide. *Cancer Chemother Pharmacol.* 2005; 55:143-151. Reprinted with kind permission of Springer Science and Business Media.

Skubitz et al²⁸ and our group²⁹ have extensively used ifosfamide plus mesna mixed 1:1 as a continuous infusion in a low volume without supplemental intravenous hydration with an extremely low incidence of hemorrhagic cystitis. Intravenous hydration protocols for ifosfamide might result in dilution of mesna that could possibly reduce uroprotection and contribute to hospitalization because of complicated and unnecessary logistics of providing “around-the-clock” intravenous fluids.

Encephalopathy is occasionally seen during ifosfamide administration. This side effect might manifest as fatigue, confusion, seizures, or even coma. The chloroacetaldehyde metabolite is similar to chloral hydrate (Fig 1)³⁰ and is associated with ifosfamide neurotoxicity; chloroacetaldehyde concentrations are higher after oral administration. Thus, despite mesna now having an oral formulation, there are no oral ifosfamide/mesna protocols. Encephalopathy requires stopping ifosfamide and/or treatment with methylene blue 50 mg orally or intravenously every 6 hours until resolution of central nervous system (CNS) side effects.³¹⁻³³ Ifosfamide by continuous infusion probably has less neurotoxicity because of lower peak levels of chloroacetaldehyde.³⁰ Hypoalbuminemia has been shown to be highly associated with encephalopathy during ifosfamide administration.³⁴

Nephrotoxicity from ifosfamide is related to cumulative ifosfamide dose (about 60 g/m² to 84 g/m²).^{35,36} In our experience, high potential for chronic nephrotoxicity is usually heralded by hypophosphatemia persisting more than 3 weeks after a cycle of ifosfamide. This chronic (>3 weeks) hypophosphatemia but not acute hypophosphatemia (<3 weeks) should be considered a relative contraindication to continued cycles of ifosfamide.

Although cytopenia from high-dose ifosfamide can be impressive, requiring red blood cell and platelet transfusions, myelosuppression will generally resolve within 2 to 4 weeks. Cytokines such as granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), or pegylated G-CSF (Neulasta) can shorten the duration of neutropenia. Bone pain associated with Neulasta can be lessened when it is given 7 to 14 days after starting chemotherapy — ie, at the time of approaching or during the neutrophil nadir.

Newer agents related to ifosfamide that do not require in vivo biotransformation for activation include isophosphoramidate mustard (IPM; ZIO-201) and glufosamide (beta-D-glucosyl-IPM).^{12,16,37,38} Direct administration of IPM or glufosamide has pharmacologic advantages of avoiding generation of neurotoxic chloroacetaldehyde and urotoxic acrolein (Fig 1). Glufosamide has potential to more specifically target fluorodeoxyglucose (FDG)-avid high-grade sarcomas that image well on positron-emission tomography (PET) via an upregulated glucose

transporter.^{14,15} The effects of glufosfamide at lower-dose intermittent schedules compared with the higher dose every 3 weeks have not yet been investigated. Nephrotoxicity of IPM or glufosfamide seems similar to ifosfamide. Although IPM and glufosfamide are currently investigational, both have excellent potential for future radiosensitization strategies.

Finally, vincristine plus doxorubicin plus cyclophosphamide, alternating with ifosfamide/mesna plus etoposide, is often used in pediatric sarcomas including Ewing's sarcoma and DSRCT.³⁹⁻⁴¹ Chemotherapy during local control is important in Ewing's sarcoma and was shown to significantly improve local control from 51% to 83% ($P=.014$) in a recent analysis.⁴² Ifosfamide with or without etoposide is the chemotherapy regimen generally used during RT for Ewing's sarcoma or DSRCT; temozolomide plus irinotecan is another active regimen.⁴³

Current Children's Oncology Group protocols for rhabdomyosarcoma utilize vincristine and irinotecan or vincristine, dactinomycin, and cyclophosphamide for chemotherapy at the start of radiation. Since low-dose oral cyclophosphamide has shown some efficacy in sarcomas,⁴⁴ this is another strategy for not only radiation sensitization potential but also continuation chemotherapy in the palliative situation. Oral low-dose etoposide or cyclophosphamide also has high patient acceptance because of the ability to titrate to counts and also because of low nausea potential. Low-dose oral cyclophosphamide (eg, 25 mg daily) causes much less alopecia compared with doses of 1,000 mg/m² or more. Etoposide as a radiation sensitizer should be used with caution during RT because of increased potential for mucositis and higher risk of second malignancies.

Temozolomide Regimens

Dacarbazine (DTIC) and temozolomide are similar imidazotetrazine alkylators that methylate DNA at nucleophilic sites (Fig 2). Dacarbazine requires hepatic P450 biotransformation to monomethyl triazenoimidazole carboxamide (MTIC). Temozolomide is orally bioavailable, more lipophilic, and spontaneously converted to MTIC, and it also seems to generate less nausea.⁴⁵ The O⁶-methylguanine adduct causes mismatch during DNA replication and addition of a thymidine instead of cytosine to the newly formed DNA strand.⁴⁶ Because of excellent CNS biodistribution, temozolomide has been useful as a radiosensitizer in both primary brain tumors and CNS metastases.⁴⁷⁻⁵⁰ The pharmacokinetics of temozolomide has been studied in children, and clearance is related to body surface area.⁵¹ Temozolomide improves

quality of life when used with radiation in patients with brain metastases.⁵² Like dacarbazine, temozolomide has activity against sarcomas.⁵³⁻⁵⁵ Thus, it may be useful in sarcoma radiosensitization for primary control as well as treatment of metastases. Temozolomide is a radiosensitizer that is well tolerated and has modest side effects.^{46,48-50,52,56-63} Temozolomide-containing regimens are summarized in Table 2.

The combination of temozolomide and irinotecan is more than additive against some cancers.⁶⁴ Our experience confirms a high response rate in relapsed Ewing's sarcoma and DSRCT that is possibly even higher than that reported in the literature.^{29,43,65} The temozolomide plus irinotecan combination is less immune suppressive than standard ifosfamide- or cyclophosphamide-containing regimens.⁶⁶ This might be especially important in Ewing's sarcoma since we and others have shown that lymphocyte recovery (ie, absolute lymphocyte count >500 on day 15 after the first cycle of chemotherapy) is associated with significantly higher survival in Ewing's sarcoma.^{67,68} Temozolomide or dacarbazine has also been combined with other drugs including gemcitabine^{62,69} and doxorubicin liposomes.⁷⁰

Nucleoside Analogs for Radiosensitization: Gemcitabine and Sapacitabine

Gemcitabine is currently one of the most widely used drugs in the treatment of cancer and has activity against a variety of solid tumors including carcinomas such as pancreatic, breast, lung, bladder, biliary tract, and ovarian cancer, as well as mesothelioma and sarcomas.⁷¹⁻⁷⁹ Gemcitabine (difluorodeoxycytidine [dFdC]) enters the cell by facilitated diffusion or through co-transporters.

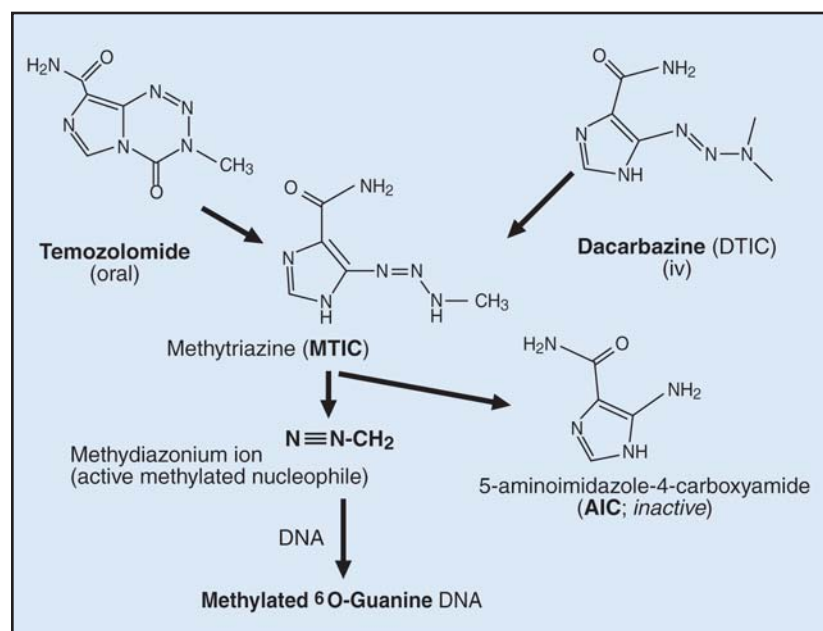


Fig 2. — Temozolomide and dacarbazine (DTIC). These are similar imidazotetrazine drugs and both are converted into monomethyl triazenoimidazole carboxamide. Temozolomide is given orally and has excellent clinical radiosensitization properties.

Table 2. — Temozolomide-Containing Regimens

Agent	Dose	Schedule	Comments
Temozolomide	75 mg/m ² daily	2 to 6 weeks	Oral home therapy; give at bedtime
Temozolomide + Irinotecan	100 mg/m ² daily × 5 10 mg/m ² /dose × 5	Week 1 and 4 Weekly × 2	Active in Ewing's sarcoma and DSRCT Week 1, 2 then 4, 5
Temozolomide + Gemcitabine	100 mg/m ² /dose × 5 600–1000 mg/m ²	Week 1, daily × 5 Week 1 and 2	IV over 1 hour

IV = intravenous infusion

Inside the cell, phosphorylation by the enzyme deoxycytidine kinase leads to gemcitabine-5'-monophosphate (dFdCMP); additional phosphorylation leads to the active metabolite 5'-diphosphate (dFdCDP), which inhibits the enzyme ribonucleotide reductase (RR). Since RR converts ribonucleotides to deoxyribonucleotides, RR is one of the rate-limiting enzymes involved in DNA synthesis. RR inhibition by gemcitabine decreases available pools of dATP, dCTP, dGTP, and dTTP and this reduction might inhibit the synthesis of DNA. Finally, the conversion of dFdCDP to dFdCTP phosphorylation of 5'-triphosphate (dFdCTP) inhibits DNA polymerase and DNA chain elongation. Heinemann et al⁸⁰ at our center have shown that gemcitabine-related RR inhibition depletes deoxynucleotide pools and incorporation into DNA, resulting in masked chain termination^{81,82} and self-potentiation.

Gemcitabine is a potent radiosensitizer; concentrations of 1,000-fold lower than typical plasma levels can be effective.⁸³⁻⁸⁷ Radiosensitization has been reviewed by Wilson et al.⁸⁷ When given at least 2 hours prior to radiation; the effect lasts for up to 48 to 60 hours after a dose.⁸³⁻⁸⁶

Because of dFdC degradation to uracil by cytidine deaminase vs rate-limiting intracellular phosphorylation of gemcitabine to the active dFdCDP and dFdCTP moieties,⁸⁸ gemcitabine dose response is related not only to the dose administered but also to the time of infusion. Longer gemcitabine infusion times might increase intracellular dFdCDP and dFdCTP in tumor cells as well as toxicity to normal cells.⁸⁹ The side effect profiles of gemcitabine infusions are excellent; myelosuppression

and emetogenic potential is modest.⁹⁰ However, the mucosal toxicity associated with gemcitabine increased in schedules using the drug more often than once weekly.^{91,92} Radiation-associated toxicity is related to the location and type of normal tissue that is also radiosensitized. Severe radiation recall is rare with gemcitabine compared to anthracyclines and taxanes and might involve pro-inflammatory cytokine production.^{93,94}

Therefore, gemcitabine schedules should balance potent radiosensitization effects for 2 days with potential increased mucosal and/or skin toxicity that could interrupt RT schedule. This is less of a problem with sarcomas with proton therapy or intensity-modulated radiotherapy (IMRT) fields that may not involve large areas of skin or mucosa. One method to balance radiosensitization indications, benefits, risks, and alternatives is to schedule the radiosensitizing drug on the Thursday or Friday morning before RT treatment of a standard Monday-through-Friday 5-day RT sequence. Also, a strategy to give the last radiosensitizing chemotherapy dose toward the end of RT will result in radiosensitization without RT treatment delay (Table 3). If gemcitabine (eg, day 1 and day 8 of a 21-day cycle) is used with docetaxel (day 8) during RT in the sequence active against sarcoma as described by Leu et al,⁹⁵ dose adjustment (ie, 60-minute gemcitabine infusion; 40 mg/m² docetaxel instead of 100 mg/m²) might be necessary to avoid severe cytopenias and toxicity.

Table 3. — Gemcitabine Schedule Recommendations for Radiosensitization*

RT Dose (Gy) × Fractions	Total RT Dose	Weeks	RT Day (fraction #) for Gemcitabine Infusions
3 Gy × 10	30	2	4, 9**
3 Gy × 15	45	3	9, 14**
1.8 Gy × 31	55.8	4	4, 9**; 24, 29**
2 Gy × 30	60	6	4, 9**; 24, 29**
2 Gy × 35	70 (proton)	7	4, 9**; 29, 34**

* Gemcitabine 600 mg/m² intravenously over 1 hour.
** If docetaxel (40 mg/m²) is also used.

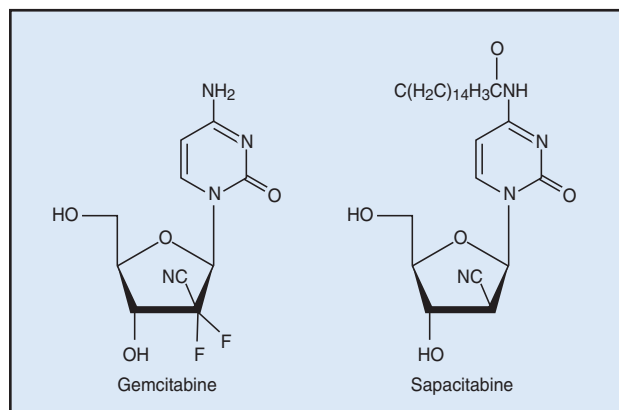


Fig 3. — Gemcitabine and sapacitabine. These substituted pyrimidine nucleoside analogs are very similar except fluorine in gemcitabine vs cyano group in sapacitabine and the addition of the palmityl group in sapacitabine to facilitate oral bioavailability.

Table 4. — Osteosarcoma Outpatient Chemotherapy Regimens for Radiosensitization

Agent	Dose/Route	Schedule	Comments
Ifosfamide	1.8 g/m ² IV 2.8 g/m ² IV	Daily × 5 Daily × 5	Standard dose High-dose
Cisplatin	60 mg/m ² IV 15 mg/m ² IV	Daily × 2 Daily × 4 × 2 wks	With hydration As radiosensitizer
Methotrexate	12 g/m ² IV	Over 4 hrs	Max 20 g + hydration Leucovorin rescue q 6 hrs, then 10 mg p.o. q 6 hrs until MTX level less 0.1 μM
153-Samarium	1 mCi/kg IV	Over 1 to 2 min	Well tolerated and bone scan predicts uptake
Gemcitabine	600 mg/m ² IV 600 mg/m ² IV	1 day after 153-Samarium Weekly	Samarium Wednesday/gemcitabine Thursday Suggest at end of 5 days of RT
Gemcitabine + docetaxel	600 mg/m ² IV 40 mg/m ² IV	Weekly × 2 Day 8	Over 60 minutes days 4 and 9 of RT IV over 1 hour day 9 3 Gy × 10–15 doses Monday–Friday

IV = intravenous route

Sapacitabine is a new oral nucleoside analog that has a cyano group in the same position as fluorine in gemcitabine (Fig 3). The addition of a palmityl group increases lipid solubility and permits effective oral administration.^{17,18} Sapacitabine causes G₂ arrest and chain termination.⁹⁶ Dose-limiting toxicity is neutropenia. Since sapacitabine has in vitro activity against a wide variety of malignancies including not only leukemias but also solid tumors, this agent appears to have promise for becoming a potent oral radiosensitizer.^{97,98}

Chemotherapy Plus Radiation Regimens in Osteosarcoma

Ifosfamide, Cisplatin, or Methotrexate Followed by Samarium + Gemcitabine

RT can facilitate local control of osteosarcoma.^{7,29,99-104} Chemotherapy seems to markedly improve effectiveness of local control RT.^{101,102} Chemotherapy agents that combine systemic osteosarcoma control and also increase radiation effectiveness include ifosfamide, cisplatin, high-dose methotrexate or gemcitabine with or without docetaxel.⁹⁵ Carboplatin has inferior activity to cisplatin in osteosarcoma.^{105,106} Since the use of carboplatin for radiosensitization risks increased myelosuppression and reduced systemic efficacy, the ifosfamide-carboplatin-etoposide combination (ICE) should have little or no role in osteosarcoma chemotherapy, including radiosensitization. To make outpatient high-dose methotrexate safer, more predictable, and more routine, a clinical trial at M.D. Anderson (2005-0246; P.Anderson, PI) is investigating carboxypeptidase G₂ (glucarpidase; Voraxaze) to rapidly degrade methotrexate at hour 26 after administration. Table 4 summarizes chemotherapy regimens possible for osteosarcoma radiosensitization that are suitable for outpatient administration.

When using 153-samarium (¹⁵³Sm-EDTMP) to target radiation to osteosarcoma lesions avid on bone scan, a radiosensitizer (eg, gemcitabine) can be given after the

unbound isotope is cleared.^{100,107} This sequence (samarium, then gemcitabine 1 day later) achieves effective sensitization in cells near the bone-bound samarium and also avoids radiosensitizing the kidneys and bladder before the radiopharmaceutical is eliminated from the urine.¹⁰⁷ Because of heterogeneity of isotope deposition in bone-forming osteosarcoma tumors, ¹⁵³samarium is most effectively used in combination with external-beam radiation and radiosensitization chemotherapy (gemcitabine, Fig 4). This strategy has been effective in high-risk or metastatic osteosarcoma tumors in difficult locations including the sacrum, ilium, pubis and acetabulum, spine, chest wall, and mediastinum.^{104,107}

Discussion

Radiation is an effective treatment modality in a variety of sarcomas. Although indications and risks of pre-adju-

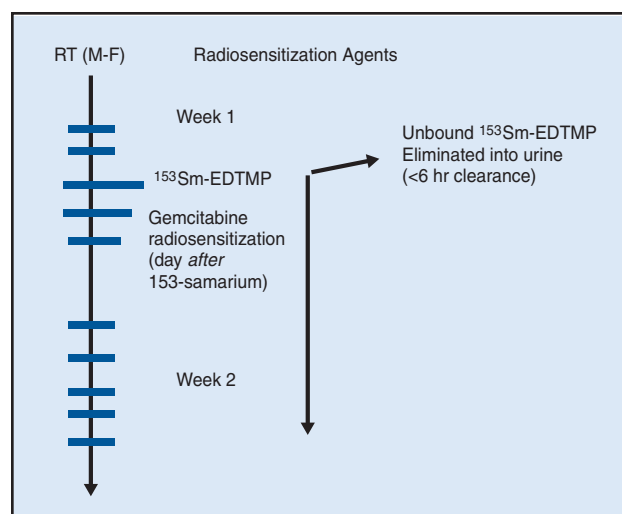


Fig 4. — Radiation plus chemotherapy radiosensitization paradigm for unresectable, recurrent, and/or metastatic osteosarcoma. This strategy is useful for facilitating local control RT of osteosarcomas that are avid on bone scan including those involving the ilium, sacrum, spine, chest wall, and mediastinum. Data from references 104 and 108.

vant sarcoma chemotherapy affect the chance of success,^{11,108} the use of concurrent outpatient chemotherapy has excellent potential to improve cancer control of radiation. Although concurrent chemotherapy requires patient education, close monitoring, and coordination of care between radiation oncology and medical or pediatric oncology, benefits can be high. An organized approach is needed to achieve the art of the possible.¹⁰⁹

As more is learned about the tumor microenvironment and effects of radiation, additional approaches to improve cancer control using concurrent chemotherapy plus radiation are possible. The effect of chemotherapy plus radiation on tumor neovasculature, vascular endothelial growth factor (VEGF) production/inhibition on tumor oxygenation, and chemotherapy penetration are probably important parameters of cancer control.¹¹⁰⁻¹¹⁴ For some chemoresistant sarcomas such as chondrosarcoma, chemotherapy with or without anti-VEGF modulation with or without radiosensitization chemotherapy could possibly provide a means to increase the clinical benefit of concurrent chemotherapy radiation.^{111,115,116} Similar new avenues of increasing chemotherapy plus radiation effectiveness might involve inhibition pathways known to be important for proliferation and apoptosis resistance and targeted therapy against Akt, mTOR, and IGFR in sarcomas.

Key concepts in the successful use of concurrent chemotherapy during radiation are maintaining a high level of supportive care, managing side effects, and using outpatient therapy to preserve quality of life. Recent studies show limb salvage has been facilitated using preoperative chemotherapy plus RT for both sarcomas and osteosarcoma with a low rate of wound complications.^{99,117} In choosing a radiosensitization strategy with a patient and family, the discussion of indications, risks, and alternatives should include the schedule of both RT and chemotherapy administration (we provide an editable pdf calendar¹¹⁴) as well as cytopenia monitoring and support including transfusions and cytokines, prevention or amelioration nausea with effective antiemetic regimens, nutrition and weight loss counseling, hospital or outpatient therapy, alopecia, mucosal toxicity, radiation recall, and increase in risk of second malignancies balanced by patterns of sarcoma treatment failure — local recurrence and/or out-of-field metastases.

Conclusions

An imprecise and often subjective balance of indications, risks, and alternatives guides the timing and sequence of interventions and the overall cancer control strategy using chemotherapy, RT, and/or surgery in sarcomas. The principles and details of current sarcoma chemotherapy regimens discussed in this review can possibly increase the effectiveness of RT. Future improvements are not only expected but probably inevitable.

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References

1. Cox JD. Chemoradiation for malignant epithelial tumors. *Cancer Radiother.* 1998;2:7-11.
2. Pawlik TM, Ahuja N, Herman JM. The role of radiation in retroperitoneal sarcomas: a surgical perspective. *Curr Opin Oncol.* 2007;19:359-366.
3. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol.* 1998;16:197-203.
4. Pisters PW, O'Sullivan B, Maki RG. Evidence-based recommendations for local therapy for soft tissue sarcomas. *J Clin Oncol.* 2007;25:1003-1008.
5. Gronchi A, Miceli R, Fiore M, et al. Extremity soft tissue sarcoma: adding to the prognostic meaning of local failure. *Ann Surg Oncol.* 2007;14:1583-1590. Epub 2007 Jan 28.
6. Cox JD. Proton beam radiation therapy in the treatment of cancer. *Clin Adv Hematol Oncol.* 2004;2:355-356.
7. DeLaney TF, Park L, Goldberg SI, et al. Radiotherapy for local control of osteosarcoma. *Int J Radiat Oncol Biol Phys.* 2005;61:492-498.
8. DeLaney TF, Kepka L, Goldberg SI, et al. Radiation therapy for control of soft-tissue sarcomas resected with positive margins. *Int J Radiat Oncol Biol Phys.* 2007;67:1460-1469.
9. DeLaney TF, Trofimov AV, Engelsman M, et al. Advanced-technology radiation therapy in the management of bone and soft tissue sarcomas. *Cancer Control.* 2005;12:27-35.
10. Ogata T, Teshima T, Kagawa K, et al. Particle irradiation suppresses metastatic potential of cancer cells. *Cancer Res.* 2005;65:113-120.
11. Pisters PW. Preoperative chemotherapy and split-course radiation therapy for patients with localized soft tissue sarcomas: home run, base hit, or strike out? *J Clin Oncol.* 2006;24:549-551.
12. Zheng JJ, Chan KK, Muggia F. Preclinical pharmacokinetics and stability of isophosphoramidate mustard. *Cancer Chemother Pharmacol.* 1994;33:391-398.
13. Briasoulis E, Pavlidis N, Terret C, et al. Glufosfamide administered using a 1-hour infusion given as first-line treatment for advanced pancreatic cancer: a phase II trial of the EORTC-new drug development group. *Eur J Cancer.* 2003;39:2334-2340.
14. Briasoulis E, Judson I, Pavlidis N, et al. Phase I trial of 6-hour infusion of glufosfamide, a new alkylating agent with potentially enhanced selectivity for tumors that overexpress transmembrane glucose transporters: a study of the European Organization for Research and Treatment of Cancer Early Clinical Studies Group. *J Clin Oncol.* 2000;18:3535-3544.
15. Seker H, Bertram B, Bürkle A, et al. Mechanistic aspects of the cytotoxic activity of glufosfamide, a new tumour therapeutic agent. *Br J Cancer.* 2000;82:629-634.
16. Zhang J, Tian Q, Chan SY, et al. Insights into oxazaphosphorine resistance and possible approaches to its circumvention. *Drug Resist Updat.* 2005;8:271-297. Epub 2005 Sep 9.

17. Galmarini CM. Drug evaluation: sapacitabine: an orally available antimetabolite in the treatment of cancer. *Curr Opin Investig Drugs*. 2006;7:565-573.
18. Delaunoy T, Burch PA, Reid JM, et al. A phase I clinical and pharmacokinetic study of CS-682 administered orally in advanced malignant solid tumors. *Invest New Drugs*. 2006;24:327-333.
19. Frustaci S, De Paoli A, Bidoli E, et al. Ifosfamide in the adjuvant therapy of soft tissue sarcomas. *Oncology*. 2003;65(suppl 2):80-84.
20. Eilber FC, Tap WD, Nelson SD, et al. Advances in chemotherapy for patients with extremity soft tissue sarcoma. *Orthop Clin North Am*. 2006;37:15-22.
21. Fahn W, Issels RD. Emerging treatments for soft tissue sarcoma of adults. *Expert Opin Emerg Drugs*. 2004;9:313-334.
22. Wagner T. Ifosfamide clinical pharmacokinetics. *Clin Pharmacokinet*. 1994;26:439-456.
23. Fleming RA. An overview of cyclophosphamide and ifosfamide pharmacology. *Pharmacotherapy*. 1997;17(5 Pt 2):146S-154S.
24. Furlanut M, Franceschi L. Pharmacology of ifosfamide. *Oncology*. 2003;65 (suppl 2):2-6.
25. Kerbusch T, de Kraker J, Keizer HJ, et al. Clinical pharmacokinetics and pharmacodynamics of ifosfamide and its metabolites. *Clin Pharmacokinet*. 2001;40:41-62.
26. Cox PJ. Cyclophosphamide cystitis: identification of acrolein as the causative agent. *Biochem Pharmacol*. 1979;28:2045-2049.
27. Brock N, Stekar J, Pohl J, et al. Acrolein, the causative factor of urotoxic side-effects of cyclophosphamide, ifosfamide, trofosfamide and sulfosfamide. *Arzneimittelforschung*. 1979;29:659-661.
28. Skubitz KM, Hamdan H, Thompson RC Jr. Ambulatory continuous infusion ifosfamide with oral etoposide in advanced sarcomas. *Cancer*. 1993;72:2963-2969.
29. Anderson PM, Pearson M. Novel therapeutic approaches in pediatric and young adult sarcomas. *Curr Oncol Rep*. 2006;8:310-315.
30. Lokiec F. Ifosfamide: pharmacokinetic properties for central nervous system metastasis prevention. *Ann Oncol*. 2006;17 (suppl 4):iv33-36.
31. Pelgrims J, De Vos F, Van den Brande J, et al. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer*. 2000;82:291-294.
32. Raj AB, Bertolone SJ, Jaffe N. Methylene blue reversal of ifosfamide-related encephalopathy. *J Pediatr Hematol Oncol*. 2004;26:116.
33. Patel PN. Methylene blue for management of ifosfamide-induced encephalopathy. *Ann Pharmacother*. 2006;40:299-303. Epub 2006 Jan 3.
34. David KA, Picus J. Evaluating risk factors for the development of ifosfamide encephalopathy. *Am J Clin Oncol*. 2005;28:277-280.
35. Loebstein R, Koren G. Ifosfamide-induced nephrotoxicity in children: critical review of predictive risk factors. *Pediatrics*. 1998;101:E8.
36. Skinner R, Cotterill SJ, Stevens MC. Risk factors for nephrotoxicity after ifosfamide treatment in children: a UKCCSG Late Effects Group study. United Kingdom Children's Cancer Study Group. *Br J Cancer*. 2000;82:1636-1645.
37. Germann N, Urien S, Rodgers AH, et al. Comparative preclinical toxicology and pharmacology of isophosphoramidate mustard, the active metabolite of ifosfamide. *Cancer Chemother Pharmacol*. 2005;55:143-151. Epub 2004 Sep 14.
38. Zhang J, Tian Q, Zhu YZ, et al. Reversal of resistance to oxazaphosphorines. *Curr Cancer Drug Targets*. 2006;6:385-407.
39. Rodriguez-Galindo C, Spunt SL, Pappo AS. Treatment of Ewing sarcoma family of tumors: current status and outlook for the future. *Med Pediatr Oncol*. 2003;40:276-287.
40. Bernstein M, Kovar H, Paulussen M, et al. Ewing's sarcoma family of tumors: current management. *Oncologist*. 2006;11:503-519.
41. Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. *Pediatr Blood Cancer*. 2006;47:22-29.
42. Paulino AC, Nguyen TX, Mai WY. An analysis of primary site control and late effects according to local control modality in non-metastatic Ewing sarcoma. *Pediatr Blood Cancer*. 2007;48:423-429.
43. Wagner LM, McAllister N, Goldsby RE, et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. *Pediatr Blood Cancer*. 2007;48:132-139.
44. Casanova M, Ferrari A, Bisogno G, et al. Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European Rhabdomyosarcoma Protocol. *Cancer*. 2004;101:1664-1671.
45. Danson SJ, Middleton MR. Temozolomide: a novel oral alkylating agent. *Expert Rev Anticancer Ther*. 2001;1:13-19.
46. Nagasubramanian R, Dolan ME. Temozolomide: realizing the promise and potential. *Curr Opin Oncol*. 2003;15:412-418.
47. Lanzetta G, Campanella C, Rozzi A, et al. Temozolomide in radiochemotherapy combined treatment for newly-diagnosed glioblastoma multiforme: phase II clinical trial. *Anticancer Res*. 2003;23:5159-5164.
48. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996.
49. Gilbert MR. Advances in the treatment of primary brain tumors: dawn of a new era? *Curr Oncol Rep*. 2006;8:45-49.
50. Atallah E, Flaherty L. Treatment of metastatic malignant melanoma. *Curr Treat Options Oncol*. 2005;6:185-193.
51. Panetta JC, Kirstein MN, Gajjar A, et al. Population pharmacokinetics of temozolomide and metabolites in infants and children with primary central nervous system tumors. *Cancer Chemother Pharmacol*. 2003;52:435-441. Epub 2003 Sep 16.
52. Addeo R, Caraglia M, Faiola V, et al. Concomitant treatment of brain metastasis with whole brain radiotherapy [WBRT] and temozolomide [TMZ] is active and improves quality of life. *BMC Cancer*. 2007;7:18.
53. Houghton PJ, Stewart CF, Cheshire PJ, et al. Antitumor activity of temozolomide combined with irinotecan is partly independent of O6-methylguanine-DNA methyltransferase and mismatch repair phenotypes in xenograft models. *Clin Cancer Res*. 2000;6:4110-4118.
54. Middlemas DS, Stewart CF, Kirstein MN, et al. Biochemical correlates of temozolomide sensitivity in pediatric solid tumor xenograft models. *Clin Cancer Res*. 2000;6:998-1007.
55. Aksoy S, Abali H, Kilickap S, et al. Successful treatment of a chemoresistant tumor with temozolomide in an adult patient: report of a recurrent intracranial mesenchymal chondrosarcoma. *J Neurooncol*. 2005;71:333-334.
56. Chakravarti A, Erkinen MG, Nestler U, et al. Temozolomide-mediated radiation enhancement in glioblastoma: a report on underlying mechanisms. *Clin Cancer Res*. 2006;12:4738-4746.
57. Donawho CK, Luo Y, Luo Y, et al. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. *Clin Cancer Res*. 2007;13:2728-2737.
58. Fountzilias G, Karkavelas G, Kalogera-Fountzila A, et al. Post-operative combined radiation and chemotherapy with temozolomide and irinotecan in patients with high-grade astrocytic tumors: a phase II study with biomarker evaluation. *Anticancer Res*. 2006;26:4675-4686.
59. Conill C, Jorcano S, Domingo-Domenech J, et al. Whole brain irradiation and temozolomide based chemotherapy in melanoma brain metastases. *Clin Transl Oncol*. 2006;8:266-270.
60. Mirimanoff RO. The evolution of chemoradiation for glioblastoma: a modern success story. *Curr Oncol Rep*. 2006;8:50-53.
61. Hermisson M, Klumpp A, Wick W, et al. O6-methylguanine DNA methyltransferase and p53 status predict temozolomide sensitivity in human malignant glioma cells. *J Neurochem*. 2006;96:766-776. Epub 2006 Jan 9.
62. Ebert BL, Niemierko E, Shaffer K, Salgia R. Use of temozolomide with other cytotoxic chemotherapy in the treatment of patients with recurrent brain metastases from lung cancer. *Oncologist*. 2003;8:69-75.
63. Wedge SR, Porteous XJ, Glaser MG, et al. In vitro evaluation of temozolomide combined with X-irradiation. *Anticancer Drugs*. 1997;8:92-97.
64. Patel VJ, Elion GB, Houghton PJ, et al. Schedule-dependent activity of temozolomide plus CPT-11 against a human central nervous system tumor-derived xenograft. *Clin Cancer Res*. 2000;6:4154-4157.
65. Wagner LM, Crews KR, Iacono LC, et al. Phase I trial of temozolomide and protracted irinotecan in pediatric patients with refractory solid tumors. *Clin Cancer Res*. 2004;10:840-848.
66. Kushner BH, Kramer K, Modak S, et al. Irinotecan plus temozolomide for relapsed or refractory neuroblastoma. *J Clin Oncol*. 2006;24:5271-5276.
67. De Angulo G, Hernandez M, Morales-Arias J, et al. Early lymphocyte recovery as a prognostic indicator for high-risk Ewing sarcoma. *J Pediatr Hematol Oncol*. 2007;29:48-52.
68. DuBois SG, Elterman K, Grier HE. Early lymphocyte recovery in Ewing sarcoma. *J Pediatr Hematol Oncol*. 2007;29:351-352.
69. Losa R, Fra J, Lopez-Pousa A, et al. Phase II study with the combination of gemcitabine and DTIC in patients with advanced soft tissue sarcomas. *Cancer Chemother Pharmacol*. 2007;59:251-259. Epub 2006 May 31.
70. Awada A, Gil T, Sales F, et al. Prolonged schedule of temozolomide (Temodal) plus liposomal doxorubicin (Caelyx) in advanced solid cancers. *Anticancer Drugs*. 2004;15:499-502.
71. Kindler HL. Pancreatic cancer: an update. *Curr Oncol Rep*. 2007;9:170-176.
72. Dent S, Messersmith H, Trudeau M. Gemcitabine in the management of metastatic breast cancer: a systematic review. *Breast Cancer Res Treat*. 2007 May 26; Epub ahead of print.
73. Smith IE. Overview of gemcitabine activity in advanced breast cancer. *Semin Oncol*. 2006;33:S19-23.
74. Mornex F, Girard N. Gemcitabine and radiation therapy in non-small cell lung cancer: state of the art. *Ann Oncol*. 2006;17:1743-1747. Epub 2006 Jun 9.
75. Garcia-Carbonero R, Paz-Ares L. Systemic chemotherapy in the management of malignant peritoneal mesothelioma. *Eur J Surg Oncol*. 2006;32:676-681. Epub 2006 Apr 17.
76. Toschi L, Finocchiaro G, Bartolini S, et al. Role of gemcitabine in cancer therapy. *Future Oncol*. 2005;1:7-17.
77. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol*. 2002;20:2824-2831.
78. Maki RG. Role of chemotherapy in patients with soft tissue sarco-

mas. *Expert Rev Anticancer Ther.* 2004;4:229-236.

79. Patel SR. Recent advances in systemic therapy of soft tissue sarcomas. *Expert Rev Anticancer Ther.* 2003;3:179-184.

80. Heinemann V, Xu YZ, Chubb S, et al. Inhibition of ribonucleotide reduction in CCRF-CEM cells by 2',2'-difluoro-deoxycytidine. *Mol Pharmacol.* 1990;38:567-572.

81. Plunkett W, Huang P, Searcy CE, Gandhi V. Gemcitabine: preclinical pharmacology and mechanisms of action. *Semin Oncol.* 1996;23(5 suppl 10):3-15.

82. Plunkett W, Huang P, Gandhi V. Preclinical characteristics of gemcitabine. *Anticancer Drugs.* 1995;6(suppl 6):7-13.

83. Shewach DS, Lawrence TS. Gemcitabine and radiosensitization in human tumor cells. *Invest New Drugs.* 1996;14:257-263.

84. Lawrence TS, Chang EY, Hahn TM, et al. Delayed radiosensitization of human colon carcinoma cells after a brief exposure to 2',2'-difluoro-2'-deoxycytidine (Gemcitabine). *Clin Cancer Res.* 1997;3:777-782.

85. Gregoire V, Hittelman WN, Rosier JF, et al. Chemo-radiotherapy: radiosensitizing nucleoside analogues (review). *Oncol Rep.* 1999;6:949-957.

86. Joschko MA, Webster LK, Groves J, et al. Enhancement of radiation-induced regrowth delay by gemcitabine in a human tumor xenograft model. *Radiat Oncol Investig.* 1997;5:62-71.

87. Wilson GD, Bentzen SM, Harari PM. Biologic basis for combining drugs with radiation. *Semin Radiat Oncol.* 2006;16:2-9.

88. Pauwels B, Korst AE, Lardon F, et al. Combined modality therapy of gemcitabine and radiation. *Oncologist.* 2005;10:34-51.

89. Plunkett W, Huang P, Xu YZ, et al. Gemcitabine: metabolism, mechanisms of action, and self-potentiation. *Semin Oncol.* 1995;22(4 suppl 11):3-10.

90. Storniolio AM, Allerheiligen SR, Pearce HL. Preclinical, pharmacologic, and phase I studies of gemcitabine. *Semin Oncol.* 1997;24(2 suppl 7):S7-2-S7-7.

91. O'Rourke TJ, Brown TD, Havlin K, et al. Phase I clinical trial of gemcitabine given as an intravenous bolus on 5 consecutive days. *Eur J Cancer.* 1994;30A:417-8.

92. Jones JA, Avritscher EB, Cooksley CD, et al. Epidemiology of treatment-associated mucosal injury after treatment with newer regimens for lymphoma, breast, lung, or colorectal cancer. *Support Care Cancer.* 2006;14:505-515. Epub 2006 Apr 7.

93. Friedlander PA, Bansal R, Schwartz L, et al. Gemcitabine-related radiation recall preferentially involves internal tissue and organs. *Cancer.* 2004;100:1793-1799.

94. Rube CE, Wilfert F, Uthe D, et al. Increased expression of pro-inflammatory cytokines as a cause of lung toxicity after combined treatment with gemcitabine and thoracic irradiation. *Radiother Oncol.* 2004;72:231-241.

95. 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;22:1706-1712.

96. Liu X, Guo Y, Li Y, et al. Molecular basis for G2 arrest induced by 2'-C-cyano-2'-deoxy-1-beta-D-arabino-pentofuranosylcytosine and consequences of checkpoint abrogation. *Cancer Res.* 2005;65:6874-6881.

97. Hanaoka K, Suzuki M, Kobayashi T, et al. Antitumor activity and novel DNA-self-strand-breaking mechanism of CNDAC (1-(2-C-cyano-2-deoxy-beta-D-arabino-pentofuranosyl) cytosine) and its N4-palmitoyl derivative (CS-682). *Int J Cancer.* 1999;82:226-236.

98. Wu M, Mazurchuk R, Chaudhary ND, et al. High-resolution magnetic resonance imaging of the efficacy of the cytosine analogue 1-[2-C-cyano-2-deoxy-beta-D-arabino-pentofuranosyl]-N(4)-palmitoyl cytosine (CS-682) in a liver-metastasis athymic nude mouse model. *Cancer Res.* 2003;63:2477-2482.

99. Dinçbaşı FO, Koca S, Mandel NM, et al. The role of preoperative radiotherapy in nonmetastatic high-grade osteosarcoma of the extremities for limb-sparing surgery. *Int J Radiat Oncol Biol Phys.* 2005;62:820-828.

100. Anderson PM, Wiseman GA, Erlandson L, et al. Gemcitabine radiosensitization after high-dose samarium for osteoblastic osteosarcoma. *Clin Cancer Res.* 2005;11:6895-6900.

101. Machak GN, Tkachev SI, Solovyev YN, et al. Neoadjuvant chemotherapy and local radiotherapy for high-grade osteosarcoma of the extremities. *Mayo Clin Proc.* 2003;78:147-155.

102. Anderson PM. Effectiveness of radiotherapy for osteosarcoma that responds to chemotherapy. *Mayo Clin Proc.* 2003;78:145-146.

103. Mueller F, Poirier V, Melzer K, et al. Palliative radiotherapy with electrons of appendicular osteosarcoma in 54 dogs. *In Vivo.* 2005;19:713-716.

104. Mahajan A, Anderson P, Woo SY, et al. Multimodality local management of recurrent osteosarcoma including radiotherapy, samarium, and chemotherapy. *Pediatr Blood Cancer.* 2006;47:501.

105. Ferguson WS, Harris MB, Goorin AM, et al. Presurgical window of carboplatin and surgery and multidrug chemotherapy for the treatment of newly diagnosed metastatic or unresectable osteosarcoma: Pediatric Oncology Group Trial. *J Pediatr Hematol Oncol.* 2001;23:340-348.

106. Daw NC, Billups CA, Rodriguez-Galindo C, et al. Metastatic osteosarcoma. *Cancer.* 2006;106:403-412.

107. Anderson P. Samarium for osteoblastic bone metastases and osteosarcoma. *Expert Opin Pharmacother.* 2006;7:1475-1486.

108. Kraybill WG, Harris J, Spiro IJ, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *J Clin Oncol.* 2006;24:619-625.

109. Anderson P, Salazar-Abshire M. Improving outcomes in difficult bone cancers using multimodality therapy, including radiation: physician and nursing perspectives. *Curr Oncol Rep.* 2006;8:415-422.

110. Winkler F, Kozin SV, Tong RT, et al. Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases. *Cancer Cell.* 2004;6:553-563.

111. Tong RT, Boucher Y, Kozin SV, et al. Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors. *Cancer Res.* 2004;64:3731-3736.

112. Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med.* 2004;10:145-147. Epub 2004 Jan 25.

113. Kozin SV, Boucher Y, Hicklin DJ, et al. Vascular endothelial growth factor receptor-2-blocking antibody potentiates radiation-induced long-term control of human tumor xenografts. *Cancer Res.* 2001;61:39-44.

114. Willett CG, Boucher Y, Duda DG, et al. Surrogate markers for antiangiogenic therapy and dose-limiting toxicities for bevacizumab with radiation and chemotherapy: continued experience of a phase I trial in rectal cancer patients. *J Clin Oncol.* 2005;23:8136-8139.

115. Lin C, McGough R, Aswad B, et al. Hypoxia induces HIF-1alpha and VEGF expression in chondrosarcoma cells and chondrocytes. *J Orthop Res.* 2004;22:1175-1181.

116. McGough RL, Lin C, Meitner P, et al. Angiogenic cytokines in cartilage tumors. *Clin Orthop Relat Res.* 2002;62-69.

117. Temple CL, Ross DC, Magi E, et al. Preoperative chemoradiation and flap reconstruction provide high local control and low wound complication rates for patients undergoing limb salvage surgery for upper extremity tumors. *J Surg Oncol.* 2007;95:135-141.