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, bigdose 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.

**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-
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.25 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 others69) 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 chemotherapeutic 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.13 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)1216 and sapacitabine17,18 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 isophosphoramide 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. 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 isophosphoramide mustard (IPM; ZIO-201) and glufosfamide (beta-D-glucosyl-IPM).12,16,37,38 Direct administration of IPM or glufosfamide has pharmacologic advantages of avoiding generation of neurotoxic chloroacetaldehyde and urotoxic acrolein (Fig 1). Glufosfamide has potential to more specifically target fluorodeoxyglucose (FDG)-avid high-grade sarcomas that image well on positron-emission tomography (PET) via an upregulated glucose
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. 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. 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.

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, 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. The O6-methylguanine adduct causes mismatch during DNA replication and addition of a thymidine instead of cytosine to the newly formed DNA strand. Because of excellent CNS biodistribution, temozolomide has been useful as a radiosensitizer in both primary brain tumors and CNS metastases. The pharmacokinetics of temozolomide has been studied in children, and clearance is related to body surface area. Temozolomide improves quality of life when used with radiation in patients with brain metastases. Like dacarbazine, temozolomide has activity against sarcomas. 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. Temozolomide-containing regimens are summarized in Table 2.

The combination of temozolomide and irinotecan is more than additive against some cancers. 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. The temozolomide plus irinotecan combination is less immune suppressive than standard ifosfamide- or cyclophosphamide-containing regimens. 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. Temozolomide or dacarbazine has also been combined with other drugs including gemcitabine and doxorubicin liposomes.

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. Gemcitabine (difluorodeoxycytidine [dFdC]) enters the cell by facilitated diffusion or through co-transporters.
Inside the cell, phosphorylation by the enzyme deoxy-cytidine 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 termination81,82 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.85,86

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 2. — Temozolomide-Containing Regimens

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temozolomide</td>
<td>75 mg/m² daily</td>
<td>2 to 6 weeks</td>
<td>Oral home therapy; give at bedtime</td>
</tr>
<tr>
<td>Temozolomide +</td>
<td>100 mg/m² daily × 5</td>
<td>Week 1 and 4</td>
<td>Active in Ewing’s sarcoma and DSRCT</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>10 mg/m²/dose × 5</td>
<td>Weekly × 2</td>
<td>Week 1, 2 then 4, 5</td>
</tr>
<tr>
<td>Temozolomide +</td>
<td>100 mg/m²/dose × 5</td>
<td>Week 1, daily × 5</td>
<td>IV over 1 hour</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>600–1000 mg/m²</td>
<td>Week 1 and 2</td>
<td></td>
</tr>
</tbody>
</table>

IV = intravenous infusion

### Table 3. — Gemcitabine Schedule Recommendations for Radiosensitization*

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

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

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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.
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.\textsuperscript{17,18} Sapacitabine causes G\textsubscript{2} arrest and chain termination.\textsuperscript{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.\textsuperscript{97,98}

**Chemotherapy Plus Radiation Regimens in Osteosarcoma**

**Ifosfamide, Cisplatin, or Methotrexate Followed by Samarium + Gemcitabine**

RT can facilitate local control of osteosarcoma.\textsuperscript{7,29,99-104} Chemotherapy seems to markedly improve effectiveness of local control RT.\textsuperscript{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.\textsuperscript{95} Carboplatin has inferior activity to cisplatin in osteosarcoma.\textsuperscript{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 G\textsubscript{2} (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 (\textsuperscript{153}Sm-EDTMP) to target radiation to osteosarcoma lesions avid on bone scan, a radiosensitizer (eg, gemcitabine) can be given after the unbound isotope is cleared.\textsuperscript{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.\textsuperscript{107} Because of heterogeneity of isotope deposition in bone-forming osteosarcoma tumors, 153-samarium 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.\textsuperscript{104,107}

**Discussion**

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

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**Table 4. — Osteosarcoma Outpatient Chemotherapy Regimens for Radiosensitization**

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

\( \text{IV} = \text{intravenous route} \)

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, \textsuperscript{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.\textsuperscript{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 chemothera-py 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.\textsuperscript{110,111} 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.\textsuperscript{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.\textsuperscript{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 calendar\textsuperscript{113}) 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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