CLINICAL UPDATE

Translating Scientific Advances into Clinical Practice

Maintenance Therapy in the Treatment of Sarcoma

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H&O What is the current treatment landscape in sarcoma?

IRC When discussing sarcoma, it is important to note the difficulty of the heterogeneous management of sarcoma patients in France, but also across the United States and Europe. One of the major problems that we face is managing sarcoma in the localized phase, particularly in terms of diagnosis and surgery. Unfortunately, more than one-third of patients to date do not receive adapted management for diagnosis or surgery. The process of diagnosis, classification, and management of sarcoma has not been well organized. However, in 2009, the National Cancer Institute of France decided to harmonize the management of this heterogeneous group of rare tumors. The reorganization included a national network supported by 3 referent institutions (Centre Léon Bérard, Lyon; Institut Gustave Roussy, Villejuif; and Institut Bergonié, Bordeaux). These institutions are in charge of coordinating the management of diagnosis via systematic second opinion provided by pathology experts dedicated to sarcoma. The goal is to obtain better and more accurate diagnoses and to train surgeons in the surgical management of sarcoma.

Concerning the management of metastatic patients, in general, more than half of patients receive treatment in a referent or an expert center. In France, there are now centers with a multidisciplinary staff that is responsible for discussing medical records of patients being treated for sarcoma. The main goal is to have discussions regarding prognosis and treatment for each patient by a team of experienced physicians. This would allow patients to be treated in other institutions outside of referent centers.

Sarcoma patients usually present with 1 of 2 scenarios: patients with metastatic disease who are unable to achieve complete remission with chemotherapy (90%) or patients with metastatic disease in whom complete remission is feasible with chemotherapy and surgery (10%). In patients who cannot undergo surgery for their metastases, we prefer to use doxorubicin alone. In the first-line setting, for patients in whom we expect to achieve remission with surgery after they have completed chemotherapy, we use a combination of adriamycin and ifosfamide. In the second-line setting, we give patients trabectedin (Yondelis, Pharmamar/Johnson & Johnson) or gemcitabine. There are exceptions based on specific subtypes of sarcoma; for example, in patients with angiosarcoma, the preferred treatment is weekly paclitaxel. Other sarcoma subtypes such as Kaposi sarcoma and alveolar soft tissue sarcoma also call for different drug therapies.

In osteosarcoma, the treatment approach is different mainly because the majority of patients are adolescent or pediatric. The majority of patients receive chemotherapy in the neoadjuvant phase before surgery, and chemotherapy in the adjuvant phase. If patients relapse—depending on the time between initial treatment and relapse—they are given the same protocol, or another drug such as ifosfamide, etoposide, or vincristine. At this time, we have no standard treatment if second-line therapy fails.

H&O Can you discuss the SUCCEED study?

IRC Our institution was one of the groups that participated in the SUCCEED (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus) trial. The findings, which were reported at the 2011

American Society of Clinical Oncology meeting, were interesting in regard to the benefit observed with the mammalian target of rapamycin (mTOR) inhibitor ridaforolimus (Ariad) in progression-free survival (PFS) and overall survival (OS). A PFS benefit was observed in patients receiving ridaforolimus compared to placebo (17.7 months in ridaforolimus patients vs 14.6 months for placebo patients). In terms of OS, the benefit seen in ridaforolimus-treated patients was small compared to patients receiving placebo. This finding can be attributed to the very heterogeneous patient population that was enrolled in the study. The side effects were consistent with the safety profile of ridaforolimus, and the agent was well tolerated in the majority of patients. The follow-up for OS is ongoing, and the medical community is awaiting more data on survival and the particular subtypes of sarcoma that appear to benefit from ridaforolimus.

H&O Are there any other studies investigating sarcoma maintenance therapy?

IRC Aside from the SUCCEED trial, there are no additional clinical trials that have shown benefit in the maintenance setting. Pazopanib (Votrient, GlaxoSmithKline), a multi-tyrosine kinase that targets the vascular endothelial growth factor (VEGF) pathway, was investigated in the PALLETE (Pazopanib Explored in Soft-Tissue Sarcoma) study. This phase III trial randomized 369 patients with metastatic soft-tissue sarcoma on a 2 to 1 basis to pazopanib or placebo. The study showed a 69% reduction in the risk of progression or death in patients who received pazopanib. The PFS in patients receiving pazopanib was superior compared to those receiving placebo, at 4.6 and 1.5 months, respectively. However, the difference in OS was not statistically significant. Pazopanib was given after 2 lines of treatment, but not specifically for maintenance therapy. The patient population was mixed. Due to the specific VEGF pathway inhibited by pazopanib, I think more physicians are going to be interested in the molecular mechanism of treatment of this drug compared to mTOR inhibitors, as it is probable that only some specific subtypes benefit from mTOR inhibition (ie, uterine leimyosarcoma for example).

H&O What are some of the prognostic factors that are important in assessing sarcoma treatment?

IRC It is important to look at the subtype of the sarcoma in addition to evaluating the patient profile in regard to safety (eg, lymphopenia). It would be ideal to have more detailed predictive and prognostic markers to guide treatment, and it is necessary to conduct more clinical trials focusing on predictive markers to determine which patients and which tumors have the best response.

H&O What can we expect in the next 5–10 years in maintenance sarcoma therapy?

IRC I think this is a complex area of investigation. We are presented with various challenges in the diagnosis, classification, and management of the myriad subtypes of sarcoma. We are able to rapidly segregate the different subtypes of sarcoma and we know that the pathways involved in the proliferation and the development of metastatic disease are not the same in the different tumor subtypes. In the near future, we hope to treat patients with sarcomas not just with chemotherapy, but also with molecularly targeted treatments appropriate for their tumor type.

Suggested Readings

Chawla SP, Blay J, Ray-Coquard IL, et al. Results of the phase III, placebo-controlled trial (SUCCEED) evaluating the mTOR inhibitor ridaforolimus (R) as maintenance therapy in advanced sarcoma patients (pts) following clinical benefit from prior standard cytotoxic chemotherapy (CT). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29:Abstract 10005.

Van Der Graaf WT, Blay J, Chawla SP, et al. PALETTE: A randomized, double-blind phase III trial of pazopanib versus placebo in patients with soft-tissue sarcoma (STS) whose disease has progressed during or following prior chemotherapy—An EORTC STBSG Global Network Study (EORTC 62072). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29:Abstract LBA10002.

Ray-Coquard I, Le Cesne A. A role for maintenance therapy in managing sarcoma. *Cancer Treat Rev*. 2011 Aug 13. [Epub ahead of print]