Quality of Life Improvements in Sarcoma Therapy

Levine Cancer Institute’s multidisciplinary sarcoma team evaluates patients for current treatment options and novel research studies. However, a major consideration is the patient’s quality of life. The two major drugs used for sarcoma therapy, doxorubicin and ifosfamide, can be given with increased safety and fewer side effects. After Europe, the Middle East and Africa banned use of dexrazoxane because of potential concern about increase in MDS in Europe, the Children’s Oncology group did an analysis of more than 1,000 osteosarcoma patients treated in four studies. Lisa Kopp, MD, reported the results at the American Society of Clinical Oncology: development of MDS was very rare in this population and there were no increased events when comparing osteosarcoma patients who had received dexrazoxane before doxorubicin versus doxorubicin alone. Therefore, to reduce incidence of long-term cardiotoxicity, the use of dexrazoxane is not contraindicated. It is Dr. Anderson’s opinion that benefit (less mucositis in the short term and less cardiotoxicity in the long term) outweighs any potential risk. For patients who have received more than 350 mg/m2 or have a more than 10 percent decrease in EF, Dr. Anderson has safely used doxorubicin liposomes in both osteosarcoma and Ewing’s sarcoma patients.

There is a new option to reduce mucositis: glutamine-disaccharide controlled (swish/swallow for 10 seconds). Dr. Anderson has published one pilot study, and two randomized placebo clinical trials, and designed a successful one in breast cancer patients, too. An improved glutamine disaccharide formulation (orange- or grape-flavored), now commercially available (healiosproducts.com), has trehalose in addition to sucrose to promote the entry (roughly 1,000 times greater) of the glutamine nutrient into mucosal cells.

Pazopanib, an oral drug for recurrent soft tissue sarcomas is now commercially available. The mechanism of action is VEGF inhibition. This drug is generally well tolerated at 800 mg per day. A common side effect is a salt and peppering or whitening of the hair. Fatigue can usually be managed by taking the drug at bedtime. Diarrhea and GI side effects, when they occur, are managed with loperamide.
Message from the President of Levine Cancer Institute

Derek Raghavan, MD, PhD
President, Levine Cancer Institute

We’ve been busy at Levine Cancer Institute, focusing on growth and review of progress. Carolinas HealthCare System was granted nursing Magnet status, and our team was delighted to be able to support our nursing leadership in the review process. Oncology nursing, and the certifications and responsibilities that go with this crucial discipline, are a huge part of Levine Cancer Institute’s values, and it was exciting to the extramural validation. We were delighted that the Commission on Cancer reviewed seven of our programs and accorded us highest honors, with eight out of eight commendations.

We continue to recruit actively. Jon Gerber, MD, and Mike Grunwald, MD, have joined us from Johns Hopkins Cancer Center to expand the leukemia program, and Saad Usmani, MD, from Bart Barlogie’s program at the University of Arkansas, now leads the myeloma program. Larry Druhan, PhD (Ohio State Comprehensive Cancer Center) and Sarah Baxter, PhD, (David Murdoch Research Institute) provide laboratory leadership in the Hematology Oncology Translational Labs. Jimmy Hwang, MD, has joined us from Georgetown University, where he was director of the Fellowship Program, to develop a Hematology and Oncology Fellowship, and to help lead in advanced upper gastro-intestinal cancers and phase I trials. Jai Patel, Pharm. D., has joined us from UNC Chapel Hill, to provide pharmacologic support for our early phase trials program. Leila Hadzikadic Gusic, MD, and Meg Forster, MD, surgical oncologists, from University of Pittsburgh Cancer Institute and the Moffitt Cancer Center, respectively will be helping develop our programs in breast cancer and upper gastrointestinal cancer. Roshan Prabhu, MD, has joined the Levine Cancer Institute /SERO collaboration, coming from the very strong radiation oncology program at Emory University.

The Levine Cancer Institute External Advisory Board completed our first formal review in late July. This true blue ribbon panel includes:

- Donald “Skip” Trump, MD, President of Roswell Park Cancer Institute (chair)
- John DiPersio, MD, chief, Hematologic Oncology and deputy director, Washington University Comprehensive Cancer Center
- Norm Hubbard, PhD, (senior administrator, Seattle Cancer Care Alliance)
- Fadlo Khuri, MD, (chief of Medical Oncology, Emory University/Winship Cancer Institute)
- David Johnson, MD, (chair of medicine, UT Southwestern and a former ASCO president), a member, but unable to attend this review
- Mark Legnini, PhD, (former leader of health policy and planning at Brookings Institute, now a consultant)
- Debasish Roychowdhury, MD, (chief medical officer, Sanofi Aventis)
- Michael Steinberg, MD, (chair, Radiation Oncology at UCLA and health consultant for many years to the Rand Corporation)
- David Winchester, MD, (surgical oncologist and medical director, American College of Surgeons Cancer Programs)

Their preliminary report indicates strong endorsement for our direction and aims, and the extraordinary progress over the past two years, with the addition of more than 80 faculty to Levine Cancer Institute.

As part of our quest for excellence, we also underwent a formal review of our Medical Physics program in Radiation Oncology, completed last month by Tim Fox, MD, (chief of Physics, Emory University) and Ping Xia, MD, (chief of Medical Physics, Cleveland Clinic Taussig Cancer Center). Their report is eagerly awaited.

We seem to be on track to develop a really unique resource for this region, providing better care and research for our patients, with a focus on innovation and support. This edition will tell you more.

Sincerely,

Derek Raghavan, MD, PhD
President, Levine Cancer Institute

We welcome your feedback at levinecancerinstitute@carolinahealthcare.org and look forward to bringing you more news in the future!
The management of multiple myeloma (MM) has seen a drastic change over the last 15 years, with the median survival for an average MM patient improving from more than 2 years to 7 to 10 years. MM represents a malignant clonal expansion of transformed plasma cells. These cells eventually undergo clonal evolution and heterogeneity, which is believed to be the basis of drug-resistance with sequencing therapy. This makes MM a complex, multi-hit malignancy with a prognosis and outcome that is extremely variable, even in the era of novel agents.

The initial prognostic models were developed based on clinical observations and routine laboratory findings. The most commonly used systems are International Staging System (ISS) and Durie-Salmon Staging (DSS), which includes data on the presence of bone lytic lesions, calcium, creatinine, albumin, b-2 microglobulin, hemoglobin concentration and serum levels of monoclonal proteins. Both these models provide an estimation of burden of disease and also capture host factors/morbidity, but do not account for the biologic heterogeneity of MM. Several techniques using comprehensive evaluation of bone marrow samples (metaphase cytogenetics, fluorescent in situ hybridization and gene expression profiling) have helped us identify the biologic bad actors in MM.

The eventual goal of prognostication for any human disease is to provide for risk-adaptive therapeutic strategy. Clinicians and cancer researchers now recognize that such prognostication needs to include the host factors (age, co-morbidities and performance status), disease burden (ISS and/or DSS) and disease biology. MM researchers recognize that our ability to assess the depth of response, by way of following serum M proteins and/or bone marrow examinations, is inadequate. Inclusion of novel imaging (PET/CT) and specialized lab tests (DNA PCR and/or flow cytometry) to assess minimal residual disease are being included to assess better depth of response in clinical trials. We also recognize that we need to find a better answer for high-risk myeloma patients and develop new drug classes that can improve their outcomes.

Levine Cancer Institute’s Plasma Cell Disorders program has opened its doors to patients at its administrative and research headquarters in Charlotte, NC. The program brings these advances in management to the MM patients being cared for in Carolinas HealthCare System. We intend to achieve this goal by establishing uniform practice guidelines which help the oncologists across the Institute’s vast network of satellite sites in treating MM patients and have readily available access to expert opinion. The program also brings value to Carolinas HealthCare System communities by offering clinical trials with novel treatments for both newly diagnosed and previously treated MM patients.
Novel Approaches for Bone Metastasis

Bone metastases are a common source of morbidity in patients with metastatic cancer. Disease involving the spine is of particular interest due to the risk of developing metastatic epidural spinal cord compression (MESCC). In addition, pain and structural instability can greatly compromise patient performance status. The management of spinal metastases presents a unique challenge, requiring a multidisciplinary approach. When evaluating metastatic involvement of the spine, one must consider current neurologic function, radiation sensitivity, mechanical stability and systemic disease characteristics [1]. Surgical resection followed by fractionated radiation is the standard of care for MESCC. However, the management of the non-compressive tumors, inoperable patients, previously irradiated lesions, or radioresistant histologies (sarcoma, renal cell carcinoma or melanoma) require a more variable approach. In all these settings, the proximity of tumor to the spinal cord makes delivering a tumor ablative dose while sparing adjacent neural tissues, a unique challenge.

Using stereotactic techniques and prior knowledge of the radiation tolerance of the spinal cord, experience with spinal SBRT has shown long-term local control of more than 90 percent, including favorable outcomes for radioresistant histologies. Common fractionation schemes include 6 to 30 Gy in 1 to 5 fractions. Multiple institutional studies suggest an SBRT approach is more effective than conventional doses in all but the most radiation-sensitive histologies (lymphoma, myeloma, germ cell tumors). Limitations of these studies include heterogeneity in patient characteristics, reported endpoints, and fractionation schemes, making it difficult to unify into concise treatment recommendations. RTOG 0631, recently opened at Levine Cancer Institute has initiated the phase III portion of the trial comparing SBRT to high dose conventional radiation for spinal metastases with a primary endpoint of pain control. Other areas of active investigation include defining the role of SBRT for inoperable spinal cord compressive lesions and residual disease post-operatively. Optimizing fractionation schemes to balance local control, pain response, and the risk of neurologic sequelae or post-treatment vertebral body fracture will be important moving forward [2]. At Levine Cancer Institute, we are participating in cooperative group studies and establishing multidisciplinary approaches to spinal tumors.

In patients with multifocal symptomatic bone metastasis, systemic Radiopharmaceuticals can be an effective pain control strategy. Agents such as Strontium89 and Samarium153-EDTMP, which decay through beta emission, have been shown to result in high rates of objective pain response [3]. Concerns regarding bone marrow suppression without demonstrated efficacy for endpoints beyond pain control have limited the broad implementation of these agents. In May, the FDA approved Radium 223 Dichloride, the first alpha particle emitting radiopharmaceutical, for use in patients with castrate-resistant metastatic prostate cancer (CRPC), with symptomatic bone disease and no visceral metastases, based upon the results of the phase III ALSYMPCA trial [4]. This study randomized 921 CRPC patients, who were otherwise receiving the highest standard of care in a 2 to 1 fashion to Radium 223 versus placebo. The study showed improvements in the trial’s primary end point of survival (14.9 months vs. 11.3 months; P<0.001) and time to skeletal-related events (15.6 months vs. 9.8 months; P<0.001). Furthermore, no clinically meaningful differences in the rate of grade 3 or 4 toxicities were observed between arms.

Radium 223 is incorporated into hydroxyapatite formation, preferentially at sites of increased bone turnover. Once deposited, it undergoes a series of alpha particle (two protons and two neutrons) emissions with a half-life of 11.6 days. An alpha particle has 7,300 times the mass of a beta particle, transferring much higher energy to the surrounding tissue and resulting in more potent anti-tumor effects via non-repairable double-stranded DNA breaks. As a result of their size, they also manifest increasing stopping power and shorter effective ranges at the target site compared to beta particles. For Radium 223 decay, the range is measured at less than 100 μm, minimizing bone marrow suppression. By comparison, therapeutic beta-emitters have a range of 2.5-7 mm. Based upon...
Update in HPV-Related Head and Neck Cancers

The incidence of oropharyngeal (tonsil and base of tongue) squamous cell carcinoma (OPSCC) is rapidly increasing and is directly associated with the rising rates of human papilloma virus (HPV) infection. Fortunately, these patients with HPV-related OPSCC are generally younger and have significantly improved survival rates in comparison to those with smoking- and alcohol-induced carcinoma.

The goals of cure and quality of life are of equal and critical importance. To achieve these goals, it takes a comprehensive team approach. Surgery, chemotherapy and radiation therapy all serve vital roles in the treatment of OPSCC. Evaluation and treatment by oral medicine, speech therapy, and physical therapy are very important to minimize post-treatment sequela.

Thus, a multidisciplinary evaluation by medical oncology, radiation oncology, and head and neck surgical oncology is necessary to chart the ideal treatment plan which is individualized for each patient and compliant with the standards of care.

Multimodality care of patients with OPSCC is critical for both curative purposes and functional outcomes. Current treatment outside of the research trial setting should still focus on standard therapy with multidisciplinary discussion prior to treatment initiation.
Progress in the treatment of metastatic gastroesophageal cancers has been slow. In patients with HER-2 overexpressing/amplified disease, the ToGA study proved the addition of trastuzumab to cisplatin/fluoropyrimidine therapy improved survival (1). Since then, other molecularly-targeted therapies, including bevacizumab, cetuximab, panitumumab, and everolimus failed to show significant survival benefits in large randomized trials (2-5). 2013 has produced mixed results.

At the Gastrointestinal Cancer Symposium, Fuchs reported a phase III study in the second-line setting comparing ramucirumab (IMC 1121), a fully human monoclonal antibody targeting VEGF Receptor 2, to placebo (Table 1). Ramicirumab significantly improved survival, primarily by stabilizing disease, and was tolerable, about as anticipated with anti-VEGF monoclonal antibodies (6). Additional data from a parallel study of paclitaxel with or without ramucirumab is expected.

Hecht presented a phase III study evaluating lapatinib in HER-2 amplified metastatic gastroesophageal adenocarcinomas at the ASCO annual meeting (Table 2). Patients were randomized to oxaliplatin and capecitabine (850 mg/m2 BID D#1-14) every three weeks with either lapatinib 1250 mg daily, or placebo. Adding lapatinib to chemotherapy increased overall survival somewhat, but not significantly. However, lapatinib also increased toxicity, especially severe diarrhea and rash (7). Lapatinib may not have performed as expected because the greater toxicities that occurred in combination with chemotherapy may have resulted in lower dose intensity. Our future approaches will focus on innovative therapies that add both clinical relevance to statistical significance.

Optimism about the potential of targeted therapy in gastroesophageal cancer continues. Further exploration of HER-2 targeting therapies persists with pertuzumab (with trastuzumab), and ado-trastuzumab-emtansine (T-DM1), in the initial and second line settings respectively, based on their efficacy in breast cancer.

Immunotherapy, especially the PD-1 pathway, is an area of investigation in many malignancies, which may overexpress the ligands PDL-1 or PDL-2, thereby suppressing immune surveillance. Inhibiting interactions between PD-1 and its ligands, currently with antibodies, may help eradicate malignancy. Data from patients with gastric cancer suggests that targeting the PD-1 pathway is beneficial (8).

Another promising target is c-Met, a tyrosine kinase receptor activated by its ligand HGF.
FLIMS Workshop Recap

Kathryn R. Mileham, MD
Medical Oncologist at Levine Cancer Institute, part of Carolinas HealthCare System, was selected to attend the 15th annual Methods in Clinical Cancer Research Meeting in Flims, Switzerland. Dr. Mileham was one of five delegates from North America selected to attend this prestigious international workshop, which focuses on the development of protocols and translational research studies. Dr. Mileham’s study proposal centered on targeting specific biomarker pathways in early stage lung cancer patients.

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Ifosfamide+ mesna is a commonly used regimen for treatment of bone and soft tissue sarcomas. Dr. Anderson recently published stability results so pharmacies have information for prolonged seven- or 14-day infusions. The excellent stability of ifosfamide+ mesna at 20 mg/mL for seven and 14 days allows portable pumps and outpatient treatment. Use at Levine Children’s Hospital and Levine Cancer Institute will involve rental/consignment of reliable pumps by InfuSystem. Oncology pharmacy will provide the mesna + ifosfamide in a 200-1000 mg bag to be carried in a backpack, handbag or other bag. This should offer an easy and reliable means to give ifosfamide/mesna to patients on an outpatient basis. The InfuSystem is also useful for overnight mesna infusions after cyclophosphamide. Using this setup, both Levine Children’s Hospital and Levine Cancer Institute can facilitate more outpatient-friendly sarcoma therapy.

Finally, there is a new targeted alpha-emitting radiopharmaceutical for bone metastases, radium-223. This drug (Xifigo) is FDA approved for prostate cancer, but should also become a useful adjunct in the treatment of osteosarcoma. The advantage of alpha emitters is low marrow toxicity and less likelihood of resistance, since the high energy charged alpha particles cause difficult-to-repair double strand breaks in cancer cells. Thus, axial or metastatic cases may have new and better means to facilitate control, with or without surgery or external beam radiotherapy. Since the radiopharmaceutical acts like calcium and is incorporated into new bone, the screening test is a routine bone scan to identify osteoblastic lesions amenable to this new alpha radiotherapy.

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(hepatocyte growth factor). About half of patients with gastroesophageal cancers express c-Met, making this an attractive target (9). Onartuzumab (MetMAb), a monoclonal antibody targeting c-Met, is being evaluated in randomized studies in combination with oxaliplatin/5FU (FOLFOX). Tivantinib (ARQ197), a tyrosine kinase inhibitor of c-Met, is also being evaluated with FOLFOX.

Hopefully, we are entering an era in gastroesophageal cancer where treatment decisions will be determined by the patient’s and their tumor’s molecular characteristics.

REFERENCES:

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the benefits and favorable side effect profile observed in this trial, expanded and evolving indications will likely be forthcoming.

REFERENCES:
Personalized Leukemia Care in the Carolinas

Levine Cancer Institute is removing obstacles to the care of oncology patients by delivering cancer care closer to home. This summer witnessed the inception of the leukemia program within the Department of Hematologic Oncology and Blood Disorders. The leukemia program provides cutting-edge care for patients with acute and chronic leukemias, as well as myelodysplastic syndrome and the myeloproliferative neoplasms. With the planned opening of the blood and marrow transplant (BMT) unit in early 2014 and the introduction of new clinical studies, Levine Cancer Institute will offer optimal and comprehensive care to leukemia patients throughout the Carolinas.

Personalization has increasingly become a goal of leukemia treatment. Indeed, the early recognition that AML is a heterogeneous disease prompted efforts to risk-stratify patients. Current risk assessment is primarily based upon cytogenetic and molecular characteristics. These features help identify poor risk patients who might benefit from consolidation with allogeneic BMT and provide promising targets for both current and future therapies. Despite this progress, most AML patients who achieve complete remission are not ultimately cured. Existing risk factors are not able to prognosticate well for individual patients, particularly those in the favorable and intermediate risk groups. The leukemia stem cell (LSC) model has gained acceptance as a potential explanation as to why remission often does not translate to cure. Standard chemotherapy is typically effective at wiping out the differentiated bulk of the leukemia, but emerging data suggests that the LSCs are more resistant. The few surviving LSCs may be too few in number to detect by clinically available means. In such cases, the patient appears to be in complete remission. However, any remaining LSCs ultimately regenerate the leukemia, with resultant clinical relapse. As such, only those patients in whom the LSCs are fully eradicated would be predicted to attain cure.

A recently developed flow cytometry-based assay is proving promising in detecting LSCs and predicting which AML patients (who are otherwise in complete remission, based on existing clinical parameters) are likely to relapse. Such assays potentially offer another manner in which leukemia care can be personalized. Patients with persistent LSCs (thus, at high risk of eventual relapse) can be assigned to more intensive therapy such as BMT or to a clinical trial.

Levine Cancer Institute will soon be offering clinical trials with novel targeted agents for hematologic malignancies. We will have the ability - also via a clinical protocol - to assess for the presence of LSCs after treatment. This assay will allow us to determine which novel agents are active against the LSCs and, thus, have curative potential. This ability to personalize therapies and administer them locally whenever feasible will ensure that Levine Cancer Institute delivers the best care possible for patients with leukemia.

REFERENCES