ASSOCIATION
OF COMMUNITY
CANCER CENTERS

MULTIDISCIPLINARY MULTIPLE MYELOMA CARE

MODELS OF EFFECTIVE
CARE DELIVERY

ACCC
Association of Community Cancer Centers

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INTRODUCTION

In the United States, approximately 30,000 patients are diagnosed with multiple myeloma each year.[1] Compared to many cancers, multiple myeloma is relatively rare and represents approximately 2% of all new cancer cases in the United States.[2] Multiple myeloma is most frequently diagnosed in people ages 65-74, and the incidence of myeloma has been rising approximately 0.9% each year between 2005 and 2015.[2] Globally, the incidence of myeloma has increased by 126% between 1990 and 2016.[3] It is estimated that the average general hematologist/oncologist in the community may only diagnose multiple myeloma in two new patients and treat six established patients with the disease each year.[4]

Multiple myeloma is a heterogeneous condition and recent advances in molecular medicine and targeted therapeutics have made it more complex to classify, risk stratify, and treat patients. Since 2006, a host of new drugs have been approved to treat multiple myeloma and treatment approaches have changed considerably. Patients with multiple myeloma may now be treated with immunomodulatory agents (IMiDs), proteasome inhibitors, monoclonal antibodies targeting SLAMF7 and CD38, and/or other therapies that are being studied in clinical trials. They may also receive bone-modifying agents such as bisphosphonates or a RANK ligand (RANKL) inhibitor (e.g., denosumab) for the prevention or management of skeletal-related events (SREs).

Stem cell transplant is often a part of the initial plan of therapy and has been shown to prolong progression-free and overall survival in transplant-eligible patients with multiple myeloma.[5] Patients who choose to receive a stem cell transplant may need to travel to transplant centers, so their pre- and post-transplant care is often co-managed between the transplant team and their local cancer care team.

Recognizing the growing complexity of managing patients with multiple myeloma, the Association of Community Cancer Centers (ACCC) launched an educational project with the Multiple Myeloma Research Foundation (MMRF) to identify effective practices and to foster a network of engaged cancer care professionals who are dedicated to the treatment of patients with multiple myeloma. ACCC conducted three cancer program site visits and spoke with clinical experts and members of the multidisciplinary team to better understand how different types of cancer centers are incorporating a multidisciplinary approach to diagnosing and managing patients with multiple myeloma.

RECENT UPDATES IN MULTIPLE MYELOMA MANAGEMENT

Diagnostic Criteria by International Myeloma Working Group (IMWG)

Historically, multiple myeloma has been defined by the presence of end-organ damage that followed the acronym CRAB: Calcium (hypercalcemia), Renal failure, Anemia, and Bone lesions.[6] In 2014, the International Myeloma Working Group (IMWG) updated the diagnostic criteria for active multiple myeloma by adding three specific biomarkers that can be used to diagnose the disease in patients who do not have CRAB features: 1) clonal bone marrow plasma cells greater than or equal to 60%; 2) serum free light chain (FLC) ratio greater than or equal to 100 provided involved FLC level is 100 mg/L or higher; 3) or more than one focal lesion on MRI.[7] The updated criteria also include CT and PET-CT as imaging modalities to diagnose bone disease. Clinicians can now diagnose active multiple myeloma and intervene before end-organ damage occurs in select patients who are at high risk of disease progression.

Revised International Staging System (R-ISS)

Historically, tumor burden in multiple myeloma was assessed using the Durie-Salmon Staging (DSS)[8] and the International Staging System (ISS).[9] Neither staging system considers important elements of disease biology such as the molecular subtype of the disease, the presence or absence of specific cytogenetic abnormalities, nor markers of disease aggressiveness such as serum lactate dehydrogenase (LDH). In 2015, the IMWG published the Revised International Staging System (R-ISS) which combines elements of tumor burden and disease biology to provide a more accurate prognostic index.[10] Advances in molecular and cytogenetic testing are allowing clinicians to use R-ISS to better predict outcomes and tailor treatment plans for each patient.

ASCO Clinical Practice Guideline Update: Role of Bone-Modifying Agents in Multiple Myeloma

Progressive skeletal destruction remains a hallmark of multiple myeloma and is responsible for significant morbidity in this disease.[11] Skeletal-related events (SREs) may include severe bone pain, pathologic fractures, vertebral collapse, hypercalcemia, and spinal cord compression.[12] In early 2018, members of an expert panel updated the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline on the role of bone-modifying agents in patients with multiple myeloma.[13] The ASCO guideline addresses the clinical question, "What is the role of bone-modifying agents in patients with multiple myeloma?" The expert panel reviewed the literature and provided an updated overview on the appropriate clinical use of pamidronate, zoledronic acid, and denosumab in patients with multiple myeloma.

MODELS OF EFFECTIVE CARE DELIVERY

To gain a deeper understanding of how multiple myeloma is managed in a variety of community settings, ACCC conducted site visits at three different types of cancer programs:

- Yuma Regional Medical Center Cancer Center in Yuma, Arizona, is a Comprehensive Community Cancer Program accredited by the Commission on Cancer (CoC). Comprehensive Community Cancer Programs represent 38% of all CoC-accredited cancer programs.[14]

- John Theurer Cancer Center at Hackensack University Medical Center in Hackensack, New Jersey, is an Academic Comprehensive Cancer Program accredited by the Commission on Cancer (CoC). Academic Comprehensive Cancer Programs represent 13% of all CoC-accredited cancer programs.

- Moffitt Cancer Center in Tampa, Florida, is a National Cancer Institute (NCI)-Designated Comprehensive Cancer Center accredited by the Commission on Cancer (CoC). NCI-Designated Comprehensive Cancer Programs represent 3% of all CoC-accredited cancer programs.

Since most cancer patients in the United States receive care in community settings, ACCC selected one Comprehensive Community Cancer Program to learn how clinicians are using team-based approaches to manage patients with multiple myeloma and coordinate care with larger centers. ACCC also selected one Academic Comprehensive Cancer Program since they participate in postgraduate medical education, assess more than 500 newly diagnosed cancer cases each year, and actively participate in cancer-related clinical research. ACCC included one NCI-Designated Comprehensive Cancer Center since these programs are recognized for their scientific leadership, resources, and the depth and breadth of their transdisciplinary research that bridges multiple scientific areas. While these three cancer programs are located in different geographical areas and serve different patient populations, they all aim to coordinate and provide optimal care to patients by incorporating a multidisciplinary approach to diagnosing and managing patients with multiple myeloma.

YUMA REGIONAL MEDICAL CENTER CANCER CENTER
YUMA, ARIZONA

The city of Yuma, Arizona, is in the southwestern corner of the state and has a population of approximately 195,000 people. Roughly 60 percent are Hispanic, and most people work in agriculture.[15] Yuma is a federally designated Health Professional Shortage Area and a Medically Underserved Area.

Yuma Regional Medical Center (YRMC) is the only hospital in the city of Yuma; its comprehensive community cancer center is a part of the Mayo Clinic Care Network, and the oncology practice has been Quality Oncology Practice Initiative (QOPI)-certified since 2014. Retirees often spend their winter months in Yuma. These "snowbirds" receive their cancer treatment at YRMC while in Yuma, and the cancer team coordinates the patients' care plans with their local oncologists throughout the country. Because YRMC utilizes Epic for its electronic health records system, the cancer team at YRMC uses Epic Care Everywhere to access and exchange patient records with other hospitals and cancer programs that are also using Epic.

Diagnosing and Managing Patients with Multiple Myeloma

The YRMC Cancer Center has a growing team of multidisciplinary oncology providers who meet twice a month for multidisciplinary tumor boards to discuss specific patient cases, evidence-based treatment options, and to incorporate the latest guidelines to ensure that patients receive optimal care. When patients are diagnosed with multiple myeloma, the clinicians send blood and bone marrow samples for diagnostic and prognostic tests that include cytogenetics, FISH, and immunophenotyping. This allows the team to use the Revised International Staging System (R-ISS) developed by the International Myeloma Working Group (IMWG) to assess prognosis and develop tailored treatment plans.

Physicians at YRMC educate patients newly diagnosed with multiple myeloma by explaining that multiple myeloma is a condition that can affect multiple body systems. Nurses educate patients about treatment side effects and social workers assess caregiver support and the home environment. To assess for health literacy, clinicians often ask patients very specific questions to elicit how much the patient truly understands about their condition. They often find that some patients have done some preliminary research online and may be quite informed, while others have very little understanding of multiple myeloma. Clinicians use many open-ended questions and listen intently to their patients as they discuss potential treatment options and actively engage patients in the shared decision-making process. Patients often want to involve their family members in their care, so over the course of several visits, members of the clinical team engage in discussions about patient preferences including goals of treatment, work schedules, infusion schedules, advance directives, and social support. The care team at YRMC discusses these issues while maintaining a high level of cultural awareness and sensitivity, since over half of their patients are Hispanic and most of their patients with multiple myeloma are elderly. In particular, they find that their older Hispanic patients who lack family support often struggle with their medication regimen and rely heavily on the cancer program to find patient assistance programs. Patient education materials often include literature provided by Chemocare.com, Multiple Myeloma Research Foundation (MMRF), UpToDate, and the American Cancer Society (ACS). Most of this information is available in English and Spanish. Through American Cancer Society programs, YRMC offers patients free educational and supportive resources through its Cancer Resource Center.

Patients with multiple myeloma who are eligible candidates for transplant are offered a referral to transplant centers based on their willingness to travel, the availability of social support, and health insurance coverage networks. Most patients are referred to Mayo Clinic in Scottsdale, Arizona; Banner MD Anderson Cancer Center in Gilbert, Arizona; University of Arizona Cancer Center in Tucson, Arizona; or UC San Diego Moores Cancer Center in La Jolla, California. YRMC social workers coordinate travel logistics, connect patients with the transplant coordinators, and provide psychosocial support as patients prepare for the transplant.

Managing Skeletal-Related Events (SREs)

At YRMC, patients with multiple myeloma who have bone lesions are usually treated with either zoledronic acid or denosumab. Zoledronic acid is given as an infusion and denosumab is an injection. Patients who receive zoledronic acid and denosumab are at greater risk of avascular necrosis of the jaw, especially if they undergo dental procedures.[16] Since many older patients often require dental procedures, the clinicians at YRMC have been treating their patients with caution and after detailed review of their history and symptoms. On January 11, 2018, the FDA approved denosumab for the prevention of skeletal-related events among patients with multiple myeloma who have bone metastases.[17] Since then, the team has noticed more patients being treated with denosumab as patients prefer injections as opposed to infusions. To monitor for SREs, physicians, advanced practice providers, nurses, and social workers routinely ask patients about symptoms of pain and other signs of potential side effects so that the care team can proactively initiate symptom management. YRMC has a team of radiation oncologists who provide radiation therapy for patients with bone lesions, offering pain relief and other symptom management.

Leveraging Technology for Care Coordination

The YRMC medical oncology team has built its own treatment plans within Epic using the Beacon module. Patients with multiple myeloma may be treated on oral oncolytic agents. The cancer team at YRMC experienced challenges with tracking adherence and monitoring for adverse events. In 2017, they built and implemented an oral chemotherapy adherence tracking program led by nurse navigators who served as oral chemotherapy navigators. These oral chemo nurse navigators coordinate prescriptions with specialty pharmacies while nurses, physicians, and pharmacists modify care plans for oral oncolytic agents and remind patients about potential adverse events. After launching the oral chemotherapy adherence tracking program, the team at YRMC saw a 72% reduction in emergency room visits from all cancer patients who were tracked on these care plans.[18] The oral chemotherapy navigation team is refining processes to optimize care coordination and they actively leverage tools like their patient portal to engage patients in their care and to maintain continuity of treatment plans for winter snowbirds. Every cancer patient who is treated with an oral oncolytic agent is tracked by the YRMC oral chemotherapy adherence tracking program.

JOHN THEURER CANCER CENTER AT HACKENSACK UNIVERSITY MEDICAL CENTER

HACKENSACK, NEW JERSEY

Hackensack University Medical Center (Hackensack UMC) is a 770-bed nonprofit, research and teaching hospital in Hackensack, New Jersey. John Theurer Cancer Center (JTCC), part of Hackensack University Medical Center, is the first program in the state to offer CAR T-cell therapy.[19] Hackensack University Medical Center is the major teaching hospital for the new Hackensack Meridian School of Medicine at Seton Hall University, which opened in 2018 with an inaugural class of 60 medical students.[20] The myeloma team at JTCC has expertise treating multiple myeloma, amyloidosis, monoclonal gammopathy of undetermined significance, and Waldenstrom's macroglobulinemia. In August 2018, Hackensack Meridian *Health*, as part of its Center for Discovery and Innovation, opened its new Institute for Multiple Myeloma which will support groundbreaking research to enhance treatment of this rare cancer.[21]

When patients with multiple myeloma are seen at JTCC, physicians carefully explain the diagnosis, prognosis, and available treatment options. Nurses provide reinforcing education and help patients understand how to identify and manage side effects. Patients learn that multiple myeloma is often managed as a chronic condition that may be treated effectively, and many patients may live for decades with the disease. Most patients are presented with several potential treatment options and clinicians engage in a shared decision-making dialogue with the patient as they discuss the patient's goals of treatment, review the different pros/cons associated with various treatment options, and allow the patient and family members to fully understand their options before choosing a care plan. As a leading transplant center for multiple myeloma, JTCC receives many patient referrals for stem cell transplant evaluation and discussions about treatment options often focus on induction regimens that may include several medications. Patients are also offered the opportunity to enroll in clinical trials for all phases of the disease including induction, transplant, and disease relapse.

Stem Cell Transplants

The stem cell transplant program at JTCC is one of the largest in the country with approximately 200 transplants performed each year in patients with multiple myeloma. The multiple myeloma team at JTCC is made up of physicians, advanced practice providers, nurses, pharmacists, and researchers who meet every week for multiple myeloma tumor boards. Physicians provide optimal care for patients with myeloma from diagnosis to salvage therapy, and they design personalized treatment approaches based on the results of prognostic biomarker tests. Since the science of multiple myeloma is changing rapidly, physicians and researchers at JTCC use sophisticated testing methods that assess predictive and prognostic biomarkers. Their specialized hematopathologists utilize the latest technology as they perform on-site flow cytometry, immunohistochemistry, cytogenetics, and molecular diagnostics.

Following transplant, patients are monitored routinely for signs of disease recurrence. Since many patients must travel to receive their transplants at JTCC, the multiple myeloma treatment team has processes to ensure coordinated co-management and smooth transitions of care as patients return to their local oncologists following transplant. A team of clinicians work with the medical records department to send and receive all the required patient records; physicians at JTCC coordinate prescription orders with local oncologists; following transplant, patients are seen by the myeloma team for long-term management. An active area of research focuses on testing for minimal residual disease (MRD), a prognostic marker that can be assessed using several highly sensitive techniques.[22] Researchers and clinicians are assessing how MRD testing may be used to evaluate treatment effectiveness and guide risk-stratified approaches to clinical management.[23]

Expanding Patient Support Groups

The team at JTCC works closely with the International Myeloma Foundation (IMF) to provide patient support groups throughout the state of New Jersey. A medical liaison from JTCC coordinates meetings, discussion topics, and organizes events. Patient support groups are offered in Hackensack, Cherry Hill, central New Jersey, and Ocean County. On average, support groups hold monthly meetings and allow patients and caregivers to learn about advances in multiple myeloma research and important aspects of survivorship care.

Working with groups like the International Myeloma Foundation (IMF), the Multiple Myeloma Research Foundation (MMRF), and The Leukemia & Lymphoma Society (LLS), the myeloma team at JTCC holds conferences like Patient Summits where they discuss the basics of multiple myeloma, stem cell transplantation, the management of relapsed and refractory disease, and ongoing research, including immunotherapy and minimal residual disease.

Advancing Research through Collaboration

As a major research center, JTCC has more than 350 ongoing clinical trials in different areas of cancer. These studies are conducted independently and in partnership with research and pharmaceutical companies, research consortiums (e.g., ECOG, Alliance, BMT CTN trials), patient advocacy groups, and the National Institutes of Health. Through a research partnership, JTCC has been collaborating with Georgetown Lombardi Comprehensive Cancer Center to accelerate cancer research from phase I studies through late-phase clinical trials. Hackensack Meridian Health is also in a collaborative partnership with Memorial Sloan Kettering Cancer Center to enhance cancer research and discovery, bring clinical trials to more areas, and develop and implement cancer care standards across the region. Some of the recent multiple myeloma trials offered at JTCC include studies with CAR T-cell therapy; SAR650984 (Anti-CD38 mAb); idasanutlin in combination with ixazomib and dexamethasone; and many others. JTCC is a member of the Multiple Myeloma Research Consortium (MRRC) and one of the sites involved in the MMRF CoMMpass (Relating Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile) Study, the largest and most comprehensive longitudinal study accelerating precision medicine in multiple myeloma. Through the MMRF CoMMpass Study, researchers have identified 12 different molecular types of multiple myeloma, each with its own level of risk.[24] These insights will enable researchers and clinicians to ensure that patients with multiple myeloma are being treated with agents targeted to their specific myeloma genetic abnormalities.

MOFFITT CANCER CENTER
TAMPA, FLORIDA

Moffitt Cancer Center opened in 1986 on the campus of the University of South Florida in Tampa, Florida. Building on its active research efforts, Moffitt achieved NCI Cancer Center designation in 1998 and NCI Comprehensive Cancer Center designation in 2001. Moffitt remains the only NCI-designated Comprehensive Cancer Center in Florida and is also a member of the National Comprehensive Cancer Network (NCCN). Most of the patients seen at Moffitt come from the southeastern region of the United States and the Caribbean islands.

Clinicians at Moffitt see more than 450 new patients with multiple myeloma. Many of these referred patients have been initially diagnosed and treated by local oncologists in the community. When they are seen at Moffitt, these patients are evaluated for transplant eligibility and their treatment regimens are often modified to maximize efficacy and minimize toxicity. By using the Revised International Staging System (R-ISS), oncologists assess risk factors and personalize treatment options to align with the goals of treatment that are expressed by patients. As part of this process, patients are educated so that they understand that treatment goals may range from maintaining stable disease to achieving complete response. This provider-patient dialogue allows the treatment team to explain their rationale for care plans that may include several different medications. Moffitt clinicians note that the majority of patients return to the community for care, and the Moffitt team promotes models of co-management with community oncologists.

Multiple Myeloma Working Group

To facilitate clinical, translational, and basic science research, the team at Moffitt formed the Multiple Myeloma Working Group (MMWG). This group includes basic scientists, clinical investigators, clinicians/surgeons, integrative mathematicians, biostatisticians, bioinformaticians, nurses, pathologists, and clinical research coordinators who are focused on multiple myeloma and other plasma cell dyscrasias. The MMWG meets weekly for a tumor board where they discuss patient cases and the complex biology of multiple myeloma subtypes that may respond to different types of therapies. The group is currently assessing optimal ways to incorporate minimal residual disease (MRD) testing into their treatment algorithms so that they can achieve a standardized approach to utilize this technique in the treatment decision process, in and outside of the research setting.

Outpatient Stem Cell Transplants

In 2016 and 2017, at Moffitt 158 and 147 patients with multiple myeloma received an autologous stem cell transplant, respectively.[25] Most transplants for multiple myeloma are performed on an outpatient basis, and the team at Moffitt has seen patients recovering faster so they may return home and receive maintenance therapy by their local oncologists. Several of the multiple myeloma clinic nurses also serve as transplant coordinators and work to maintain continuity of care, provide patient education, and manage expectations as patients prepare for transplant. After transplant, patients usually go back to their local oncologists for follow-up care, and the team at Moffitt coordinates a surveillance and monitoring schedule to look for signs of relapse. These schedules are available to patients electronically through the patient portal, and patients are also given hard copies of schedules and schedules are faxed to patients' local oncology providers so that routine diagnostic test results are available when patients are seen for follow-up visits.

Managing Severe Skeletal-Related Events (SREs)

Spinal cord compression and vertebral compression fractures are severe skeletal-related events that may occur in patients with multiple myeloma.[26] When symptoms present as oncologic emergencies, immediate intervention by trained experts is required to prevent permanent paralysis.[27] Experts at the Moffitt Neuro-

Oncology Program have significant experience managing severe SREs in patients with multiple myeloma, and they have formed a medical neuro-oncology fellowship program to train physicians and to advance research in this area. Proper management of SREs is integral to comprehensive multiple myeloma care and has a positive impact on patients' quality of life.[28] The neurosurgeons at Moffitt routinely perform procedures like kyphoplasty and vertebroplasty to reconstruct compressed vertebrae, restore alignment, and relieve neural pressure in patients with multiple myeloma. Radiation therapy is provided by a multispecialty radiation oncology team where dedicated radiation oncologists specialize in treating just one or two specific types of cancers.

Advancing Patient Education

Multiple myeloma is a complex condition and patients often have difficulty understanding their cancer. Patients and family members may not understand the meaning of terms like "remission" or "complete response." To facilitate communication, clinicians at Moffitt often use patient education materials from The Leukemia & Lymphoma Society, the Multiple Myeloma Research Foundation, or the International Myeloma Foundation. Clinic nurses spend a considerable amount of time educating patients about multiple myeloma treatments, managing expectations, coordinating care, and discussing survivorship. Moffitt also holds regional on-site conferences throughout the year to provide education to patients and their family members about the latest advances in multiple myeloma research. These outreach efforts remain an effective way to stay connected with patients who are eager to learn about advances in drug development and new treatment approaches.

Focus on Research

Moffitt is a founding member of the Oncology Research Information Exchange Network (ORIEN) (http://oriencancer.org), a research partnership with large cancer centers across the United States. Researchers have access to a shared data warehouse and can participate in cross-institutional collaborations. Cancer patients treated at Moffitt may participate in the Total Cancer Care initiative, a longitudinal study that began in 2006 as a personalized cancer care initiative designed to examine the effects of different cancers, treatment choices, and lifestyle so that physicians can have a better understanding of patient outcomes and treatment options.

Moffitt has an extensive history of conducting basic science and clinical research in multiple myeloma. Some recent multiple myeloma trials at Moffitt include anti-BCMA CAR T-cell therapy; ex-vivo expanded donor regulatory T-cells; oprozomib in combination with pomalidomide and dexamethasone; and many others.

SUMMARY

Multiple myeloma may not be curable in most cases, but it is highly treatable. Advances in research and understanding of biomarkers are leading to more personalized treatment approaches that extend survival, improve health-related quality of life, and achieve better patient outcomes. Given the unique characteristics of individual patients, including factors such as demographics, genomic profile, and performance status, treatment should be tailored to match each patient's needs and goals of therapy. As the landscape of multiple myeloma treatment continues to rapidly evolve with the wealth of new insights that are being generated by the medical community, oncology clinicians need to stay updated on the latest practice-changing advances and understand how to utilize the best available treatment options. Multidisciplinary care teams must stay current on practices to ensure that patients receive accurate diagnoses and coordinated treatment along the care continuum.

More information about the ACCC Multidisciplinary Multiple Myeloma Care project and additional resources are available at accc-cancer.org/multiple-myeloma.

APPENDIX

Drug Therapy for Multiple Myeloma and Skeletal-Related Events[29, 30]

DRUG NAME	BRAND NAME
Bendamustine	Bendeka
Bortezomib	Velcade
Carfilzomib	Kyprolis
Carmustine	BiCNU
Cyclophosphamide	Cytoxan
Daratumumab	Darzalex
Denosumab	Xgeva
Dexamethasone	Decadron
Doxorubicin	Adriamycin
Doxorubicin hydrochloride liposome	Doxil, Dox-SL, Evacet, LipoDox
Elotuzumab	Empliciti
Etoposide	VP-16 (Toposar, VePesid, Etopophos)
Ixazomib citrate	Ninlaro
Lenalidomide	Revlimid
Melphalan hydrochloride	Alkeran, Evomela
Pamidronate disodium	Aredia
Panobinostat	Farydak
Plerixafor	Mozobil
Pomalidomide	Pomalyst
Thalidomide	Thalomid
Vincristine	Oncovin
Zoledronic Acid	Zometa

*list of drugs from the American Cancer Society and the National Cancer Institute websites

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- Moffitt Cancer Center in Tampa, Florida

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