Nursing Management of Advanced Merkel Cell Carcinoma

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Merkel cell carcinoma (MCC) is a rare and lethal skin cancer with few known treatment options. Management of this disease is challenging, and oncology nurses must understand the medical, physical, and psychosocial burden that MCC places on the patient and family caregivers. Patients must navigate a complex medical and insurance network that often fails to support patients with rare cancers. Nurses must advocate for these patients to ensure quality comprehensive cancer care.

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Merkel cell carcinoma (MCC) is a rare and aggressive nonmelanoma skin cancer, derived from cutaneous tactile nerve cells, that behaves similarly to small cell lung cancer (SCLC) (Becker, 2010). MCCs are neuroendocrine tumors with an increased growth rate and may rapidly reoccur locally and distantly. Mortality rates are significant and exceed that of melanoma (Allen et al., 2005). Risk factors for MCC include a prior history of sun exposure (i.e., work, recreation, or fair skin) and being Caucasian, male, and older than age 65 years (Agelli & Clegg, 2003). The disease tends to originate in sun-exposed areas and frequently will spread via the lymphatic system to either dermal metastasis or visceral organ involvement. Prior reports have also suggested that immunocompromised patients may be at higher risk for developing MCC (Becker, 2010). Two similar and challenging patients with MCC presented to the authors' cancer center.

Case Study 1

B.Y. was a 61-year-old Caucasian woman with a past medical history of epilepsy, fibromyalgia, and diverticulosis who developed a left groin mass that was biopsied. The pathology confirmed MCC. Positron-emission tomography (PET) demonstrated multiple inguinal, internal, and external iliac lymph nodes and a left breast lesion, but no superficial cutaneous lesions. B.Y. was started on chemotherapy with cisplatin (Platinol®) and etoposide (VePesid®) for two cycles but had complications related to neutropenia. Repeat imaging showed progressive disease in the left breast and inguinal regions. The patient was enrolled in a clinical trial for an anti-PDL1 antibody; however, prior to treatment, she developed hydronephrosis of the renal pelvis related to retroperitoneal lymph node enlargement. After receiving two doses of the anti-PDL1 antibody, she quickly began to decline clinically. B.Y. was placed on hospice care and died about nine months after her initial diagnosis.

Case Study 2

P.C. was a 46-year-old Caucasian man with a past medical history of squamous cell carcinoma of the lip who presented with a nodule along the fifth digit of the left hand. The excisional biopsy pathology was positive for MCC. A PET scan, performed for staging purposes, found distant disease in the left axilla. An amputation of the digit was performed, as well as a left axillary lymph node dissection. Merkel cells were found within the resected lymph nodes, and P.C. was counseled about the need for postoperative radiation therapy to the axilla. A review of the patient's complete blood count (CBC) showed the presence of a sudden

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and dramatic thrombocytopenia. A bone marrow biopsy was performed and confirmed MCC. He was treated with a platinum/etoposide chemotherapy regimen for four cycles. A follow-up PET scan revealed only one small lung nodule, a repeat bone marrow biopsy was negative for MCC involvement, and his blood counts improved. Given his high-risk disease state, P.C. was evaluated for additional adjuvant therapy, and the decision was made to request pembrolizumab (Keytruda®), a PD-1 inhibitor on a compassionate-use basis. However, the patient's platelet count began to drop rapidly, which was highly suspicious for recurrent bone marrow involvement. He tolerated two doses of PD-1 therapy but was admitted several times for confusion, dehydration, and pain control. In addition, his cytopenia failed to improve with treatment. Given his poor performance status, P.C. was placed on hospice care and died from his disease about 10 months after his initial diagnosis.

Background

MCC is a difficult diagnosis because it appears to be similar to other small, round, blue cell tumors (i.e., SCLC or high-grade carcinoid tumors) and requires careful pathologic analysis. Feng, Shuda, Chang, and Moore (2008) identified a novel polyomavirus in MCC tissues. The Merkel cell virus (MCV) is typically found in about 80% of patient tissue samples, and the MCV proteins may target the tumor suppressor genes *TP53* and *RB*. However, whether the MCV is a good or poor prognostic indicator of disease is unclear. For the other 20% of patients without the MCV, ultraviolet light may be the primary agent that damages the *TP53* and *RB* genes (Goh et al., 2016). Therefore, different types of cellular injury may drive the same molecular pathways and result in tumor development.

Treatment

All individuals diagnosed with MCC require the care of a multidisciplinary team, including dermatopathology, surgical oncology, radiation, and medical oncology. Surgery is considered the primary treatment modality and should be pursued with the goal of obtaining clear margins (1–2 cm wide) (Tai, 2013). Sentinel lymph node biopsy (SLNB) is performed to identify micrometastasis in regional lymph nodes that would prompt a full lymph node dissection and warrant adjuvant radiation (Boyer, Zitelli, Brodland, & D'Angelo, 2002). However, the overall impact of SLNB on patient survival remains mixed (Gupta et al., 2006). Research has supported that surgery followed by adjuvant radiation leads to better outcomes than surgery alone (Strom, Carr, et al., 2016; Strom, Naghavi, et al., 2016). Radiation can be considered as a primary treatment if a patient refuses surgery or if surgery is not feasible (Bishop et al., 2016; Strom, Naghavi, et al., 2016). Some institutions have used combinations of radiation and chemotherapy (often platinum-based) in the adjuvant setting. Although there does not appear to be a clear overall survival benefit for combinational therapy, it may delay the time to recurrence (Garneski & Nghiem, 2007).

In MCC, chemotherapy options are poorly defined in the literature and are used in the metastatic setting (Desch & Kunstfeld, 2013). First-line chemotherapy regimens typically involve a platinum-based doublet (cisplatin or carboplatin [Paraplatin®]) combined with etoposide. Common side effects include nausea, vomiting, diarrhea, myelosuppression, peripheral neuropathy, renal dysfunction, alopecia, and fatigue. Because of the risk of neutropenia, growth factor support may be required. For second-line therapy, data is very sparse, but topotecan (Hycamtin®) as a single agent or a combination chemotherapy regimen using cyclophosphamide (Cytoxan®), doxorubicin (Adriamycin®), and vincristine (Oncovin®) may have some benefit against the disease, but these treatments often have significant toxicities (Tai et al., 2000). When a clinical trial is available and appropriate, it is strongly recommended that patients and their providers consider this as their primary treatment option. PET often is used to monitor clinical response and is performed after every 2–3 cycles of therapy.

Several reports have suggested that immunotherapy may be beneficial to patients with MCC. Given the involvement of a virus in the tumor and the high frequency of the disease in immunosuppressed patients, it was only natural that immunotherapy agents, specifically PD-1/PDL-1 antibodies that block critical immune checkpoints, may have activity against the cancer. In a phase II study of treatment-naive patients with MCC (N = 26), Nghiem et al. (2016) demonstrated that the use of an anti–PD-1 antibody, pembrolizumab, resulted in an objective response rate of 56%, with a few complete and partial responses documented. In addition, Kaufman et al. (2016) reported that a cohort of patients with MCC previously treated with chemotherapy (N = 88) had response rates of 30%–40% using an anti–PDL-1 antibody. Although immunotherapy has promise in this disease, there still is a small risk of severe adverse immunologic events. Typical side effects of immune checkpoint blockade include fever, flu-like symptoms, malaise, diarrhea, colitis, pneumonitis, myalgias, fatigue, and endocrinopathies (hyper/hypothyroidism). Careful monitoring of immune-related side effects

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is essential. For severe reactions, high-dose steroids or other immunosuppressive agents, such as infliximab (Remicade®), are used and patients may require hospitalizations and/or monitoring. Clinical trials are ongoing to compare first-line immunotherapy versus standard chemotherapy regimens in patients with advanced disease to determine which agent has the best response.

Implications for Oncology Nurses

Many nurses have never heard of this rare form of skin cancer. The diagnosis often is made by a dermatologist, and patients are then referred to specialty oncology centers. Very little information is available to individuals diagnosed with MCC, and available resources frequently illustrate a grim prognosis. A challenge for nurses in this patient population is the unpredictability of the disease, with the median survival for advanced MCC being less than 12 months (American Joint Committee on Cancer, 2009). Just as each cancer journey is unique, individuals diagnosed with MCC often have varied presentations and disease trajectories, as demonstrated by the two case studies in this article. The trajectory may be slow and simmering, with escalation to rapid disease progression leading to quick death. Although MCC typically responds to initial treatments, its ability to reoccur rapidly and in new locations is very frustrating for patients, particularly after suffering through prior treatment-related toxicities.

Caring for patients with a rare and aggressive cancer may be a mental and emotional challenge for patients and nurses. Given that these tumors frequently reside internally rather than superficially, as with other forms of skin cancer, patients are told that they "look fine," and asked, "How can you be sick?" Increased toxicities often come from more complex treatment regimens; therefore, patients need strong nursing support to address the physiologic and psychological changes that are associated with the treatment regimens and with rapid disease progression. An early discussion of advanced directives and possible care through hospice is essential. Because of the potential rapid growth rate of the disease, patients and their caregivers must develop a strong relationship with all members of the care team (including social workers and pastoral care), but particularly with the nurse. To illustrate this point, Griffiths, Willard, Burgess, Amir, and Luker (2007) found a clear need to improve coping skills, as well as family and social support, in a subset of survivors of rare cancers.

With MCC, patients must be encouraged to contact the oncology team for any new physical symptom lasting longer than 48 hours

TABLE 1. Symptom Management of Progressive Merkel Cell Carcinoma

Disease Location	Symptom	Other Disease Complications	Nursing Intervention	Other Interventions
Any site	Pain	–	Narcotic management: somnolence, constipation	–
Abdomen	Abdominal pain	Bowel obstruction	Patient education	Urgent surgery
	Right upper quadrant pain, jaundice	Biliary obstruction	Patient education	Biliary stent, percutaneous drain
Bone marrow	Bleeding, infection risk	Myelosuppression	Patient education	Transfusion, growth factors
Central nervous system	Focal deficits	Metastasis	Seizure precautions	Surgery, radiation
	Seizures, global decline	Leptomeningeal	Seizure precautions	Radiation
	Lower extremity weakness or sensory loss	Cord compression	Emergency management	Surgery, radiation
Dermal lesions	Pain, bleeding	Infection, chronic wounds	Wound care	Radiation
Heart	Chest pain	Pericardial effusion	Patient education	Cardiocentesis
Lung	Cough, shortness of breath	Pleural effusion	Patient education	Thoracentesis
Pelvis	Pelvic pain	Hydronephrosis	Patient education	Nephrostomy tube, stent

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CLINICAL HIGHLIGHTS

- Merkel cell carcinoma (MCC) is a neuroendocrine carcinoma of the skin that is rare, aggressive, and lethal.
- Risk factors for MCC include prior sun exposure, age 65 years or older, Caucasian/fair skin, male gender, and a history of immunosuppression.
- Treatment of MCC is multidisciplinary; surgery and radiation are often used for primary lesions and chemotherapy or clinical trials are used for advanced cases. Preliminary reports using immunotherapy in metastatic MCC have shown promising results.

(see Table 1). Getting a patient or his or her family to understand the need for real-time reporting often is very challenging. However, patients need to be encouraged to freely interact with the care team and to break down those fears that they are "bothering" the team. For nurses, it can be challenging to help patients find a balance between living with the new normal of cancer and their fear that every new pain or lump means that the cancer has returned or is growing. Nurses are key advocates for maintaining quality of life.

Another challenge for nurses is that the difficult conversations between patients and their families, caregivers, or support person need to be encouraged early in the treatment process. All too often, the disease progresses so rapidly that a patient and his or her family have not had time to come to terms with the diagnosis and may not have an idea of what the patient's wishes are toward life support measures or a plan in place to manage a patient's inability to care for themselves. MCC has no known cure and patients have limited options; however, the one constant treatment for these patients is the care and support from the nursing team.

Conclusion

MCC is a rare and lethal skin cancer. Little is known about optimal treatment strategies, but discoveries are ongoing to address immunotherapy strategies, in addition to evaluating the genetic basis of the disease. Rare cancers and orphan diseases often have high burdens (medical, physical, and psychosocial) for patients and family members, as well as the nursing team. These patients need to have full support programs in place to ensure the best outcomes for themselves and their families.

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