END OF LIFE OPTIONS IN THE CONTEXT OF WALDENSTRÖM MACROGLOBULINEMIA

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Abstract:

A 79-year-old male previously diagnosed with Waldenström macroglobulinemia presented to hospital feeling unwell due to relapse of his disease. During his stay in hospital, the patient's condition deteriorated, and his physician began end of life discussions, presenting several options to the patient. A literature search revealed methods of prognostication and current chemotherapeutic options for treating Waldenström macroglobulinemia, statistics of medical assistance in dying in Manitoba, and goals of medical assistance in dying versus sedation for palliative purposes. Both options were discussed with the patient and his family, and ultimately it was his wish to receive sedation for palliative purposes. This was an opportunity to begin end of life discussions in the context of a rare and incurable disease and provided clarification of two different options that both reduce suffering.

Case History:

A 79-year-old male diagnosed with Waldenström macroglobulinemia (WM) presented to Pinawa Hospital, unwell due to relapse of his disease. He was diagnosed with WM, a type of lymphoplasmacytic lymphoma (LPL), in April 2000 after experiencing typical signs and symptoms of hyperviscosity syndrome, including parasthesias in his toes for six months, as well as fundoscopic changes, or "sausaging", of the retinal arterioles. He had a past medical history of anxiety disorder, coronary artery disease, dyslipidemia, GERD, and a past surgical history of aortic valve replacement, coronary bypass surgery, appendectomy and tonsillectomy.

He had been treated with multiple courses of chemotherapy and steroids, with periods of remission and relapse over the past 19 years. During his well periods, he was very active and exercising daily. A year before presentation to hospital, he had progressive anemia and increasing fatigue, and three months before presentation, he began to complain of weakness, episodes of epistaxis and increase in bruising. He reported night sweats, a 3 to 5 pound weight loss, and poor appetite. This disease relapse led to the start of treatment with bendamustine and rituximab chemotherapy, as well as daily prednisone. Following his first cycle of treatment, he was admitted to Pinawa Hospital with weakness, fever and rigors, and discharged after 5 days.

Upon current presentation, he was admitted due to hypotension, dyspnea, bilateral basilar crackles, bilateral pedal edema, fever, rigor, and weakness. Due to the fever of unknown cause, sepsis protocol was initiated, later treated as community acquired pneumonia. Chest x-ray showed right upper lobe consolidation and the patient was started on piperacillin-tazobactam and vancomycin antibiotics. Further hypoxemia and desaturation required transfer and care at the Grace Hospital Intensive Care Unit in Winnipeg, including intubation for respiratory failure, IVIG and steroids for treatment of his WM, and dalteparin for deep vein thrombosis prophylaxis. Cultures from blood, endotracheal tube and urinary catheter were all negative. On return and re-admission to the Pinawa Hospital, the patient was very weak. He complained of pain all over and developed sores in his mouth that made eating and drinking very difficult. A nasogastric tube was placed briefly for feeding but was not tolerated and had to be removed.

Throughout these recurrent hospital admissions, it remained the patient's wish to be Advanced Care Plan level Resuscitation during each discussion with his physicians. His

condition, energy and pain levels fluctuated daily, with periods of apparent improvement followed by steady decline. During these times, the patient experienced emotional distress anxiety, but remained hopeful, stating that he did not want to die.

Two weeks after admission, the patient asked for information regarding Medical Assistance in Dying (MAID) and a consult was sent to the provincial MAID team. He refused the consult a few days later after there was improvement in his condition. He then experienced another decline in function. In discussion with his physician, and in the presence of his wife, he was presented with several options on how to proceed with his care; first, current treatments could continue; second, all treatments could stop and comfort care with sedation for palliative purpose could be provided; and third, the MAID team could be consulted again to make an assessment. It was the patient's wish to continue medical treatment and consult MAID again. At this time, he also expressed his wish to be ACP level Medical and receive all medical care excluding resuscitation.

The next morning during rounds, the patient told his physician that he wanted to stop all treatments and that he wanted to die. The severity of disease progression and expected prognosis were discussed between the physician and the patient, with his wife present. The patient's ACP level changed to Comfort Care only and sedation for palliative purposes (SPP) was initiated based on the patient's wish. He passed 4 days later.

Literature Search:

Information regarding Waldenström macroglobulinemia, including its prognostication and success of current treatments, as well as end of life discussions and options, including sedation for palliative purposes and medical assistance in dying, was sought in order to better understand the outcomes of this case. A literature search was done across multiple databases and resources, such as UpToDate and PubMed, the Winnipeg Regional Health Authority (WRHA) website, as well as requesting information from the provincial MAID team.

UpToDate was used to gather information regarding the pathogenesis of Waldenström macroglobulinemia, as well as the clinical manifestations and criteria for diagnosis. Another UpToDate article was reviewed for treatment and prognostic information. A PubMed search was done using terms "Waldenström macroglobulinemia" and "treatment", as well as searches for "medical assistance in dying" with "Canada" and "end of life discussions". Information regarding the current MAID statistics in Manitoba was obtained from Dr. Kim Wiebe, the administrative lead for the provincial MAID team. Information about SPP was found through the WRHA website. Overall, six articles and documents were reviewed in the writing of this case report.

Discussion:

In cases of incurable illnesses with advanced disease progression, it is expected that patients will either succumb to their illnesses or suffer from complications of their illnesses. In this patient's case, he had lived with his WM diagnosis for 19 years, almost two times longer

than the median survival of WM. However, his last several weeks spent in hospital made it clear that his disease had progressed too far for him to recover the quality of life that he had had in the years since his diagnosis. The discussion below speaks to the current treatments available and prognoses that patients with WM can expect, followed by explanations of the end of life care options that were discussed with the patient.

Waldenström macroglobulinemia is a type of lymphoplasmacytic lymphoma (LPL), which affects the bone marrow, causing an overproduction of immunoglobulin M (IgM) monoclonal protein in the blood[1,2]. It is a rare disease with an incidence of three per million people per year, affecting 1400 new cases per year in the United States[1]. The median survival is approximately 10 years. The median age of patients with WM is 64 to 71 years of age, with a male predominance. One quarter of patients are asymptomatic at diagnosis, however common signs and symptoms are funduscopic changes, lymphadenopathy, organomegaly, bleeding from the nose and gums, neurologic symptoms, symptoms secondary to hyperviscosity, as well as constitutional "B" symptoms [1,2]. Laboratory findings include anemia, neutropenia, thrombocytopenia, elevated lactate dehydrogenase, and elevated beta-2 microglobulin levels[1,2].

Bone marrow biopsy and serum protein samples are required for the diagnosis of WM, and must meet the criteria of IgM monoclonal protein gammopathy in the serum and histological evidence that greater or equal to 10 percent of the bone marrow sample is infiltrated by lymphoplasmacytic cells[1,3].

In 2009, an International Prognostic Scoring System for WM (ISSWM) was developed to stratify patients with WM into three risk categories in order to determine best treatment options for each category of patients. Five adverse variables were used to categorize patients before treatment initiation: advanced age (greater than 65 years of age), hemoglobin less than or equal to 115g/L, platelet count less than or equal 100 x 10^9/L, beta-2 microglobulin greater than 3mg/L, and serum IgM concentration greater than 70g/L[2,4].

Low risk patients are those who are less than 65 years of age, and have zero to one adverse variable, giving them a five-year survival of 87%. Intermediate risk patients are those who are 65 years of age and older, or have two adverse variables, with a five-year survival of 68%. High risk patients are those with 3 or more adverse variables, with a five-year survival of 36%[2,4].

There are currently no curative treatments for WM, and all available treatments have risks of short and long-term complications that can lead to decreased quality of life and decreased survival. It is not recommended that asymptomatic WM patients receive any treatment until symptoms begin[4]. Treatment goals are to maximize quality of life by controlling symptoms and preventing end organ damage. Alkylating agents, purine analogs, anti-CD20 monoclonal antibody rituximab, intensive therapy with autologous stem cell transplantation, and allogenic stem cell transplantation are the current treatments for symptomatic patients[2]. Rituximab is a preferred initial therapy, either alone or in combination with the other mentioned chemotherapies[4].

For patients with life-threatening illnesses MAID may be appropriate. Medical assistance in dying, or MAID, can be provided in one of two ways in Canada. First, there is self-administered MAID, by which the physician prescribes medications to the patient for self-administration orally. Second, there is clinician-assisted MAID, by which the physician prescribes the medications and administers them intravenously to the patient. The latter is currently the only option available in Manitoba. It involves the intravenous administration of a sedative, anesthetic, and a muscle relaxant over the course of 10-15 minutes[5].

To be eligible for MAID the patient must be Canadian, 18 years of age or older, have capacity to make medical decisions, make the request voluntarily without external influence, and have a grievous and irremediable medical condition [5]. To meet the last criterion, the patient must have a serious and incurable illness, disease or disability, be in advanced state of irreversible decline in capability, have enduring and intolerable suffering, and have a reasonably foreseeable natural death[5].

Before a patient receives approval for the provision of MAID, they must have two assessments by a physician where their case is reviewed, make a request for MAID in writing, followed by 10 legal days of reflection, which may be shortened in some circumstances. The patient can withdraw their request at any time during this process, including the moments before the medications are administered. All options, including pain and symptom management, must be presented and reviewed with the patient, in order for them to give informed consent[5].

On June 16, 2016, the Criminal Code of Canada was amended by Bill C-14, decriminalizing medical assistance in dying. Between February 29, 2016 and the date of legislation change, 3 provisions of MAID occurred in Manitoba via court order. As of July 31, 2019, there have been 1257 contacts made with the provincial MAID services, including patient and non-patient inquiries. There have been 591 written requests for MAID, with 316 MAID provisions completed and 48 cancellations, in all of Manitoba. 179 patients were declined MAID in cases where the criteria were not fulfilled. 327 deaths have occurred unassisted, while patients were in the process of approval for MAID. Within the Interlake-Eastern Regional Health Authority, where the patient in this case resided, there have been 36 provisions of MAID[6].

163 females and 153 males have been provided MAID, with illnesses such as cancer, end-stage organ disease, and neurodegenerative conditions. Patients have been within the range of 29 to 100 years of age, with the average being 75 years of age[6]. Overall, approximately 20% of all contacts with the MAID team go on to have an assisted death[5].

Sedation for palliative purposes (SPP) is the "planned and proportionate use of sedation to reduce consciousness in an imminently dying patient with the goal to relieve suffering that is intolerable to the patient and refractory to interventions that are acceptable to the patient."[7]. It can be provided in a palliative care unit, hospice, community and tertiary healthcare facilities, long term care facilities and at the home of the patient. SPP can be part of the care for patients with ACP level Comfort Care and should only be provided when death due to the underlying condition is expected within 2 weeks, by judgement of the healthcare providers. It is not a temporary sedation and is not used to shorten a patient's lifespan.

Both MAID and SPP are intended to reduce suffering but differ in all other respects. SPP is provided for sedation while MAID is provided for ending a patient's life. SPP dosing is titrated to effect and MAID is a lethal dose. Patients die due to natural progression of their underlying illnesses when receiving SPP, while respiratory arrest followed by cardiac arrest causes death in cases where MAID is provided.

Although more treatments existed for WM that had not yet been tried for the patient, his decline in hospital made him unable to pursue any course of chemotherapy. The disease progression, in addition to the patient's clinical anxiety, made his stay in hospital difficult both physically and emotionally. After speaking with the patient over the course of his hospital admission, his wishes for levels of care were not constant throughout, but rather along a continuum. Fortunately, in this case these discussions were often in the presence of his family, ensuring that he had support in making decisions when it came to his end of life care. The patient's final choice to have sedation for palliative purposes was made after many weeks of suffering and he was ultimately able to have comfort and peace.

Conclusion:

This case provided an opportunity to explore and examine end of life discussions and options in the context of a rare and incurable disease. Care of this patient involved not only knowledge of a specific oncological condition and its therapies, but also required the ability to have personal and meaningful discussions with a person at the end of his life.

The literature and resources found helped in the discussion around medical assistance in dying versus sedation for palliative purposes and clarified two very different end of life options, that share the intention of reducing suffering. Ultimately as physicians we provide options to our patients and assist them in making an informed decision that best suits their needs.

References:

1. Rajkumar ASV, Ansell SM. Epidemiology , pathogenesis , clinical manifestations , and diagnosis of Waldenström macroglobulinemia. UpToDate. https://www-uptodate-com.uml.idm.oclc.org/contents/epidemiology-pathogenesis-clinical-manifestations-and-diagnosis-of-waldenstrom-macroglobulinemia?search=waldenstrom macroglobulinemia&source=search_result&selectedTitle=1~103&usage_type=default&display_rank=1. Published 2019. Accessed August 18, 2019.
2. Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. *Blood*. 2009;113(18):4163-4171. doi:10.1182/blood-2008-08-174961.The
3. Buske C, Leblond V. How to manage Waldenstrom's macroglobulinemia. *Leukemia*. 2013;(February):762-772. doi:10.1038/leu.2013.36
4. Rajkumar ASV, Ansell SM. Treatment and prognosis of Waldenström macroglobulinemia. UpToDate. https://www-uptodate-com.uml.idm.oclc.org/contents/treatment-and-prognosis-of-waldenstrom-macroglobulinemia?search=waldenstrom macroglobulinemia&source=search_result&selectedTitle=2~103&usage_type=default&display_rank=2. Published 2019. Accessed August 18, 2019.
5. Manitoba Provincial MAID Team. *Medical Assistance in Dying (MAID) Presentation*.; 2019.
6. Manitoba Provincial MAID Team. *MAID Statistics Summary February 29/16 to July 31/19*.; 2019.
7. WRHA Palliative Care Program. *Sedation for Palliative Purposes Guideline*.; 2017:1-21.