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REVIEW ARTICLE

Diagnosis and Management of Waldenstrom's Macroglobulinemia

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A B S T R A C T

Purpose
To review the diagnostic criteria, prognostic factors, response criteria, and treatment options of patients with Waldenstrom's macroglobulinemia (WM).

Methods
A review of published reports was facilitated by the use of a MEDLINE computer search and by manual search of the Index Medicus.

Results
WM should be regarded as a distinct clinicopathologic entity and confined to those patients with lymphoplasmacytoid lymphoma who have demonstrable serum immunoglobulin M monoclonal protein. Treatment decisions should rely on specific clinical and laboratory criteria. Initiation of therapy should not be based on serum monoclonal protein levels per se. The three main choices for systemic primary treatment of symptomatic patients with WM include alkylating agents (chlorambucil), nucleoside analogs (fludarabine and cladribine), and the monoclonal antibody rituximab. There are no data from prospective randomized studies to recommend the use of one first-line agent over another, although consideration of a patient's candidacy for autologous stem-cell transplantation (ASCT) should be taken into account to avoid stem cell–damaging agents. There are preliminary data to suggest that combinations of nucleoside analogs and alkylating agents with or without rituximab may improve response rates at the expense of higher toxicity.

Conclusion
WM is a distinct low-grade lymphoproliferative disorder. When therapy is indicated, alkylating agents, nucleoside analogs, and rituximab are reasonable choices. Several factors, including the presence of cytopenias, need for rapid disease control, candidacy for ASCT, age, and comorbidities, should be taken into consideration when choosing the most appropriate primary treatment.

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DEFINITION OF WALDENSTROM'S MACROGLOBULINEMIA AND RELATED DISORDERS

Waldenstrom's macroglobulinemia (WM) is an uncommon B-cell lymphoproliferative disorder characterized by bone marrow infiltration and production of monoclonal immunoglobulin (Ig) M.[1] The proposed diagnostic criteria that were defined during the Second International Workshop on Waldenstrom's Macroglobulinemia (September 26-30, 2002, Athens, Greece) are listed in Table 1. WM should be regarded as a distinct clinicopathologic entity and be confined to those patients with lymphoplasmacytoid lymphoma who have demonstrable serum IgM monoclonal protein. The demonstration of an IgM monoclonal protein is not synonymous with the diagnosis of WM because this abnormality may be seen in several forms of B-cell lymphoproliferative disorders as well as in monoclonal gammopathy of undetermined significance (MGUS). The concentration of IgM varies widely in WM, and it is

Table 1. Diagnostic Criteria of WM

Criteria
IgM monoclonal protein of any concentration
Bone marrow infiltration by small lymphocytes showing plasmacytoid/plasma-cell differentiation
Intertrabecular pattern of bone marrow infiltration*
Surface IgM+, CD5±, CD10−, CD19+, CD20+, CD22+, CD23−, CD25+, CD27+, FMC7+, CD103−, CD138 immunophenotype*

Abbreviations: WM, Waldenstrom's macroglobulinemia; IgM, immunoglobulin M.
*Supportive of but not necessary for the diagnosis of WM.

not possible to define a concentration that reliably distinguishes WM from other lymphoproliferative disorders.[2] Therefore, a diagnosis of WM can be made irrespective of IgM concentration if there is evidence of bone marrow infiltration by lymphoplasmacytoid lymphoma as defined by the Revised European-American Lymphoma classification and WHO criteria.[3,4] This is a tumor of small lymphocytes showing evidence of plasmacytoid or plasma-cell differentiation. A recent study found that, in 39% of patients, the bone marrow aspirate contained a spectrum of small lymphocytes, plasmacytoid lymphocytes, and plasma cells; in 39% of patients, there was a predominance of small lymphocytes with fewer plasmacytoid lymphocytes or plasma cells, and 22% of patients contained a mixture of small lymphocytes and plasma cells, with rare plasmacytoid cells. Mast cells were increased in 26% of patients.[5] A bone marrow biopsy should be regarded as a mandatory requirement for the assessment of patients. The pattern of marrow infiltration is usually intertrabecular. The diagnosis of WM is supported by immunophenotypic studies by flow cytometry and/or immunohistochemistry. The characteristic immunophenotypic profile of WM is shown in Table 1. Heterogeneous expression of CD5, CD10, and CD23 may be seen in 10% to 20% of patients and should not preclude the diagnosis of WM, provided that chronic lymphocytic leukemia and mantle-cell lymphoma have been satisfactorily excluded.[5,6]

Most patients with the diagnosis of WM have symptoms attributable to tumor infiltration and/or monoclonal protein (Table 2).[7] However, some patients who fulfill the diagnostic criteria of WM are being diagnosed by chance without any symptoms or signs. These patients should be classified as asymptomatic WM (Table 3). Some patients may have symptoms as a result of the biologic effects of the monoclonal IgM protein but no overt evidence of lymphoma. Such patients may have any of the complications listed in Table 2, with the exception of hyperviscosity. It is appropriate to consider these patients as a clinically distinct group under the term of IgM-related disorders (Table 3).[2] The more common conditions associated with an IgM-related disorder include peripheral neuropathy, cryoglobulinemia, cold agglutinin disease, and primary amyloidosis.

Table 2. Symptoms of WM

Cause	Symptoms
Tumor infiltration	Cytopenia
	Fever
	Night sweats
	Weight loss
	Lymphadenopathy
	Organomegaly
Monoclonal IgM	Hyperviscosity
	Cryoglobulinemia
	Cold agglutinin
	Neuropathy
	Amyloidosis

Abbreviations: WM, Waldenstrom's macroglobulinemia; IgM, immunoglobulin M.

These patients need treatment to control complications from the monoclonal IgM (which is often present at low levels) produced by a small clone of lymphocytes, which is usually undetected by morphology. Finally, asymptomatic individuals with a monoclonal IgM level of less than 30 g/L, hemoglobin more than 120 g/L, and no morphologic evidence of marrow infiltration may be classified as having IgM MGUS (Table 3). This condition is discovered by chance and is the most common diagnosis among individuals with a monoclonal IgM.[8] Differentiation of IgM MGUS from asymptomatic WM is not possible on clinical grounds but is made by the demonstration of bone marrow infiltration in the latter diagnosis.

PATHOGENESIS OF MANIFESTATIONS IN WM

The clinical manifestations and laboratory abnormalities associated with WM are related to direct tumor infiltration and to the amount and specific properties of monoclonal IgM.

Manifestations Related to Direct Tumor Infiltration

The malignant cells divide slowly, but they can disseminate throughout the lymphoid system and other tissues where B lymphocytes recirculate. WM always involves the bone marrow, and approximately one third of patients presents with lymphadenopathy, splenomegaly, or hepatomegaly.[7] Occasional patients with WM have been reported with infiltration of virtually every organ.[7,9-12] Three to 5% of patients with WM present with or develop lung involvement, such as diffuse pulmonary infiltrates, nodules, masses, or pleural effusion.[13] Malignant infiltration of the stomach and the bowel has been reported.[12] Infiltration of the kidney interstitium by lymphoplasmacytoid cells, as well as renal or perirenal masses, can be observed.[14] Infiltration of the dermis with malignant cells has caused maculopapular lesions, plaques, or nodules.[12,15] Orbital

Table 3. Classification of WM and Related Disorders

Criteria	Symptomatic WM	Asymptomatic WM	IgM-Related Disorders	MGUS
IgM monoclonal protein	+	+	+	+
Bone marrow infiltration	+	+	−*	−*
Symptoms attributable to IgM	+	−	+	−
Symptoms attributable to tumor infiltration	+	−	−	−

Abbreviations: WM, Waldenstrom's macroglobulinemia; IgM, immunoglobulin M.
*In some patients, equivocal evidence of marrow infiltration is demonstrable. This may include detection of clonal B lymphocytes by flow cytometry or polymerase chain reaction in the absence of morphologic evidence of marrow infiltration.

involvement can be caused by lesions involving the retroorbital lymphoid tissue and lacrimal glands. Infiltration of the conjunctiva and malignant vitreitis have been reported.[16] Malignant infiltration of the CNS is rare. The Bing-Neel syndrome consists of confusion, memory loss, disorientation, motor dysfunction, and eventually coma. This syndrome is a result of long-standing hyperviscosity that alters vascular permeability and allows for perivascular infiltration of lymphoplasmacytoid cells.[17]

Manifestation Related to Circulating IgM

Several manifestations of WM are a result of the unique properties of monoclonal IgM, including its large size and high carbohydrate content. These large, asymmetric molecules are 80% intravascular. An increased concentration of these proteins, which may form aggregates and may bind water through their carbohydrate component, results in an increased osmotic pressure, an increase in the resistance to blood flow, and impaired transit through the microcirculation. Thus, symptoms and signs of hyperviscosity syndrome may occur (see Clinical and Laboratory Considerations for Initiation of Treatment). Hyperviscosity may be further aggravated because monoclonal IgM may interact with RBCs, increase the internal viscosity of RBCs, and reduce the deformability of RBCs.[11,18]

In up to 20% of patients, monoclonal IgM may have the tendency to precipitate upon cooling and can, thus, behave as a type I cryoglobulin. However, clinically evident cryoglobulinemia, consisting of Raynaud's phenomenon, skin ulcers, and necrosis and cold urticaria, occurs in less than 5% of patients. Finally, monoclonal IgM can interact with circulating proteins, including several coagulation factors, and may cause prolonged clotting times. The macroglobulin can coat platelets, may impair their adhesion and aggregation, and may result in prolonged bleeding time.[19]

Manifestations Related to IgM Deposition Into Tissues

The monoclonal protein can be deposited into several tissues. The circulating macroglobulin can be trapped in the glomerular loops and can precipitate and form subendothelial deposits that may cause glomerular damage, resulting in nonselective proteinuria, dehydration, and uremia. This complication can be aggravated by hyperviscosity and can be completely reversed by plasmapheresis.[11] Firm, flesh-colored skin papules and nodules have been reported and are called macroglobulinemia cutis. Histology and immunohistochemistry show amorphous IgM deposits in the dermis (storage papules) without evidence of malignant infiltration.[15] Finally, occasional patients have been reported who develop diarrhea, malabsorption, or gastrointestinal bleeding. Biopsy and histologic examination show deposition of IgM in the lamina propria and submucosa of the intestine.[20]

Manifestations Related to Amyloidogenic Properties of IgM

Deposition of monoclonal light chain as fibrillar amyloid deposits (primary amyloidosis) has been occasionally reported in WM. In a large series of patients from the Mayo Clinic, amyloidosis developed in 2% of patients with monoclonal IgM. Among those patients, 21% had WM. Organs more commonly affected by amyloidosis were the heart (44%), the peripheral nerves (38%), the kidneys (32%), the soft tissues (18%), the liver (14%), and lungs (10%).[21] The incidence of cardiac and pulmonary involvement seemed to be higher in patients with IgM-related amyloidosis than with other immunoglobulin types.[21,22] The median age of the patients was 68 years, and lambda light chain was detected in 68% of the patients. In 60% of patients, the serum monoclonal protein levels were less than 1.5 g/dL. Virtually every patient with amyloid could be diagnosed by biopsy of the subcutaneous fat or bone marrow.[22] Most patients received conventional chemotherapy based on melphalan or chlorambucil. Organ responses were observed in 70% patients, and the median overall survival time was 24.6 months. Organ dysfunction as a result of amyloidosis was the cause of death more often than the underlying WM. Fifty-three percent of patients died of cardiac amyloidosis, and the most powerful variable predictive of survival was the presence or absence of cardiomyopathy.

Rarely, secondary amyloidosis has been reported in the context of WM. In secondary amyloidosis, fibrils are derived from the acute-phase reactant serum amyloid A protein, probably by dysregulated proteolytic cleavage, with

subsequent deposition in tissues. Such rare patients may present primarily with nephrotic syndrome and gastrointestinal involvement.[23]

Manifestations Related to Autoantibody Activity of IgM

Monoclonal IgM may behave as an antibody against autologous antigens. Up to 20% of patients with WM present with or develop IgM-related peripheral neuropathy. This is an immunochemically and clinically heterogeneous group of neuropathies in which monoclonal IgM is an antibody against various glycoproteins or glycolipids of the peripheral nerve. The most common entity is a distal, symmetric, chronic demyelinating peripheral neuropathy in which IgM is directed against a glycoprotein component of nerve called myelin-associated glycoprotein.[24,25] The antibody activity of monoclonal IgM against polyclonal IgG is responsible for type II cryoglobulinemia. This is an immune complex disease characterized by vasculitis affecting small vessels of skin, kidneys, liver, and peripheral nerves.[19] Monoclonal IgM may react with specific red-cell antigens at temperatures less than 37°C and may cause a chronic hemolytic anemia called cold agglutinin disease. The hemolysis is usually extravascular and can be exacerbated after cold exposure.[19,26] Furthermore, occasional patients with WM have been reported in whom monoclonal IgM may behave as an antibody against basement membrane of glomeruli, skin, and retina. As a consequence glomerulonephritis, paraneoplastic pemphigus, and retinitis may occur.[27,15,28]

ASYMPTOMATIC MACROGLOBULINEMIA

Some patients with WM may present with a high monoclonal protein level ($>$ 30g/L) and have a significant infiltration of the bone marrow with lymphocytes and plasma cells but have no constitutional symptoms, hepatosplenomegaly, or lymphadenopathy. They also have no anemia or thrombocytopenia. Such patients with asymptomatic macroglobulinemia should be recognized and not treated because they may remain stable for many years.[29] In a recent analysis of 31 asymptomatic patients, the median time to disease progression was 6.9 years. Prognostic factors for early progression were hemoglobin less than 115 g/L, beta$_2$-microglobulin $\geq$ 3.0 mg/dL, and serum monoclonal protein more than 30 g/L. Combinations of these variables defined three risk groups with markedly different times to progression. The median time to progression was expected to be 10 years with no adverse feature (55% of patients), 2 years with one abnormality (29% of patients), and 0.5 year with two or more abnormalities (16% of patients).[30] Response rate and survival after institution of treatment were similar to those patients treated promptly for symptomatic disease. The projected median survival time from diagnosis of patients with asymptomatic WM (15 years) was longer than that of patients who required treatment at diagnosis (8 years), but the median survival from treatment was similar in both groups.[10] Another study of patients with asymptomatic macroglobulinemia who were followed without treatment reported a median event-free survival time of 7.8 years. A multivariate analysis showed that monoclonal protein more than 30 g/L and hemoglobin less than 125 g/L were independent predictive factors for progression.[31]

CLINICAL AND LABORATORY CONSIDERATIONS FOR INITIATION OF TREATMENT

Initiation of therapy is appropriate for patients who present with or develop disease-related symptoms and signs such as fever, night sweats, weight loss, fatigue, hyperviscosity, severe neuropathy, amyloidosis, symptomatic cryoglobulinemia, cold agglutinin disease, or evidence of disease transformation. Furthermore, patients who demonstrate a hemoglobin level less than 100 g/L and/or platelet count less than 100×10^9/L, bulky adenopathy, or organomegaly should be considered for treatment.[29] Initiation of therapy should not be based on serum monoclonal protein levels per se because these may not correlate with clinical manifestations of WM. However, a serum monoclonal protein level more than 50 g/L places patients at higher risk for hyperviscosity and requires a thorough history and physical examination for evidence of oronasal bleeding, blurred vision, headache, dizziness, vertigo, ataxia, encephalopathy, or altered consciousness.[29] Funduscopic examination is necessary to exclude retinal vein engorgement, hemorrhages, and exudates. Measurement of serum viscosity should be performed, despite the fact that the correlation between serum viscosity levels and symptoms is often poor from patient to patient. However, most patients with a serum viscosity less than 4 cp (normal = 1.8 cp) will not have symptoms of hyperviscosity.

PROGNOSIS

The median survival time of patients with WM ranges between 5 to 10 years in different series. This discrepancy likely reflects different inclusion criteria. Several studies have evaluated the impact of several clinical and laboratory variables on patient outcome. Table 4 includes all studies with at least 100 patients each.[32-39] Age is consistently an important prognostic factor for survival. Anemia, which reflects both marrow infiltration and the serum level of monoclonal protein, is a strong predictor of survival in all published series. Leukopenia and thrombocytopenia are identified as significant survival predictors in most studies. However, the precise levels of cytopenia with prognostic

Table 4. Prognostic Factors for Survival in WM

Reference	No. of Patients	Median Survival (years)	Adverse Prognostic Factor (multivariate)
Gobbi et al[32]	144	6	Age ≥ 70 years; anemia; weight loss; cryoglobulinemia
Morel et al[33]	232	5.1	Age ≥ 65 years; low albumin; at least one cytopenia; at least two cytopenias
Garcia-Sanz et al[34]	217	> 10	Without $beta_2$-microglobulin: age > 65 years; anemia; with $beta_2$-microglobulin: $beta_2$ microglobulin; hyperviscosity
Owen et al[35]	105	5	Age > 60 years; PS > 1; platelets < 100×10^9/L
Dimopoulos et al[36]	122	8.8	Age ≥ 65 years; anemia
Dhodapkar et al[37]	118	7	B_2-m $Beta_2$-microglobulin; IgM < 40 g/L
Merlini et al[38]	215	6.4	Without $beta_2$-microglobulin: age ≥ 60 years; anemia; low albumin; with $beta_2$-microglobulin: $beta_2$-microglobulin; low albumin
Ghobrial et al[39]	410	6.4	Age > 65 years; organomegaly; platelets < 150×10^9/L

Abbreviations: WM, Waldenstrom's macroglobulinemia; PS, performance status; IgM, immunoglobulin M.

significance remain to be determined. Serum albumin levels were correlated with survival in three studies by multivariate analysis.[33,38,40] High β_2-microglobulin values were linked to poor survival in all of the studies in which they were analyzed.[34,37,38,40] In conclusion, hemoglobin and β_2-microglobulin levels at diagnosis are important prognostic markers in WM. Their influence on the timing of treatment and choice of treatment remain to be established. Studies that prospectively apply prognostic markers in WM are needed.

RESPONSE CRITERIA IN WM

Assessment of response to treatment in WM has been widely heterogeneous. As a consequence, studies using the same regimen have reported significantly different response rates. During the Second International Workshop on Waldenstrom's Macroglobulinemia, a consensus panel proposed guidelines for standardized response criteria that were subsequently discussed and modified. These response criteria are summarized in the following sections.[41]

Complete Response

Complete response is defined as complete disappearance of serum and urine monoclonal protein by immunofixation, resolution of lymphadenopathy and organomegaly, and no signs or symptoms that are directly attributable to WM. These findings must be confirmed 6 weeks later. Absence of malignant cells by bone marrow histologic evaluation is required.

Partial Response

Partial response is defined as a ≥ 50% reduction of serum monoclonal protein concentration on electrophoresis and a ≥ 50% reduction of lymphadenopathy and organomegaly on physical examination or computed tomography. Symptoms and signs that are directly attributable to WM must resolve.

Relapse From Complete Response

Relapse from complete response is defined as reappearance of serum monoclonal protein as determined by immunofixation confirmed by a second measurement or reappearance of clinically significant symptoms and signs attributable to WM or development of any other clinically significant disease-related complication.

Progressive Disease

Progressive disease is defined as a greater than 25% increase in serum monoclonal protein levels from the lowest attained response value as determined by serum electrophoresis and confirmed by measurement 3 weeks later. For monoclonal protein nadirs ≤ 20 g/L, an absolute increase of 5 g/L is required to determine progressive disease. Progressive disease may also be documented if there is worsening of anemia, thrombocytopenia, leukopenia, lymphocytosis, lymphadenopathy, or organomegaly directly attributable to WM or appearance of disease-related complications, such as unexplained fever, night sweats, weight loss, neuropathy, nephropathy, symptomatic cryoglobulinemia, or amyloidosis.

Serum monoclonal protein should be measured by serum protein electrophoresis, and the use of nephelometry to determine total serum IgM should be discouraged because this method is unreliable, especially when the levels of monoclonal protein are high. The presence of cryoglobulin or cold agglutinin may affect determination of IgM. Testing of cryoglobulin and cold agglutinin at baseline should be considered, and if present, serum samples should be re-evaluated at 37°C to ensure accurate and consistent determination of the monoclonal protein levels.[41]

TREATMENT OF WM AND OF IgM-RELATED DISORDERS

Multiple retrospective and prospective studies regarding the systemic treatment of WM have been published. However, it is difficult to compare the results of these studies because of several factors. In view of the rarity of WM, most studies include a small number of patients and are not adequately powered. It is important to note that, so far, only two randomized studies have been published.[42,43] As has

been stated earlier, some patients with WM are being diagnosed during an asymptomatic phase of their disease. In many studies, the indication for treatment is not clearly stated, and thus, it is unclear whether some asymptomatic patients may have been included. Furthermore, clearly defined response criteria for WM had not been established until recently. Thus, the interpretation of treatment results may also be hampered by the fact that different response criteria have been applied.

Plasmapheresis

In some patients with WM, the predominant symptoms are caused by elevated serum viscosity. Because 70% to 80% of monoclonal IgM protein is contained within the intravascular space, plasmapheresis is an effective means of rapidly reducing the amount of circulating IgM. Continuous-flow centrifugation systems, which are fully automated, are usually used. In most instances, it is considered acceptable to perform a 1 to 1.5 times plasma volume exchange per procedure, which will lower plasma IgM levels by 60% to 75%, respectively.[44] Higher exchange volumes will double or triple the time required to perform the procedure without significant clinical benefit. The typical replacement fluid is 5% human albumin and 0.9% saline. Blood flow rates are approximately 80 mL/min. In case of monoclonal IgM protein, a single plasmapheresis session can result in significant clinical improvement and serum viscosity reduction by 50% or more.[45] In severe cases, daily or every other day single plasma volume exchanges are used initially until symptoms are relieved. Because hyperviscosity is a direct result of Ig production by the underlying lymphoma, concomitant administration of systemic cytoreductive therapy should be administered. Drug therapy should be withheld until after plasma exchange so that protein-bound drugs are not removed from circulation by this procedure. Long-term plasma exchange alone may be justified in patients who suffer predominantly from hyperviscosity and who are resistant to systemic treatment.[46]

Intensive plasmapheresis has also been used successfully in patients with IgM-related disorders, such as peripheral neuropathy and cryoglobulinemia.[47-49] In such patients, a series of plasmapheresis may reduce the monoclonal protein, provide an opportunity for symptomatic improvement, and justify the subsequent administration of systemic therapy to achieve long-term control. Cryofiltration apheresis using the high-capacity cryofilter is the most selective procedure to remove cryoglobulins. In this method, the plasma is cooled to 4°C, and the precipitated cryoproteins are removed by the cryofilter. The cryoprotein-free plasma is subsequently rewarmed to body temperature, mixed with the cells, and returned to the patient.[45]

Splenectomy

A small number of chemotherapy-resistant patients with WM have been described in whom a major decrease in monoclonal protein concentration occurred after splenectomy alone. Some of these remissions lasted for many years and were associated with resolution of bone marrow lymphoplasmacytic infiltration as well. Possible mechanisms that could explain the beneficial effect of splenectomy include the removal of a major source of IgM-producing cells, the elimination of hypersplenism, and removal of T cells necessary for B-lymphocyte differentiation into IgM-producing cells.[50] It is unclear whether some of the patients who benefited from splenectomy might have had splenic marginal-zone lymphoma. With currently available data, it is not possible to predict how often splenectomy may be helpful, and the possible role of this procedure requires prospective evaluation.

Chemotherapy

Alkylating agents. The standard primary therapy for patients with WM has been the administration of oral alkylating agents, such as chlorambucil, melphalan, or cyclophosphamide. The agent most commonly used agent has been oral chlorambucil. Approximately 50% of patients achieve a partial response, but complete responses are rare. After treatment with chlorambucil, the rate of decrease of monoclonal protein level is slow, and several months are required to determine the chemosensitivity of the disease. Chlorambucil has been administered either on a daily basis at low doses or intermittently at higher doses. A prospective randomized trial reported a similar median survival of 5.4 years with both schedules.[42] The addition of corticosteroids does not seem to increase response rate or survival, although they may be useful in patients who present or develop autoimmune hemolytic anemia, mixed cryoglobulinemia, or cold agglutinin disease.[7,10]

The optimal duration of chlorambucil administration has not been prospectively defined. In some studies, treatment was continued until a maximum reduction of monoclonal protein was reached, and then patients were followed without treatment until there was evidence of disease progression. In other studies, chlorambucil has been administered for 1 or 2 years. Despite the lack of prospective randomized trials, there is no evidence that maintenance therapy prolongs the survival of patients with WM. Prolonged treatment with alkylating agents increases the likelihood of myelodysplasia and secondary leukemia.[7]

Nucleoside analogs. Fludarabine and 2-chlorodeoxyadenosine (cladribine) are purine nucleoside analogs that have been effective for many patients with a variety of low-grade lymphoid malignancies. A European multicenter trial included 20 previously untreated patients who received fludarabine 25 mg/m^2 intravenous daily for 5 consecutive days every 4 weeks. Objective responses occurred in 79% of patients, and the median time to progression was 40 months.[51] The largest fludarabine trial was performed by the Southwest Oncology Group and included 118 previously untreated symptomatic patients. An at least 50%

reduction of serum monoclonal protein levels was documented in 40% of patients, including complete response in 3%. The median time to response was 2.8 months (range, 0.7 to 22.5 months). The median event-free and overall survival times were 43 and 84 months, respectively.[37]

The published experience of single-agent cladribine in previously untreated patients is more restricted. Continuous intravenous infusion for 7 days, 2-hour intravenous infusion daily for 5 days, and subcutaneous injection of the drug are schedules that have been used. Objective responses have been documented in 64% to 90% of patients.[52-56] The number of cycles administered in these studies varied considerably, but objective responses have been documented when patients were restricted to a maximum of two cycles of cladribine. The median time to a 50% reduction of monoclonal protein was 1.2 months, and the median progression-free survival was 18 months in one study.[52] However, other studies have reported longer times to response (median, 5.8 months).[56]

Both fludarabine and cladribine have been administered to patients who experience primary treatment failure with alkylating agents. Studies with higher numbers of patients are listed in Table 5.[37,56-60] More experience has been accumulated with fludarabine. Approximately one third of patients respond to fludarabine, and the activity of this agent has been confirmed in a randomized trial that compared salvage treatment with either fludarabine or cyclophosphamide, doxorubicin, and prednisone (CAP); 28% of fludarabine-treated patients versus 11% of CAP-treated patients responded ($P = .019$). The median time to treatment failure was significantly longer in patients treated with fludarabine, but the median survival was similar in both arms. This may be partially explained by the fact that patients randomly assigned to CAP were subsequently treated with fludarabine.[43] Cladribine is also active in previously treated patients with WM (Table 5).[54-56,59,60] Treatment with a nucleoside analog is more effective in patients who do not respond to primary treatment with alkylating agents, especially when treated within the first year. The response rate among patients with a longer duration of primary resistance or during refractory relapse is significantly lower, and the toxicity associated with nucleoside analogs in these patients is more severe. Prior resistance to fludarabine is also associated with cross-resistance to cladribine.[61]

Table 5. Salvage Treatment of Waldenstrom's Macroglobulinemia With Nucleoside Analogs

Reference	No. of Patients	% Response
Fludarabine		
Dimopoulos et al[57]	26	31
Leblond et al[58]	71	30
Dhodapkar et al[37]	64	34
Cladribine		
Dimopoulos et al[59]	46	45
Betticher et al[60]	24	38
Hampshire and Saven[56]	19	63

Combination chemotherapy. Combinations of alkylating agents with or without a vinca alkaloid, a nitrosourea, or an anthracycline have been used as primary treatment of WM. These regimens include the melphalan, cyclophosphamide, carmustine, vincristine, and prednisone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; and cyclophosphamide, melphalan, and prednisone.[62,34,10,62,63] Although these regimens have not been prospectively compared with standard chlorambucil, there is no evidence of benefit from these combinations. In a limited number of studies, alkylating agents have been added to nucleoside analogs. Two cycles of oral cyclophosphamide and subcutaneous cladribine were administered to 37 patients with previously untreated WM. At least a partial response was documented in 84% of patients, and the median duration of response was 36 months.[64] Fludarabine has been combined with intravenous cyclophosphamide, with a 55% response rate in 11 symptomatic patients with mainly primary refractory disease or relapse on treatment.[65] The same regimen induced responses in 76% of 35 pretreated patients.[66]

High-Dose Therapy

Autologous stem-cell transplantation (ASCT). Despite being a chemosensitive disease, WM remains virtually incurable, and all patients will experience refractoriness to standard chemotherapy. High-dose therapy followed by ASCT has shown activity in several malignancies that share similarities with WM, such as multiple myeloma, follicular lymphoma, and chronic lymphocytic leukemia. The published experience with ASCT in WM is relatively limited, and it is primarily based on retrospective studies (Table 6).[67-71] Patients received ASCT during various phases of their disease, usually several years after their original diagnosis, and most patients were heavily pretreated. A variety of preparative regimens have been used that were adapted from studies designed for multiple myeloma or follicular lymphoma. Some patients received high-dose chemotherapy alone, such as melphalan or the combination of carmustine, etoposide, cytarabine, and melphalan (BEAM), whereas others were treated with total-body irradiation (TBI) combined with melphalan, cyclophosphamide, or etoposide. The median age of these patients was approximately 55 years (ie, several years younger than the average patient with WM). High-dose therapy was well tolerated, with a treatment-related mortality of less than 5%. This modality induced objective responses in almost all patients, even in patients who were clearly refractory to several regimens of standard chemotherapy. Because the series contained a small number of patients treated at various phases of their disease, it is not possible to assess the duration of response

Table 6. Autologous Stem-Cell Transplantation in WM

Reference	No. of Patients	Median Age (years)	Disease Status	Response (%)	CR (%)
Desikan et al[67]	8	58	Relapse	100	13
Anagnostopoulos et al[68]	4	49	Refractory	75	0
Tournilhac et al[69]	18	55	Chemosensitive, n = 14; chemoresistant, n = 4	95	11
Dreger et al[70]	10	51	First response or primary refractory	100	14
Fassas et al[71]	21	NA	Various phases	100	62

Abbreviations: WM, Waldenstrom's macroglobulinemia; CR, complete response.

after ASCT. However, there are reports of some patients who survived without progression for at least 5 years. A recent series of 14 patients treated with high-dose cyclophosphamide and TBI early in the course of the disease reported a median progression-free survival time of 70 months and a 4-year estimate of overall survival of 93%.[70] There are preliminary data regarding high-dose therapy and ASCT in patients with IgM-related amyloidosis. So far, one of six patients has fulfilled criteria for organ response.[22]

These data indicate that ASCT in WM is feasible, safe, and associated with significant cytoreduction. In view of the prolonged survival of most patients with WM, prospective studies with a larger number of patients are needed to define the role of ASCT, focusing primarily on patients with poor prognostic features at diagnosis. It should also be mentioned that prior exposure to nucleoside analogs may impair stem-cell collection.[71] Thus, patients who are candidates for high-dose therapy should proceed to stem-cell collection before initiation of treatment with nucleoside analogs.

Allogeneic stem-cell transplantation. Limited results have been reported with the use of allogeneic transplantation in WM.[68,69,72] The largest study comprised 10 patients with a median age of 46 years (range, 38 to 56 years) and with a median interval from initial diagnosis to allogeneic transplantation of 3 years.[69] All patients received a TBI-containing preparative regimen. The treatment-related mortality was 40%, and 80% of patients achieved an objective response, including complete response in six patients. Among the patients who achieved a complete response, one died at 3 months of treatment-related complications, and the remaining five patients have remained in complete response for 23+ to 76+ months. Allogeneic transplantation should be considered only in young patients with far advanced, refractory disease for whom no other options are available.

A nonmyeloablative conditioning regimen involving low-dose TBI at 2 Gy with fludarabine 90 mg/m^2 and postgrafting immunosuppression with mycophenolate mofetil and cyclosporine was administered to nine WM patients with a median age of 54 years who had failed a median of four prior regimens. Six patients received stem-cell transplantations from HLA-matched siblings, and three patients received stem-cell transplantations from HLA-matched unrelated donors. Among the eight patients evaluated for response, there were four complete responses and two partial responses. There was no transplantation-related mortality.[73] Allogeneic stem-cell transplantation after nonmyeloablative conditioning may provide a new treatment option for young patients with far advanced, refractory disease.

Monoclonal Antibody Therapy

One novel approach to the treatment of WM involves the use of monoclonal antibody therapy. Monoclonal antibodies targeting CD20, CD22, CD52, and HU1D10 have been successfully used in the treatment of various B-cell malignancies.[74-77]

Rituximab. Rituximab is a chimeric human-mouse antibody with human constant regions and mouse variable regions isolated from a murine anti-CD20 antibody. Rituximab binds avidly to the CD20 antigen, which is expressed on 95% of B-cell lymphoma cells and on normal B cells but not present on precursor B cells or stem cells. Because CD20 is almost always present on WM cells, rituximab became a rational treatment for this disease.

Five years ago, case reports and small retrospective series indicated that treatment with single-agent rituximab may induce responses in patients with resistant WM.[78,79] Subsequently, several retrospective and prospective studies have indicated that rituximab may induce major responses in approximately 30% to 40% of previously treated patients (Table 7).[80-86] Furthermore, some studies showed that

Table 7. Rituximab for WM

Reference	No. of Patients	Response Rate (%)
Previously treated patients		
Weber et al[80]	8	75
Foran et al[81]	7	29
Treon et al[82]	23	30
Dimopoulos et al[83*]	29	52
Treon et al[85*]	29	48
Gertz et al[86]	35	20
Untreated patients		
Dimopoulos et al[84*]	23	35
Gertz et al[86]	34	35

Abbreviation: WM, Waldenstrom's macroglobulinemia.
*These patients received extended rituximab therapy.

patients who achieve minor responses or even stable disease benefited from rituximab, as evidenced by improved hemoglobin and platelet counts and reduction of lymphadenopathy and/or splenomegaly.[84,85] In most of the initial studies, rituximab was administered at the standard dose of 375 mg/m^2/wk for 4 weeks. The median time to treatment failure in these studies was approximately 8 months.[79-82] Subsequent studies evaluating an extended rituximab schedule consisting of 4 weekly courses at 375 mg/m^2/wk, which was repeated later by another 4-week course, demonstrated response rates that were on par with those previously reported with standard-dose rituximab. However, the time to progression was considerably prolonged at 16+ to 29+ months.[83-85]

Response rate may be influenced by the previous treatment status as suggested by a recent Eastern Cooperative Oncology Group study that included 34 untreated and 35 previously treated patients. Using standard-dose rituximab, at least a 50% reduction of serum IgM was observed in 35% of untreated and 20% of pretreated patients.[86]

Rituximab is a well-tolerated treatment. Approximately one quarter of patients may develop grade 1 or 2 infusion-related symptoms consisting primarily of fever, chills, and headache, whereas a cytokine-release syndrome has rarely occurred. Because myelosuppression is negligible, rituximab may represent the treatment of choice for patients who present or develop cytopenias. Moreover, the lack of early or delayed myelosuppression makes rituximab an attractive treatment for patients who are candidates for stem-cell collection and high-dose therapy.

Time to response after rituximab is slow and exceeds 3 months on the average. In some studies, an inferior response to rituximab was noted when the baseline serum monoclonal protein exceeded 40 g/L or the total IgM exceeded 6,000 mg/dL.[84,85] In many patients, a transient increase of serum IgM may be noted immediately after initiation of treatment. Such an increase does not herald treatment failure, and most patients will return to their baseline serum IgM level by 12 weeks.[83,87,88] However, patients with baseline serum IgM levels of more than 50 g/dL or serum viscosity of more than 3.5 cp may be particularly at risk for a hyperviscosity-related event, and in such patients, plasmapheresis should be considered in advance of rituximab therapy.[88] Because of the decreased likelihood of response in patients with higher IgM levels as well as the possibility that serum IgM and viscosity levels may abruptly increase, rituximab monotherapy should be used with caution for the treatment of patients at risk for hyperviscosity symptoms. Polymorphisms in Fcγ IIIA (CD16) receptor expression modulate human IgG1 binding and antibody-dependent, cell-mediated cytotoxicity and may, therefore, impact responses to rituximab. In a recent analysis of 58 patients with WM, Treon et al[89] identified a predictive role for Fcγ IIIA-158 polymorphisms and response to rituximab. More specifically, when valine was absent from Fcγ IIIA-158, the response rate to rituximab was only 9%. When at least one valine was present, the response rate ranged between 35% and 40%.[89]

Single-agent rituximab has also been administered to patients with IgM-related disorders. There is preliminary evidence that this agent may improve the symptoms in some patients with an IgM-related peripheral neuropathy.[90] Furthermore, rituximab was effective in 54% of patients with cold agglutinin disease and in up to 80% of patients with type II cryoglobulinemia.[91-93]

Because rituximab is an active and nonmyelosuppressive agent, its combination with chemotherapy has a sound rationale. Weber et al[64] administered the combination of rituximab, cladribine, and cyclophosphamide to 17 previously untreated patients with WM. At least a partial response was documented in 94% of patients, including a complete response in 18%. With a median follow-up of 21 months, no patient has relapsed.[64] Treon et al[94] administered a combination of rituximab and fludarabine to 32 previously untreated patients. An objective response was noted in 80% of patients with a median follow-up of 17 months, and 92% of patients remain without progression.[94] Hensel et al[95] administered pentostatin, cyclophosphamide, and rituximab in 11 patients with WM, and an objective response rate was documented in 90% of patients.

Alemtuzumab. Alemtuzumab is a monoclonal antibody against the CD52 antigen and is effective treatment for patients with chronic lymphocytic leukemia who have previously received a purine analog. With the use of three-color flow cytometry, Owen et al[96] showed that CD52 expression was demonstrable in all 20 patients with WM who were assessed. In fact, the antigen density (median, 99.7% of cells) was similar to that seen in chronic lymphocytic leukemia. Preliminary clinical data on seven heavily pretreated patients who received treatment with alemtuzumab showed four partial responses, one complete response, and a median response duration of 13 months. Infectious complications were common and included cytomegalovirus reactivation, herpes simplex reactivation, aspergillosis, and tuberculosis.[96] In another ongoing study, three of five patients achieved a partial response, and despite hematologic toxicity, no infectious complications have been noted so far.[97]

Interferon Alfa (IFN-α)

IFN-α has been evaluated in a limited number of patients with WM. This agent was administered at low doses and induced at least a 25% reduction of serum monoclonal protein in approximately one third of patients.[98,99] These observations indicate that IFN-α may be worthy of further assessment in patients with WM. IFN-α has been effective in several patients with mixed cryoglobulinemia, especially in patients positive for hepatitis C virus.[100]

New Agents

Thalidomide. Because thalidomide is active in multiple myeloma, this agent has been administered to patients with WM. In the initial phase II study of single-agent thalidomide, the drug was administered at a starting dose of 200 mg orally at bedtime, with dose escalation in 200-mg increments every 14 days, as tolerated, to a maximum dose of 600 mg. Five (25%) of 20 patients achieved a partial response. The time to response was short, ranging between 0.8 and 2.8 months, and the median duration of response was 11 months. Because of several side effects, most patients could not tolerate more than 400 mg of thalidomide daily.[101] Two subsequent studies assessed the activity of the combination of clarithromycin, low-dose thalidomide, and dexamethasone in patients with WM. The partial response rate was 83% in one study and 25% in the other.[102,103] From this limited experience, it seems that thalidomide with or without clarithromycin and dexamethasone may be of benefit for some patients with WM. This treatment could be administered to previously treated patients with prominent cytopenias who have failed treatment with other more active regimens. The combination of rituximab with thalidomide has been administered to 25 patients with WM, 20 of whom were previously untreated. Thus far, responses among the 23 assessable patients include one complete response and 12 partial responses (57%). Approximately one half of patients developed thalidomide-related side effects, which led to discontinuation of this drug in 60% of patients.[104] Thalidomide derivatives such as CC-5013 (lenalidomide) and CC-4047 are active in patients with multiple myeloma, including some patients with previous thalidomide exposure. There is evidence that CC-4027 has direct proapoptotic effect against the WM-WSU cell line model and tumor cells freshly isolated from WM patients.[105] Clinical evaluation of these compounds in WM is ongoing.

Bortezomib. Bortezomib (PS-341) is a reversible proteasome inhibitor that has shown remarkable efficacy in multiple myeloma. Bortezomib at clinically relevant doses induced growth arrest and apoptosis of both the Waldenstrom's Macroglobulinemia–Wayne State Univeristy (WM-WSU) cell line model and tumor cells freshly isolated from WM patients. Furthermore, bortezomib induced suppression of nuclear factor-kappa B activity in WM-WSU cells, decreased expression of kinases implicated in growth and survival, and conferred increased chemosensitivity to the tumor cells.[105] Several ongoing phase II studies are evaluating the activity of bortezomib in patients with WM. Preliminary data suggest activity in patients with refractory disease.[106]

Oblimersen sodium. Because the proliferative rate of WM is low, expansion of the malignant clone is likely a result of the dysregulation of pathways of programmed cell death (apoptosis). Bcl-2 protein is located on the inner mitochondrial membrane and serves as a key inhibitor of apoptosis. By inhibiting apoptosis, Bcl-2 confers resistance to treatment with traditional cytotoxic chemotherapy, radiotherapy, and monoclonal antibodies. Bcl-2 expression is universally present in WM. However, the biologic importance of Bcl-2 expression in WM remains to be established. Oblimersen sodium (G3139) is an antisense phosphorothioate oligonucleotide compound designed specifically to bind to the first six codons of the human Bcl-2 mRNA sequence. This binding results in degradation of bcl-2 mRNA and subsequent decrease in Bcl-2 protein translation and intracellular concentration.[107] Nichols and Stein[108] demonstrated overexpression of Bcl-2 in the WM cell line WM-WSU and specific downregulation of Bcl-2 protein by oblimersen sodium. Treatment with oblimersen alone was associated with a decrease in cell viability in tissue culture compared with control treatments. The coadministration of oblimersen with fludarabine or cladribine showed an additive effect compared with oblimersen alone.[108] A phase I trial of oblimersen for relapsed or refractory WM is ongoing. Hematologic toxicity seems to determine the maximum-tolerated dose. So far, one of six assessable patients has shown a partial response.[109]

Sildenafil. Reduction of serum monoclonal protein was noted in five WM patients who were using sildenafil, a phosphodiesterase inhibitor, to treat erectile dysfunction. In vitro experiments demonstrated that sildenafil increased the spontaneous apoptosis rate of lymphoplasmacytic cells by a mean of 2.1-fold.[110] Clinical trials evaluating sildenafil and related phosphodiesterase inhibitors in WM are planned.

Vaccines. Attempts to develop vaccines against cancer have been stimulated by the understanding that all tumors express antigenic determinants and by molecular identification of tumor antigens. Recent progress in cancer immunotherapy has been based on newer insights in dendritic-cell biology. Dendritic cells are antigen-presenting cells that are specialized to initiate and regulate immunity. These cells can now be obtained in large amounts and, when loaded with tumor-associated antigens, are able to induce protective antitumor responses. There is preliminary evidence that tumor cell–loaded dendritic cells can elicit WM-specific T cells in culture.[111] Such an approach may be more useful in asymptomatic patients with early WM who are more likely to have preserved antitumor immune effector function and most likely to benefit from specific approaches to boost antitumor immune resistance.

Other agents. Some new agents have shown in vitro and in vivo preclinical activity in multiple myeloma and may induce apoptosis of the WM-WSU cell line model and tumor cells isolated from WM patients. These agents include the ansamycins, which inhibit the heat shock protein 90 molecular chaperone, histone deacetylase inhibitors, and thiazolidinediones. The precise mechanisms whereby each

of these classes of agents exerts its in vitro anti-WM activity are currently under investigation.[105]

TREATMENT STRATEGIES

The three main choices for systemic primary treatment of symptomatic patients with WM include alkylating agents (chlorambucil), nucleoside analogs (fludarabine and cladribine), and the monoclonal antibody rituximab. There are no data from prospective randomized studies to recommend the use of one first-line agent over another. Nevertheless, several factors, including the presence of cytopenias, need for rapid disease control, candidacy for ASCT, age, and comorbidities, should be taken into consideration when choosing the most appropriate primary treatment.[112] For patients who are potential candidates for high-dose therapy and ASCT, exposure to alkylating agents or nucleoside analogs should be avoided. Such patients may proceed directly to rituximab followed by stem-cell collection. If there is evidence of significantly elevated serum monoclonal protein or asymptomatic hyperviscosity, plasmapheresis may be considered before rituximab to prevent potentially harmful clinical consequences from IgM flare. The patient may receive further treatment according to his response to rituximab. For patients who are not (and will not be) candidates for high-dose therapy and for whom a rapid tumor control is needed, nucleoside analogs are preferred. Either fludarabine or cladribine should be used. If there is no need for rapid disease control but there is evidence of moderate to severe leukopenia and/or thrombocytopenia, rituximab may represent the treatment of choice. Otherwise, chlorambucil may be used.

For patients with refractory or relapsing disease, the use of an alternate first-line agent is reasonable.[112] For refractory or relapsing patients who are considered for high-dose therapy, rituximab would be preferable if stem cells have not been previously collected. For patients relapsing from unmaintained remission, the readministration of the same agent has a high likelihood of activity. For patients who develop resistance to all three classes of agents, limited experience suggests modest benefit from treatment with thalidomide with or without dexamethasone and clarithromycin, from IFN-α, and from alemtuzumab. However, such patients should be encouraged to participate in innovative trials of new agents.

FUTURE DIRECTIONS AND TRIAL DESIGNS

Over the last 10 years, the treatment options for patients with WM have increased. Furthermore, recent advances in the pathogenesis and biology of WM may result in the development of novel, specific treatments for WM. Until then, several questions regarding the treatment of these patients should be addressed.

Because WM is a low-grade lymphoproliferative disorder affecting primarily elderly individuals, a significant number of patients die from unrelated diseases. A large retrospective analysis from Mayo Clinic indicated that, in only 50% of patients, the cause of death could be attributed to the disease or complications of therapy, including myelodysplastic syndrome or acute leukemia. In 15% of patients, the cause of death was unrelated, and in 35%, it was not well defined. Thus, the median overall survival was 6.4 years, but the median disease-specific survival was 10.4 years.[39] Disease-specific survival, rather than overall survival, should be a more accurate end point of prospective trials involving patients with WM.

There is increasing evidence that rituximab is safe and effective in at least 30% of patients with previously untreated and pretreated WM. Studies that address the mechanisms of resistance to this monoclonal antibody may help us select patients who are more likely to benefit and may provide an opportunity to circumvent primary or secondary resistance. Furthermore, it is unclear whether standard administration of rituximab, extended rituximab, or even maintenance rituximab is the best way to administer this agent.

Besides rituximab, other monoclonal antibodies are worthy of study in WM. Radiolabeled anti-CD20 antibodies require evaluation in carefully selected patients without extensive bone marrow involvement.[113] Preliminary evidence suggests that the anti-CD52 antibody alemtuzumab is active in heavily pretreated patients with WM. Studies with anti-CD22 and anti-CD40 are ongoing or are about to start. Initial studies in profiling tumor cells from patients with WM for serotherapy target antigens show that there is considerable intrapatient clonal variation in antigen expression and that combined monoclonal antibody therapy may permit targeting of all members of the tumor clone. Screening patients may also permit customized combination monoclonal antibody therapy.[77]

There is evidence from small phase II studies that the combination of chemotherapy (nucleoside analogs in particular) with rituximab is associated with improved response rates. Furthermore, with these combinations, a sizeable number of patients may achieve a complete response. However, the optimal duration of such regimens has not been defined. This is an important issue in view of the cumulative myelosuppression and immunosuppression that these combinations may induce. Prospective studies are needed to assess whether rituximab should be combined with nucleoside analogs, alkylating agents, or both classes of agents. End points of such studies should include not only response rates but also response duration, feasibility of stem-cell collection, incidence and severity of infections, and overall survival.

Macroglobulinemia has a relatively protracted course, with a median survival ranging from 7 to 10 years in most series. However, several patients die as a result of complications of WM within a few years after diagnosis. Such patients, when $\leq$ 70 years of age, could be appropriate candidates for trials that incorporate high-dose therapy with ASCT early in the course of the disease. Preliminary evidence suggests that the presence of both anemia and elevated serum β_2-microglobulin may identify at diagnosis patients with impaired prognosis. A total therapy program is ongoing at the University of Arkansas for Medical Science for patients with anticipated poor prognosis. Such patients receive induction treatment with dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and cytarabine for two courses. After each course of this regimen, blood stem cells are collected to support tandem administration of high-dose melphalan (200 mg/m^2 intravenous), and then patients receive rituximab maintenance for 2 years. Among the 11 patients assessable for response thus far, all had achieved an objective response, and 91% had achieved a complete response.[71]

Developments in cell and molecular biology are likely to help us develop targeted therapies for WM. Comparative studies of gene expression profiling and proteomic analysis of WM versus multiple myeloma reveal significant overlap but also distinct differences.[105] These differences may be associated with differential features in the biologic behavior and drug sensitivity of these diseases.

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