Clinical Reasoning in Oncology

REASONING BY IDENTIFYING GOALS OF TREATMENT

Different physicians tend to learn in different ways, but most retain and use needed information when it is presented in a clinically relevant manner and when the reasoning behind decisions on clinical care is explained and demonstrated. Clear identification of the goals of treatment for any patient at any stage of management greatly facilitates optimal management decisions.

The following new journal feature, "Clinical Reasoning in Oncology," attempts to demonstrate the clinical reasoning based on defining specific goals for treatment of an actual case. A consultant's comments are incorporated regarding various parts of the treating physician's description of the course of the patient, followed by a discussion of approaches to the various goals of treatment that were encountered. We would appreciate your feedback on the value of this educational approach. In future issues, we plan to illustrate other types of reasoning processes in the care of patients with cancer.

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A Young Man With Lymphocytosis

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Case Description

A 45-year-old man with persistent lymphocytosis that was noted during a routine annual examination was referred for hematologic evaluation. Laboratory studies yielded the following values: white blood cell (WBC) count, 18,200/mm$^3$ with 81% lymphocytes, 16% neutrophils, 2% monocytes, and 1% basophils; hemoglobin level, 14.5 g/dL; hematocrit, 42.7%; mean corpuscular volume (mm$^3$), 86.8; red cell distribution width, 12.8; and platelet count, 245,000/mm$^3$.

Peripheral smear showed normal red blood cell morphology with predominant, small, round lymphocytes. The patient was otherwise in apparent good health. Three years earlier, he had a normal complete blood count. Physical examination and routine laboratory test results were normal.

Consultant: There are many causes of lymphocytosis. From the data that have been provided, this man appears to have chronic lymphocytic leukemia (CLL) that has developed within a period of three years, despite his relatively young age. Presuming that the physical examination is as stated, I would confirm the diagnosis by performing either a bone marrow aspirate/biopsy or flow cytometry on the peripheral blood. For the sake of simplicity, I would choose flow cytometry.

A bone marrow biopsy showed hypercellular bone marrow with 90% lymphocytes. Immunophenotyping revealed a monoclonal B-cell population coexpressing CD5 and CD23 antigens. Chromosome analysis was normal. The diagnosis of stage 0 CLL was made, and the patient returned for a discussion of future management.

Consultant: I agree with that diagnosis, although less than 10% of patients with CLL are under 50 years of age. This immunophenotype is virtually diagnostic of CLL. Further management depends on our estimate of the course of the disease. To this end, identification of favorable or adverse prognostic factors can be helpful. The most important prognostic factors include stage of disease, lymphocyte doubling time, pattern of marrow infiltration by lymphocytes, and chromosomal abnormalities. This patient has only one adverse prognostic factor, a marrow diffusely infiltrated with CLL. The other prognostic factors appear favorable. Since all clinical studies have shown no survival advantage in treating patients with low-stage CLL over observation alone, I recommend that no therapy is warranted and that the patient be followed regularly, every three months.

The natural history of CLL was discussed extensively with the patient, and he was given estimates of favorable prognosis. The patient agreed to regular follow-up with no planned intervention. He asked about the prospects of bone marrow transplantation (BMT), which was dismissed at the time, given the estimates of good prognosis. Three months later, his WBC count was 25,100/mm$^3$ (86% lymphocytes) with a normal hemoglobin level and platelet count. Physical examination and overall well-being were unchanged. Six months after the diagnosis, the patient started to complain of fatigue and night sweats. Some enlarged lymph nodes had developed in the cervical and inguinal areas without splenomegaly. The WBC count increased to 50,800/mm$^3$ with 86% lymphocytes. His hemoglobin level remained at 13.3 g/dL with a platelet count of 299,000/mm$^3$.

Consultant: When a patient with CLL develops systemic symptoms, the issue is whether the symptoms are due to progression of CLL or to viral or opportunistic infection. To distinguish between these two possibilities, I would obtain a chest radiograph, computed tomography scans of the chest and abdomen, liver function tests, viral titers, and quantitative immunoglobulins.

The patient returned in a month with progressive fatigue, weakness, and night sweats. Laboratory studies were negative for hepatitis A, B, and C, human immunodeficiency virus, and human T-cell lymphotropic virus-1, as well as for active infection of cytomegalovirus and Epstein-Barr virus.

Consultant: Following documentation of no active viral or opportunistic infections complicating CLL, the patient is a candidate for cytoreductive chemotherapy. Observation alone is not adequate management, since survival is clearly compromised without therapy. The choices would be treatment with alkylating agents such as chlorambucil or with a purine analog such as fludarabine. I would choose chlorambucil at this point, since no data show that starting with fludarabine prolongs a patient's life.

The patient was told that therapy is indicated at this time and that chemotherapy should be started. Three chemotherapeutic options were presented that included chlorambucil plus prednisone, fludarabine, and cladribine. After consulting two other physicians in the community, he chose cladribine as the treatment option, although he was told that the data about fludarabine efficacy in CLL were more mature. A purine analog was selected due to the lower response rate to chlorambucil. Since patients treated with fludarabine do not respond well to salvage therapy with cladribine, it was explained to the patient that if cladribine failed, fludarabine would remain an option. For this reason, the patient was started on cladribine. During the following two to three months, while the patient considered the therapeutic options, his disease had progressed with generalized adenopathy and splenomegaly. His WBC count increased to 124,000/mm$^3$ with 89% lymphocytes. His hemoglobin level had dropped to 9.4 g/dL, but the platelet count remained normal at 188,000/mm$^3$. 
Consultant: I agree that chemotherapy is indicated. Evidence suggests that chemotherapy can prolong survival in intermediate and advanced stages of CLL. Whether purine analogues are superior to alkylating agents remains unproven, and whether cross resistance occurs when fludarabine follows cladribine failure is controversial. The limited data indicate that cladribine is not beneficial when used as a salvage treatment after failing a trial of fludarabine.

After the first cycle of cladribine, the patient’s hemoglobin level dropped to 7.4 g/dL, and a transfusion with two units of packed red blood cells was administered. Direct and indirect Coombs tests were negative, and there was no evidence of blood loss. After two courses of chemotherapy, lymph nodes had decreased somewhat in size, and the spleen decreased from 6 cm below the left costal margin to 4 cm. His WBC count decreased to 20,000/mm³, his hemoglobin level was 9.3 g/dL, and his platelet count was 198,000/mm³. Chemotherapy was continued and trimethoprim-sulfamethoxazole was administered as prophylaxis against Pneumocystis carinii pneumonia (PCP) infection.

Consultant: The patient seems to be responding to chemotherapy, although the drop in hemoglobin level after one course of chemotherapy is unusual. The drop does not appear to be due to hemolysis of red blood cells or bleeding. Purine analogues can cause profound CD4 lymphocyte depletion. Many physicians use trimethoprim-sulfamethoxazole for PCP prophylaxis analogous to prophylaxis in patients with AIDS. However, there are few empiric data to support this practice in cladribine/fludarabine treatment of CLL. I believe that continuing treatment with cladribine is reasonable as long as the patient is responding and there is no significant toxicity.

The patient received another two courses of cladribine. His WBC count further decreased to 3,700/mm³ with 35% lymphocytes, 60% neutrophils, 2% monocytés, and 3% eosinophils. His hemoglobin level remained stable at 9.8 g/dL, and his platelet count was 148,000/mm³. However, he developed bulky cervical, axillary, and inguinal lymphadenopathy. Two weeks after the fourth course of cladribine, he was admitted to the hospital with neutropenic sepsis. His WBC count was 1,000/mm³ with 7% neutrophils, with a hemoglobin level of 10 g/dL and a platelet count of 115,000/mm³. He was treated successfully with broad-spectrum antibiotics and discharged with a WBC count of 3,200/mm³. A bone marrow biopsy revealed almost 100% infiltration with leukemic cells.

Consultant: While the WBC count decreased with cladribine, the marrow remains packed with CLL cells. Furthermore, he has developed bulky disease. His response to cladribine has been poor. Since a complete remission was not attained with cladribine, I would evaluate the patient for the possibility of an autologous transplant. Because of the progressive nodal disease, I would switch to fludarabine while awaiting HLA-matching results.

The patient was referred to a bone marrow transplant specialist who recommended a transplant if the patient’s tumor burden could be reduced. The patient was started on fludarabine. Since a compatible HLA match was not found among the patient’s siblings, a search for a matched unrelated donor (MUD) began. An unrelated donor match was identified.

Consultant: The patient has been switched to fludarabine and is not a candidate for bone marrow transplant because of persistent bulky disease. He would be considered for transplant only if he showed a response to fludarabine. Evaluating for responding relapse is often used in the setting of lymphoma as a predictor for successful BMT. However, transplantations in refractory relapse have been successful in some CLL patients. I am not aware of data demonstrating the use of BMT with MUDs in CLL.

The patient was treated with three courses of cladribine. The patient had a partial response but experienced severe neutropenia. He underwent a MUD bone marrow transplant after treatment with high-dose cyclophosphamide and total body irradiation. He tolerated the transplant well except for mild graft-vs-host disease (GVHD) involving the skin, which was successfully treated with glucocorticoids. Two months after transplant, a bone marrow biopsy and flow cytometry showed no evidence of CLL. Restriction-fragment polymorphism analysis was consistent with the engraftment. Three months after transplant, he was doing well. His WBC count was 3,700/mm³ with 60% neutrophils and 30% lymphocytes, his hemoglobin level was 8 g/dL, and his platelet count 20,000/mm³. He continued to receive cyclosporine and corticosteroids for GVHD prophylaxis, and penicillin, trimethoprim-sulfamethoxazole, fluconazole, acyclovir, and weekly gamma globulins for infection prophylaxis. He still required occasional hemoglobin and platelet transfusions.

Consultant: The patient appears to be doing well. However, he is only several months posttransplant, and the development of chronic GVHD or other BMT complications remains highly likely, particularly following a MUD transplant. Although he seems engrafted, secondary graft failure is still possible. The recurrence of his leukemia is always possible, since we do not know whether CLL can be cured. Much longer follow-up is necessary to establish this.

Eight months after transplant, the patient developed fever associated with shortness of breath and coughing. A chest radiograph showed a cavitary lesion in the right upper lobe consistent with an aspergillosis infection. Despite treatment with amphotericin B, his condition continued to deteriorate, and the patient died 14 days after treatment with amphotericin B.

Discussion

This case illustrates several aspects of clinical reasoning often used by physicians in managing malignant diseases. As in other areas in medicine, the initial approach is to establish a diagnosis, which lays the groundwork for determining prognosis or management goals. The Table summarizes salient features of decision making presented in this case.

![Reasoning Principles Illustrated in This Case](image)

Diagnosis is frequently less of a cognitive challenge in oncology than in other aspects of patient care. Our discussant rapidly arrived at the diagnosis of CLL. Although many factors can lead to an increase in lymphocyte count, few induce slowly progressive lymphocytosis in an asymptomatic patient. When CLL is suspected, the diagnosis should be confirmed with bone marrow studies and/or immunotyping to document a monoclonal expansion of lymphocytes. Confirmation of the diagnosis is facilitated by detection of a unique combination of B-cell differentiation antigens such as CD19, CD20, CD21, and CD23 with a normal T-cell antigen, CD5, on the CLL cells. As the consultant pointed out, the presence of these antigens, detected via antigen-specific monoclonal antibodies using flow cytometry, immunohistochemical reactions, or fluorescence microscopy, is diagnostic of CLL.

The major thrust of the illustrated case is reasoning by identification of management goals. To determine the goals, physicians attempt to predict the course of the disease in the individual patient by using statistical rules (prognostic factors) derived from groups of patients. They also use reasoning by extrapolation of data from one clinical setting to another. To determine the most appropriate treatment option, they weigh the available data about benefits and risks in a comparison among competing therapeutic strategies.

Goal-oriented management in oncology typically begins with the question, “Can disease in this patient be cured?” If the answer is yes, the next questions are, “What is the price of cure? Do the benefits of treatment exceed the risks?” For example, chronic myelogenous leukemia can be cured in a 70-year-old patient using BMT with the risk of a high short-term mortality. In this situation, an appropriate approach may be a conservative, less risky treatment that cannot cure the disease but consistently results in several years of survival.
If the disease is not curable, the next question is, “Can survival be prolonged in our patient?” Again, if the answer is yes, the question is, “Does the benefit of treatment justify its risk?” For example, survival in most patients with acute myelogenous leukemia can be prolonged with autologous BMT (auto-BMT) but not in a 70-year-old patient because of the high treatment mortality.

If survival cannot be prolonged, usually the next question is, “Can the quality of life be improved in our patient?” The decision to administer palliative treatment will again depend on the risk-benefit ratio of the treatment. For example, we would not administer additional chemotherapy to a patient with widespread metastatic disease who had failed conventional treatment, because the chemotherapy would add to the patient’s misery and would not significantly improve survival or quality of life. Our treatment would focus on supportive care.

In the present case, both the physician-in-charge and our discussant concluded at the first encounter that CLL cannot be cured. The treatment of early-stage CLL does not prolong survival and can result in shortened survival due to an increased incidence of secondary malignancies associated with chemotherapy. Furthermore, survival in patients with early clinical stage can be long (10 years or more), and some of these patients have a median survival duration equal to that of the control population. These patients are said to have “smoldering” CLL. The critical problem for the physician is to distinguish these patients from those in whom disease will behave more aggressively. Both the physician-in-charge and our discussant used prognostic factors to estimate the likely course of the disease.

Several prognostic factors have been proposed to describe “smoldering” CLL and to identify those patients who do not need immediate treatment. Smoldering CLL is characterized by normal hemoglobin and platelet values, fewer than two areas of lymph node enlargement, peripheral blood lymphocytes of less than 30,000/mm³, lymphocyte doubling time greater than 12 months, and nondiffuse bone marrow involvement. Our patient had only one adverse factor — diffuse bone marrow infiltration. However, all other prognostic factors were favorable. The physician-in-charge and our discussant therefore believed that the patient would do well and indicated no therapeutic intervention. In doing so, they relied on the use of prognostic factors. In addition to the stage of the disease, five other prognostic factors are typically used in CLL: (1) the number of lymphocytes in blood (<50,000 vs >50,000/mm³), (2) doubling time (<12 months vs >12 months), (3) lymphocyte morphology in peripheral blood (<5% prolymphocytes vs >5% prolymphocytes), (4) cytogenetic abnormalities (normal karyotype vs multiple and complex abnormalities), and (5) bone marrow histopathologic pattern (nodular vs diffuse). Our patient was stage I and had one of the five unfavorable prognosticators (diffuse bone marrow involvement). No method has been developed to use all prognostic factors in a single score to indicate probability of long-term survival. Instead, physicians and patients must make their “best” guesses as to which one of these factors would determine the prognosis. To supplement the lack of accurate prognostic tools, physicians usually resort to a time-honored practice: regular patient follow-up.

Unfortunately, the outcome in this case did not occur as predicted. Within six months of diagnosing “favorable” CLL, the disease had progressed to an advanced stage. The patient’s survival was now estimated to be jeopardized, and an intervention could possibly lead to prolonged survival.

Once the need for intervention is identified, the next dilemma faced by physicians who care for patients with CLL is choice of therapy. Standard therapy with alkylating agents and multiagent combinations results in prolonged survival but not in cure. Furthermore, true complete remissions with standard chemotherapy are rare, usually not exceeding 10% even by standard hematologic criteria. New purine analogues, however, have much higher remission rates. Some of these agents appear to induce true, durable, complete molecular remissions and thus raise the possibility of cure. Faced with aggressive disease in a young patient with CLL who has a significantly reduced life expectancy, the physician-in-charge in the illustrated case and two other consultants recommended purine analogues as first-line treatment for this patient. They believed that treatment with chlorambucil would be palliative at best and that the treatment with purine analogues might result in long-term remission, if not in cure. However, our discussant was correct to point out that the remissions achieved by purine analogues have not as yet been shown to result in a survival advantage and certainly not in cures. Chlorambucil is still considered standard initial therapy by many physicians. However, in a recent US randomized trial, the complete remission rate for fludarabine was 33% vs 8% for chlorambucil. Whether this will translate into a survival advantage for fludarabine is not clear at this time.

The next dilemma for the physician-in-charge was determining which purine analog to recommend. Cladribine and fludarabine have been shown to be equally effective. However, cladribine is not effective salvage therapy after fludarabine failure, whereas fludarabine has not been shown to be ineffective salvage therapy following cladribine failure. Initial treatment with fludarabine might narrow the future treatment options in the case of a treatment failure. For this reason, cladribine was chosen as the initial therapy. Faced with two uncertain options, physicians frequently choose to avoid regret that commonly occurs when expectations do not meet outcomes.

After treatment with cladribine resulted in a poor response and fludarabine led only to tumor reduction rather than complete remission, it was estimated that life expectancy of our patient was dismal. What should be the goal of treatment now?

The physician extrapolated data from other clinical trials despite the absence of CLL studies that high-dose chemotherapy followed by BMT could potentially cure this patient’s CLL. But what type of BMT should be recommended? The choice lies between allogeneic BMT (allo-BMT), with a matched related or unrelated donor, and auto-BMT. If a matched related donor were not available, would BMT with MUD be preferred over auto-BMT? Comparison of benefits and risks among competing therapeutic options is the reasoning principle used to select of the final treatment.

The main limitation of auto-BMT for CLL is a high relapse rate and questionable curative potential. Allo-BMT can eradicate CLL and can result in a complete clinical and molecular remission. Due to short follow-up, it is unclear whether these remissions will translate into cures. Following allogeneic stem cell transplantation with matched siblings for CLL, the complete remission rate is 80% to 90%. The projected disease-free survival plateaus at approximately 55%. Most such patients undergoing allo-BMT have a chemoresistant disease, similar to our patient. However, the main obstacle for the allo-BMT is a transplantation-related mortality that varies between 10% to 50%; a large series for HLA-identical siblings reported a 47% mortality. No extensive series of MUD transplants in CLL are available, only limited case reports. However, complete hematologic, immunologic, and molecular remissions have been readily achieved and long-term survivors (1 to 4 years) have been reported.

The National Marrow Donor Program data show that at least 38 patients with CLL have been transplanted with matched unrelated donors. However, complete hematologic, immunologic, and molecular remissions have been readily achieved and long-term survivors (1 to 4 years) have been reported. The National Marrow Donor Program data show that at least 38 patients with CLL have been transplanted with matched unrelated donors. The transplant-related mortality in MUD transplants for chronic leukemias is approximately 50%. Therefore, evidence-based recommendations are difficult to make in this clinical setting. When data are lacking, how should physicians and their patients proceed?

Faced with a dilemma of a severely compromised life expectancy vs the possibility of cure, the physician-in-charge, two BMT specialists, and the discussant in the above case believed that the potential benefits of BMT justified its risks.

Unfortunately, a matched related donor was not found. Auto-BMT would have been less toxic but would have had less chance at achieving a long-term remission.

Facing the alternatives of auto-BMT, a MUD transplant, or palliative therapy in the setting of rapidly progressive, chemoresistant disease, the clinicians chose the most aggressive approach of a MUD transplant. They felt that a high-risk procedure such as MUD BMT had a greater potential benefit than either palliative care or auto-BMT. Although the patient’s risk of life-threatening complications was exceedingly high with MUD, his prognosis with palliative treatment and auto-BMT were believed to be equally dismal. Thus, the physician-in-charge, two BMT specialists, and the discussant recommended MUD, the therapeutic approach with the potential for a long-term benefit. They recommended this treatment without firm data on benefits and risks of MUD BMT in CLL, assuming analogy to the treatment of other chronic leukemias, such as chronic myelogenous leukemia.

Using the principle of analogy to extrapolate data from one setting to another is not unique to oncology and is deeply woven into the fabric of medical thought. How should physicians and their patients proceed?
their individual patients that has a chance of success.\textsuperscript{45} Therefore, as illustrated in this case, when data are not available, physicians often define goals of treatment based on their own understanding of the biology of disease and extrapolation of data from one clinical setting to another.\textsuperscript{40,41} Without further treatment, prognosis in chemotherapy-refractory patients with CLL is dismal,\textsuperscript{21} and in the absence of curative options for patients with high-risk B-CLL, consideration of MUD BMT is a reasonable alternative. When expected benefits of the treatment exceed its risks, the regret associated with a wrong decision becomes negligible.\textsuperscript{26} Perhaps this explains why the patient and his physicians embarked on the course of risky treatment without solid evidence of proven efficacy.

Whatever the course of action pursued by physicians, it must be taken in concert with the patient. In our case, after the patient and physician agreed on the problem, the physician-in-charge presented one or more courses of action to the patient. On multiple occasions, the patient sought the aid of additional consultants. The decisions that were made and the course of medical action were based on the mutual consent of the patient, several consultants, and the physician-in-charge.\textsuperscript{46}

\textbf{References}


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