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COMMENTS AND CONTROVERSIES

Novel Targeted Agents and the Need to Refine Clinical End Points in Chronic Lymphocytic Leukemia

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Standardized criteria for response to therapy in patients with chronic lymphocytic leukemia (CLL), lymphoma, and other malignancies allow for comparisons of outcome between clinical trials and have facilitated regulatory agency approval of novel active agents for use in current standard therapy. In 1988, the National Cancer Institute (NCI) Working Group published the first widely accepted criteria for CLL,[1] which were revised in 1996.[2] Such recommendations were developed in the context of currently available cytotoxic therapies. Later, in 2008, the International Workshop on CLL published criteria that incorporated much of the 1996 guidelines but also included guidance on how to assess minimal residual disease after therapy.[3] These published guidelines defined therapy outcome as either complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), based on surrogate markers of tumor burden, such as blood lymphocyte count, lymph node size, or spleen size, and indicators of improved marrow function or clearance of leukemia cells from the marrow, as assessed by serial blood counts and/or marrow aspirate and biopsy. In general, these response criteria (CR, PR, SD, and PD) in therapeutic trials have correlated with the length of progression-free survival (PFS) and occasionally overall survival after treatment. Because assessment of response using these criteria can often be made years before survival data are available, response criteria have served as useful surrogate markers for assessing the clinical benefit of therapy, thereby accelerating the pace of approval of novel agents for use in the treatment of patients.

Whereas the defined criteria of CR, PR, SD, and PD have helped to stratify patients into subgroups that correlate with PFS in many studies involving the use of traditional chemotherapy, it has recently become evident that these definitions may not faithfully predict outcome with newer agents under clinical investigation. In particular, the current definition of PD may not adequately serve as a surrogate marker for poor outcome, particularly for therapeutics that activate CLL B cells for subsequent immunologic destruction or generate an altered trafficking of B cells from different compartments to the blood. As a result, the Lymphoma Research Foundation sponsored a workshop in May 2011 to determine whether current response end points should be modified in light of the now well-recognized effects of such agents for treatment of patients with CLL. A brief description of therapeutic agents that highlight the confounding issues related to response assessment by current criteria is included, along with suggested changes to the guidelines that may assist in evaluating therapeutic benefit of these newer agents.

Immune-Modulating Agents

Thalidomide and lenalidomide are immune-modulating agents with activity in CLL. Thalidomide has rather modest single-agent activity but may enhance response to chemotherapy. In contrast, the second-generation immune-modulating agent lenalidomide seems to provide significant clinical benefit in a variety of doses and schedules.[4,5] On initial treatment, approximately 15% of patients may experience a tumor flare, which is a reaction to drug treatment predominately characterized by a rapid and often painful, but self-limited, increase in the size of lymph nodes, fever, lymphocytosis, rash, and bone pain. The pathophysiology of this tumor flare may be related in part to the activation of CLL B cells[6] and the patient immune system.[7] In general, tumor flares can be mitigated by temporarily withholding treatment with lenalidomide and/or by administering a short course of nonsteroidals or glucocorticosteroids. Over time, patients who experience these transient changes suggestive of PD may improve and ultimately meet criteria for response. Studies have suggested that this tumor flare may in fact correlate with clinical benefit from lenalidomide.[8] Because continued investigation of lenalidomide has proceeded since the initial publication of its activity, efforts to diminish tumor flare with stepped-up dosing, early use of prednisone, and pretreatment with agents such as rituximab have diminished the morbidity of tumor flare. However, rigorous application of the 1988[1] and 1996 guidelines[2] of the NCI Working Group or the current International Workshop on CLL 2008 criteria[3] among patients receiving such immune-modulating agents could result in incorrect assessment

as PD, mandating early cessation of lenalidomide therapy before observation of clinical benefit and possibly premature withdrawal from a clinical trial.

B-Cell Receptor and Adhesion-Related Kinase Inhibitors

The introduction of inhibitors of B-cell receptor (BCR) signaling kinases, such as fostamatinib disodium (Syk), dasatinib (Lyn kinase), GS1101 (phosphatidylinositol 3-kinase delta), and ibrutinib (PCI-32765; Bruton's tyrosine kinase inhibitor [BTK]), and mammalian target of rapamycin (mTOR) inhibitors in CLL has generated significant excitement based on clinical benefit observed in these patients. Although fostamatinib disodium and dasatinib have both demonstrated clinical activity in CLL/small lymphocytic lymphoma, the duration of clinical benefit has been relatively short.[9-11] In contrast, GS1101 (formerly CAL-101) and ibrutinib seem to have substantial and prolonged clinical activity in patients with CLL based on results from early clinical trials.[12,13] Both GS1101 and ibrutinib, when administered to symptomatic patients with CLL, can cause a rapid reduction in lymph node size and spleen mass concomitant with an increase in lymphocytosis from baseline.[14] With continued therapy, many patients receiving GS1101 or ibrutinib have experienced improvement in cytopenias as well as some resolution of lymphocytosis. However, with extended follow-up beyond 1 year, reduction in blood lymphocyte counts is not always observed, despite patients remaining on continuous treatment with no other signs or symptoms referable to the disease. Subsequent combination studies with other agents used in CLL, including bendamustine, rituximab, and ofatumumab, have been pursued with GS1101 and have shown a marked reduction in early lymphocytosis.[15] Nevertheless, rigorous application of the current International Workshop on CLL 2008[3] or NCI Working Group 1996[2] criteria among patients receiving treatment with GS1101 or ibrutinib would result in incorrect assessment as PD, which might mandate early treatment cessation when studies have demonstrated long-term benefit from administration of these drugs. Because ibrutinib and GS1101 target kinases associated with CLL B-cell adhesion, it is likely that many other agents that also target these pathways will have a similar response pattern, confounding response classification according to the current response criteria. Currently, the designation of nodal response has been used in clinical trials with GS1101 and ibrutinib to describe those patients who experience a clinical response with a reduction in lymphadenopathy but with persistent lymphocytosis.[12,13] Over time, many such responses become PRs or even CRs as the lymphocytosis resolves. Thus, we feel that a focus on overall response rate as defined in the traditional response criteria is misleading and underestimates the magnitude of the clinical benefit of these agents, potentially interfering with their regulatory approval.

Summary of Issues With Response Assessment and Solutions

The growing number of new therapeutics that affect signal pathways for B cells or the tumor microenvironment for treatment of patients with CLL has generated significant excitement because of their clinical activity and safety. However, with the development of new therapeutics, it is important that early surrogate markers for patient benefit or PD are not misinterpreted, leading to dismissal of what are active agents. Thus, there are some specific recommendations going forward:

One. In the setting of an immunomodulatory agent, caution must be exercised not to confuse possible tumor flare with PD.[8] The assessment of PD in patients treated with immune-modulating agents should require repeated observations and incorporate indicators of PD that are not typically associated with tumor flare or rely on indicators of PD that do not resolve after use of measures to mitigate the signs or symptoms of tumor flare.

Two. GS-1101, ibrutinib, or other BCR-targeted therapeutics as well as mTOR inhibitors can mobilize CLL cells from tissues into the peripheral blood,[14] interfering with their homing.[16,17] This characteristic pharmacologic action, especially when the drug is administered as a single agent, can be prominent early in therapy, but it can also persist over time. This occurrence should not be confused with PD unless the treated patient develops other CLL-related signs or symptoms of PD. In the absence of other objective evidence of PD, lymphocytosis alone should not be considered an indicator of PD. Patients with lymphocytosis and no other evidence of PD should continue therapy until they develop other definitive signs of PD (ie, at least one feature suggesting worsening CLL other than lymphocytosis [eg, anemia, thrombocytopenia, lymphadenopathy, or hepatosplenomegaly]) or the occurrence of another reason to discontinue therapy. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening disease should also not be considered definitive evidence of PD until other potential causes are ruled out. If PD is suspected, clinical examination, computed tomography, and peripheral blood counts should be obtained, and a bone marrow biopsy considered, to provide objective assessment of CLL status. Similarly, persistent lymphocytosis should not interfere with the time of designation of a PR, which should be based more on the other measurable aspects of the disease than on lymphocytosis. It is important that the term tumor flare be used in the setting of immunomodulatory drug therapy. Tumor flare should not be used inappropriately to describe lymphocytosis in a patient who also shows other signs of progression while receiving a BCR antagonist.

These recommendations from this Lymphoma Research Foundation–sponsored workshop are intended to facilitate the evaluation, development, and potential regulatory approval of novel nonchemotherapeutic agents with unique mechanisms of action and unique sequelae that render more traditional surrogate markers of PD less reliable in predicting clinical outcome. Clearly, as other agents are encountered that challenge other surrogate markers of PD, additional modifications may be required.

It is important to recognize that this issue is not restricted to CLL.[18] For example, in lymphomas, standard response criteria[19] recommend restaging 6 to 8 weeks after completion of chemotherapy, whereas the maximal effect of many of the newer targeted agents may not be exhibited until months later.[20] In addition, an inflammatory response to such drugs may result in a transient increase in lymph node size, which might be confused with PD, because this can also be associated with [^{18}F]fluorodeoxyglucose avidity.

We must remember that in CLL, lymphocytosis in and of itself is rarely detrimental to patient health. For an incurable yet relatively indolent and often asymptomatic disease such as CLL (and the same could be said about indolent non-Hodgkin's lymphoma), clinical benefit evaluation needs to consider quality of life; nontoxic oral therapies that reduce the size of lymph nodes and spleen and improve normal blood cell counts have been demonstrated to accomplish this goal.

It is critical that we reconsider and revise current inflexible response criteria for CLL and lymphoma to correctly interpret results with an increasing number of agents with novel mechanisms of actions and clinical effects so that major clinical benefit and, subsequently, regulatory approval are not obfuscated by observations that are potentially clinically irrelevant.

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