The Evolving Role of Outcomes and End Points in Evaluating Therapy for Hematologic Malignancies: Value-Driven Benefit Design and Utilization Management Strategies

While healthcare reform is on the horizon, the pipeline for new cancer therapies continues to grow and cancer care costs are on the rise. More than 90% of the anticancer agents approved by the US Food and Drug Administration (FDA) between 2004 and 2008 cost more than $20,000 for a 12-week course of treatment.1 The practice of managed care pharmacy frequently involves making decisions about whether a given drug or a regimen is covered under a patient’s pharmacy benefit or health insurance plan. The question that managed care payers are asking is, will the health outcomes produced by these expensive therapies justify the increased cost? Payers are increasingly insisting that newly introduced agents and regimens demonstrate improvement in patient outcomes before their cost will be fully reimbursed.

End Point versus Outcome: What Is the Difference?

Avedis Donabedian, MD, MPH, public health pioneer, defined outcomes as the “consequences to the health and welfare of individuals and of society.”2 He noted that “outcomes, by and large, remain the ultimate validation of the effectiveness and quality of medical care.”2 Ultimately, cure is the desired outcome for patients with any disease. However, this is not currently a realistic goal for most patients with cancer who are undergoing the therapies available today. As advances are made in our understanding of molecular oncology and new targeted therapies are developed, many malignancies are being treated as chronic diseases, and patients diagnosed today may expect to live longer than patients diagnosed in years past. A patient’s quality of life and freedom from disease progression may become more important outcomes than survival if differences in overall survival (OS) are not apparent when comparing therapies and regimens.

The economic evaluations involved in making managed care decisions often consider the likely costs and outcomes of new therapies over time, based primarily on safety and efficacy end point data from the clinical trials that led to the approval. A clinical trial will usually define or specify a primary end point as an objective measure that will indicate the success of the therapy being investigated. A trial may also define 1 or more secondary end points that will be measured and are expected to be met.

Some of these end points may be surrogate end points, which are biomarkers that may correlate with a real clinical outcome but do not necessarily have a guaranteed relationship. In addition, a primary end point that supports efficacy in previous and ongoing clinical trials may be different from the primary end point in subsequent trials, making it difficult to compare agents and regimens and their effect on the desired outcome. Although an improvement in OS had historically been the gold standard end point for a new oncology drug approval, 68% of the regular approvals and 100% of the accelerated approvals for oncology drugs between 1990 and 2002 were based on clinical trial end points other than survival, including the objective response rate, progression-free survival (PFS), disease-free survival (DFS), and time to progression (TTP).3

In 2003, the FDA began a project to evaluate potential end points for cancer drug approval.4 End points were examined for the most common cancers during public workshops, important issues were identified, and these issues were discussed in meetings of the Oncologic Drugs Advisory Committee. Subsequently, a guidance document was published in 2007, describing the FDA’s current thinking on end points for cancer drug approval.5 Although the FDA still regarded OS as the preferred end point in a cancer trial, FDA members found a clear disadvantage in the necessity of a long observation period. During this same

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In combination with dexamethasone (high-dose); MM, multiple myeloma; MP, melphalan/prednisone; ORR, overall response rate; TD, thalidomide/dexamethasone (high-dose); TTP, time to progression; VM, bortezomib/melphalan/prednisone.

A plateau in OS was observed after 11 years; 35% of patients achieving CR are alive at 17 years.

For patients who are transplant-eligible, recent clinical trials have evaluated combined modality induction regimens with the novel agents in an attempt to increase the rate of response to induction therapy to improve the quality of response to transplantation. In the HOVON-65/GMMG-HD4 (Dutch-Belgian Hemato-Oncology/ German Cooperative Groups) trial, patients were randomized to induction therapy with bortezomib, doxorubicin, and dexamethasone (PAD) or with vincristine, doxorubicin, and dexamethasone (VAD). After undergoing high-dose therapy and ASCT, patients who were randomized to PAD received bortezomib as maintenance therapy for as long as 2 years, and those randomized to VAD received thalidomide. The postinduction response rate of VGP or better was 42% in patients receiving PAD and 15% in those receiving VAD (P < .001). The response rates improved to 61% and 36%, respectively, posttransplantation and to 76% and 55% during maintenance. Patients receiving PAD induction with bortezomib maintenance showed significantly improved OS (HR = 0.75; P = .005) and OR (HR = 0.73; P = .02).

In the phase 3 GIMEMA (Gruppo Italiano Malattie Ematologiche dell’Adulto) trial, the safety and efficacy of induction therapy and consolidation with thalidomide plus dexamethasone did not apply to patients aged ≥75 years (MPR-R vs MPR; P = .118). Although a median OS has not been reached among any of the 3 arms, there is currently no significant difference between the arms in the estimated 1-year and 2-year OS rates.

Transplant-eligible patients

The quality of posttransplantation response, especially the achievement of complete response (CR), is now well established as a prognostic indicator of improved long-term survival for previously untreated MM in patients who receive high-dose therapy and ASCT. In a retrospective analysis of 344 patients with MM who underwent transplantation between 1989 and 1998, after a median follow-up of 12.75 years, the OS rate at 12 years was 35% for patients achieving CR, 22% for those demonstrating near CR (nCR), and 16% for those achieving very good partial response (VGPR). Significant differences in OS and PFS were found between the CR and nCR groups (P = .01 and P = .002, respectively), as well as between CR and VGPR (P = .0001 and .003). A plateau in OS was observed after 11 years; 35% of patients achieving CR are alive at 17 years.

In D ecem ber 2009 , survival benefit was added to the VMP label after further analysis of the VISTA trial demonstrated that OS continued to improve significantly in the VMP arm during a median follow-up of 36.7 months despite subsequent therapies, including bortezomib-based regimens. Median OS was not reached with VMP versus 43.1 months with MP (P < .001); after 3 years, the OS rates were 68.5% versus 54.0%, respectively.5

Several phase 3 trials have compared the use of melphalan, prednisone, and thalidomide (MPT) with that of MP for the treatment of newly diagnosed MM in patients who were not eligible for ASCT, showing mixed results. Although these trials have consistently shown better response rates with MPT than with MP, only 4 of the 5 trials showed a significant improvement in PFS, and only 2 showed a significant improvement in OS (P < .05). A meta-analysis of these 5 trials (N = 1568) showed a pooled hazard ratio (HR) of 0.68 for PFS (P < .001; 95% confidence interval [CI], 0.55-0.82) and 0.80 for OS (P = .07; 95% CI, 0.63-1.02) in favor of MPT.5 Although the addition of thalidomide to MP results in significantly improved PFS, MP alone demonstrates only a nonsignificant improvement in OS, with the additional burden of significantly increased toxicity.

Recent data were reported from a phase 3 trial comparing the combination of lenalidomide plus MP (MPR) with MP in patients aged ≥65 years who were ineligible for ASCT.6 The median TTP—the primary efficacy end point in the study—was 24.0 months in the VMP group compared with 16.6 months in the MP group (P < .001).

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The importance of early optimal response

It was established that patients with CML had prolonged survival after achieving a cytogenetic response (CCyR) to interferon-alpha. In 2001, imatinib was approved for newly diagnosed CML-CP based on the surrogate end points of major CyR and complete CyR (CCyR). Since then, much has been learned regarding the accepted milestones for response to first-line therapy and the timing of those responses. Patients with suboptimal or poor response within the first 6 months of therapy are far more likely to experience early disease progression to advanced phase or blast crisis, in which long-term responses to TKIs are unlikely to occur and overall healthcare costs are much higher. In a study comparing patients with a suboptimal response or failure within 6 months of initiating imatinib therapy and those who responded during that same period, the likelihood of achieving CCyR was 39% versus 96%, respectively (P < .0001), the rate of PFS was 87% versus 98% (P = .04), and the rate of OS was 70% versus 92% (P = .001). In the IRIS (Insulin Resistance Intervention after Randomization) trial, patients who achieved a CCyR had a lower annual incidence of events (loss of response, transformation to advanced phase or blast crisis, or death) than the overall group after 5 years of follow-up. In addition, 100% of patients in the imatinib arm of the IRIS trial who had achieved both a CCyR and a major molecular response (MMR) by 12 months were free from progression to advanced phase or blast crisis at 8 years, and the achievement of CCyR by 12 months was associated with improved survival.

Second-generation TKIs

Second-generation TKIs (nilotinib, dasatinib, and bosutinib) are being compared with imatinib in clinical trials in patients with newly diagnosed CML-CP. Nilotinib (300 mg twice daily) received FDA approval in June 2010 for the treatment of newly diagnosed CML, based on results from the ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients) trial. The primary end point in this trial is the MMR rate at 12 months. After a median follow-up of 18 months, the rate of confirmed CCyR at 12 months was significantly higher in patients receiving dasatinib (77%) than in those receiving imatinib (66%; P = .007). In addition, the rate of MMR at any time was significantly higher among patients receiving dasatinib (52%) than among patients receiving imatinib (34%; P < .0001). Among patients who achieved an MMR, the median time to MMR was 8.3 months for dasatinib and 11.8 months for imatinib. Fewer patients receiving dasatinib (1.9%) than those receiving imatinib (3.5%) had progressed to advanced phase or blast crisis. The rates of discontinuation as a result of adverse events were similar for dasatinib and imatinib. An updated analysis of data covering a median follow-up of 18 months was presented at ASH 2010.

First-line second-generation TKIs provide optimal outcomes

In January 2011, nilotinib and dasatinib were added to the National Comprehensive Cancer Network (NCCN) treatment guidelines as category 1 options for the primary treatment of Ph+ or BCR-ABL+ CML. With 3 FDA-approved and NCCN-recommended therapies, what will drive the choice of treatment? Should the higher cost of the second-generation TKIs be a factor? A recent study examined the association between adherence to imatinib therapy and direct healthcare costs and resource utilization in a large group (N = 592) of privately insured patients with CML. Patients with CML who do not adhere to treatment may have suboptimal outcomes and higher rates of progression to advanced phase or blast crisis. In this study, patients with low adherence had more all-cause inpatient visits (4.1) compared with those who demonstrated higher adherence (0.4; P < .001) and more all-cause inpatient days (14.8 days vs 1.8 days, respectively; P < .001). In regression models, non-adherence costs were 283% higher in the nonadherent group ($324) than in the adherent group ($56; P < .001). Therapy failure occurred in approximately 22% of patients receiving first-line imatinib therapy (the vast majority of failures being early events) compared with approximately 4% of patients receiving first-line therapy with a second-generation TKI. One may ask, “Why not wait until patients have a suboptimal response to imatinib or fail treatment before prescribing a higher-priced second-generation TKI?” This may be risky, and, in the long run, incur higher costs. Treatment at suboptimal response or failure is salvage therapy. In such cases, the likelihood that the patient has developed drug-resistant mutations has increased, requiring the use of a third-generation TKI or a very expensive stem-cell transplant. The 8-year analysis of the IRIS trial demonstrated that imatinib was effective in preventing prospective events but not the loss of response or progression events that occur early (Figure). The ENESTnd and DASISION trials suggest that frontline therapy with second-generation TKIs produces higher rates of CCyR and MMR than the standard-dose imatinib, and these responses are achieved at earlier time points. On the basis of data derived from the IRIS trial that highlighted the prognostic importance of achieving early CCyR and MMR, it is reasonable to expect that the use of nilotinib or dasatinib in the frontline setting might render higher rates of event-free survival and transformation-free survival and may therefore offset the high costs associated with progression.

Non-Hodgkin Lymphoma

NHL is a highly heterogeneous group of cancers affecting the lymph...
system, with variable cytogenetic, cellular, and clinical features and natural histories that range from indolent to very aggressive.\textsuperscript{20} NHL is the most common hematologic malignancy in the United States.\textsuperscript{2} It is estimated that 65,540 Americans were diagnosed with various forms of NHL in 2010, and 20,210 deaths were attributed to the disease. The prevalence of NHL in the United States is approximately 440,000 patients.\textsuperscript{5} Most patients with NHL have a B-cell subtype: 31% of patients with NHL have diffuse large B-cell lymphoma (DLBCL), 22% have follicular lymphoma, 5% to 10% have marginal zone lymphoma (MZL), and 6% have mantle-cell lymphoma (MCL).\textsuperscript{3} T-cell lymphomas comprise about 15% of NHL cases.\textsuperscript{30}

**Indolent versus aggressive: desired outcomes of therapy**

Both B-cell and T-cell lymphomas are categorized into indolent and aggressive types. DLBCL, MCL, peripheral T-cell lymphoma, and anaplastic large-cell lymphoma (ALCL) are considered aggressive lymphomas. The goal of treatment is to cure an aggressive lymphoma; this may be achieved in 30% to 60% of patients for some subtypes.\textsuperscript{41} DLBCL can be cured in a significant proportion of patients,\textsuperscript{42} but MCL cannot.\textsuperscript{43} The response rate and OS are often the end points in clinical trials for aggressive lymphomas that are curable, whereas response rate and duration of response and PFS are end points in trials for those that are not. For aggressive lymphomas that cannot be consistently cured at this time, the search continues for treatment that can become a curative standard of care. The lack of cure along with treatment failure exacts an enormous socioeconomic toll. For example, the mean cost of treatment failure in aggressive NHL has been reported to be as high as $14,174 monthly and reaches $85,934 over a period of 2 years (1999-2000 dollars).\textsuperscript{34}

In contrast, indolent lymphomas are characterized by long, slowly progressive clinical courses; examples include follicular lymphoma, MZL, Waldenstrom's macroglobulinemia, and the cutaneous T-cell lymphoma mycosis fungoides. The goal of treatment is often long-term management, as indolent lymphomas are rarely cured unless diagnosed when still localized. The response rate, DFS, event-free survival, duration of response, and PFS are often the primary end points in clinical trials for indolent lymphomas.

Clinical trials have attempted to improve on the best available accepted therapy by adding an additional agent or substituting one active agent for another; therefore, there is a virtual “alphabet soup” of therapeutic regimens available to treat this group of cancers. In the past decade, the treatment of NHL has changed dramatically, with the advent of molecularly targeted anticancer therapies. For example, the development of the CD20 monoclonal antibody rituximab has changed the treatment paradigm for B-cell lymphomas and, in some subtypes of the disease, has markedly improved prognosis.

Bortezomib, lenalidomide, bendamustine, alemtuzumab, and other novel agents have also demonstrated clinical benefit in B-cell lymphomas. T-cell subtypes and ALCL are being treated with a number of approved and investigational targeted agents, including romidepsin, pralatrexate, brentuximab vedotin, denileukin difitox, and vorinostat. The use of targeted therapies for NHL, combined with refinements in cytotoxic chemotherpay and stem-cell transplantation, continue to alter the therapeutic landscape at a rapid pace.

**Indolent versus aggressive: clinical trial end points**

In 1999, an international working group of clinicians, radiologists, and pathologists with expertise in the evaluation and management of patients with NHL published guidelines for response assessment and outcomes measurement.\textsuperscript{44} These were revised in 2007, when interobserver and intraobserver variations were identified and recommended technologies were no longer considered state-of-the-art.\textsuperscript{45} In addition to defining response criteria and making recommendations for disease evaluation, this group proposed that the major end points of clinical trials should reflect the histology, clinical situation, and objectives of the study and be defined consistently across clinical trials.

Response rates as a trial end point are greatly influenced by the defined response criteria used. In addition, response rates do not necessarily influence other measures of overall clinical benefit or outcome in patients with NHL. OS is the least ambiguous of the trial end points, but it is not optimal for use in an indolent or incurable aggressive lymphoma trial. PFS is often considered the preferred end point in lymphoma clinical trials, especially those involving incurable subtypes (indolent and aggressive). Event-free survival is generally not encouraged by the FDA, because it combines efficacy, toxicity, and patient withdrawal. However, it may be useful in the evaluation of novel agents that may be highly toxic and have a high risk-benefit ratio. Duration of response, if associated with measures of clinical benefit, may also be an important and relevant end point in lymphoma trials.

One of the most important outcomes for patients with NHL has been evidence of clinical benefit. Clinical benefit may reflect improvement in quality of life or a reduction in symptoms, transfusion requirements, frequent infections, or other parameters. As the symptoms associated with lymphoma can greatly impact a patient’s quality of life, time to reappearance or progression of lymphoma-related symptoms may also be an important measure, especially for incurable lymphomas.

Rituximab was first approved by the FDA in 1997 for the treatment of relapsed or refractory low-grade or follicular, B-cell NHL as a single agent based on the overall response rate.\textsuperscript{46} Since that time, rituximab has received 5 additional indications as a single agent or as part of a chemotherapeutic regimen. The *Appendix* (available at www.valuebasedcancercare.com/P10067E) lists some of the targeted agents and new therapies approved within the past decade for various subtypes of NHL and the primary and secondary end points used in the registration trials. Care must be taken when making cross-trial comparisons to ensure that the patient populations are comparable and that defined end points and response criteria have been used consistently.

**Evolutionary Outcomes and End Points and Value-Based Care**

As progress is made in the treatment of MM, CML, and NHL, as with any cancer, the ultimate outcome of therapy for patients also evolves. Although OS remains the optimal outcome for patients with MM, surrogate end points used in clinical trials do not always translate into a survival benefit as long-term data mature. The use of TKIs for CML-CP has drastically changed the natural history of this disease. Freedom from treatment failure and from progression to advanced phase or blast crisis is the preferred outcome. Early and durable CCyR and MMR are reliable surrogate end points for this outcome. For patients with some subtypes of aggressive NHL, a cure is possible and OS is both the trial end point and the desired outcome. However, for patients with indolent and incurable-aggressive NHL, an extended period without progression that may be compounded by lymphoma-associated symptoms is preferred. PFS and duration of response are acceptable surrogate end points for this outcome.

![Figure](https://example.com/kinetics_of_resistance_to_imatinib_in_the_iris_trial)

**Figure**

**Kinetics of Resistance to Imatinib in the IRIS Trial**

- **Event:** Loss of CHR, Loss of M CyR, AP/BC, Death
- **Year:** 1, 2, 3, 4, 5, 6, 7, 8
- **Event rates or patients at AP/BC:** 3.3, 1.7, 2.8, 4.8, 1.8, 1.7, 0.9, 0.5, 0.3, 0.1

**References**

8. Rajkumar SV, Harousseau J, Durie B, et al, for the International Myeloma Workshop Consensus Panel. Consensus recommendations for the uniform report...
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Commentary
New End Points Can Create Novel Challenges for Health Plans in Oncology Drug Management

James T. Kenney Jr, RPh, MBA

The management of complex oncology drugs in pharmacy and in medical benefits presents unique challenges for all parties who seek cost-effective, positive clinical outcomes for patients with cancer. New therapies are offering the exciting prospect of improved outcomes, prolonged life, and, in some cases, a cure for specific diseases. Targeted oncologies and pharmacogenomics, which carry the promise of improved likelihood of successful treatment, have become welcome additions to the current standards of care. The concept of cancer as a chronic disease is becoming accepted in pharmacy oncology management. Targeted therapies are now standard treatments for multiple myeloma (MM), non-Hodgkin lymphoma (NHL), and chronic myelogenous leukemia (CML).

Recent trials in MM have used time to progression and progression-free survival as primary end points (as recommended by the International Myeloma Workship Consensus Panel 1). The use of different end points in clinical trials for the same disease, however, has complicated the analysis and evaluation process for the pharmacy and therapeutics (P & T) committees of health plans in comparing competing therapies to select the most efficacious and cost-effective treatment options for their members. The ability to diagnose cancer earlier in the disease process and to begin life-saving treatment in a shorter time will place even more strain on pharmacy managers to maximize the value from all therapies in the treatment algorithm of a particular cancer type.

The tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of CML by extending survival. It is now possible to achieve long-term success with these agents if treatment is initiated early enough in the course of disease, and a positive early response can be a good predictor of long-term survival. As clinical studies are able to demonstrate clinically meaningful differences between first- and second-generation TKIs, health plans can consider promoting specific treatment pathways to maximize cost-savings and outcomes.

NHL affects a diverse population of patients with various disease subtypes that require careful diagnosis to be treated with specific drug treatment protocols. The International Working Group has attempted to define appropriate clinical trial end points and response criteria to effectively differentiate titerates. This process is critical for managed care plans to manage specific therapies effectively and control costs in the treatment of NHL and other cancer types.

It is clear that in the near-term, overall survival will remain the gold standard for P & T committees in their assessment of drug efficacy. However, other end points will continue to be assessed as clinical trial results become available. The development of pharmaceuticals with biomarkers can increasingly give providers and health plans the confidence that patients will have a greater likelihood of response. This new trend also has the potential to decrease waste and reduce costs for patients who are not good candidates for a particular treatment. As health plans progress in the management of oncology drugs, the ability to target patients, predict outcomes, and reduce costs will drive the most successful programs.
### Appendix: Recently Approved Medications for NHL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Registration trial</th>
<th>End point/result</th>
</tr>
</thead>
</table>
| **Rituximab**<sup>a</sup> | As a single agent, for relapsed or refractory low-grade or follicular, CD20-positive B-cell NHL | 3 Single-arm studies  
N = 166  
N = 37  
N = 60 | ORR, %  
48  
57  
38  
Median DOR, mo  
11.2  
13.4  
15.0 |
| &nbsp; | As single-agent maintenance therapy, for previously untreated follicular, CD20-positive B-cell NHL in combination with first-line chemotherapy, and in patients achieving CR or PR to rituximab in combination with chemotherapy | CVP-R vs CVP; N = 322  
Rituximab vs observation; N = 1018 | Median PFS  
2.4 vs 1.4 yr  
HR, 0.54; 95% CI, 0.42-0.70 |
| &nbsp; | As a single agent, after first-line CVP chemotherapy, for nonprogressing (including stable disease), low-grade, CD20-positive B-cell NHL | Rituximab vs observation; N = 322 | PFS  
HR, 0.36-0.49 |
| &nbsp; | In combination with CHOP or other anthracycline-based chemotherapy regimens for previously untreated DLBC, CD20-positive NHL | 3 Randomized studies  
Study 1: N = 632, R-CHOP vs CHOP  
Study 2: N = 399, R-CHOP vs CHOP  
Study 3: N = 832, Rituximab-chemotherapy vs chemotherapy | Median PFS  
2.9 vs 1.1 yr  
Median EPS  
3.1 vs 1.6 yr  
Median TTF  
HR, 0.40 |
| **Tositumomab and 131I tositumomab**<sup>b</sup> | CD20 antigen-expressing relapsed or refractory, low-grade, follicular, or transformed NHL, including patients with rituximab-refractory NHL | 2 Single-arm studies  
Study 1: N = 40, Relapsed/refractory disease after rituximab  
Study 2: N = 60, Chemotherapy refractory | ORR, %  
68  
47  
Median DOR, mo  
16  
12 |
| **Ibritumomab tiuxetan**<sup>c</sup> | Relapsed or refractory low-grade, follicular, or transformed B-cell NHL | Study 1: single-arm; N = 54  
Ibritumomab tiuxetan vs rituximab | ORR (IWRC), %  
83 vs 55 |
| &nbsp; | Indolent B-cell NHL that has progressed during or within 6 mo of treatment with rituximab or a rituximab-containing regimen | Single-arm study: N = 100 | ORR (IWRC)  
64.3%  
DOR  
9.2 mo |
| **Bendamustine hydrochloride**<sup>d</sup> | CTCL in patients who have received at least 1 prior systemic therapy | 2 Single-arm studies  
Study 1: N = 96  
Study 2: N = 71 | ORR (investigator assessments), %  
34  
35 |
| **Romidepsin**<sup>e</sup> | Cutaneous manifestations in patients with CTCL who have progressive, persistent, or recurrent disease on or after 2 systemic therapies | 2 Single-arm studies  
Study 1: N = 74  
Study 2: N = 33 | ORR, %  
29.7  
24.2 |
| **Vorinostat**<sup>f</sup> | Relapsed or refractory PTCL | Single-arm study: N = 111 | ORR (IWRC)  
27%  
Median DOR  
9.4 mo |
| **Pralatrexate injection**<sup>g</sup> | Treatment of MCL in patients who have received at least 1 previous therapy | Single-arm study: N = 155 | ORR  
31%  
Median DOR  
9.3 mo |