LYMPHOMA AND PLASMA CELL DISORDERS

Hot Pathways for Targeted Therapy of B-Cell Malignancies

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Developing Novel Strategies to Target B-Cell Malignancies

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OVERVIEW

In the past several years we have seen the identification and validation of several key pathways that drive malignant B-cell development. In addition, the effect nonmalignant effector cells within the immune microenvironment have on tumor survival, proliferation, and possibly chemotherapy resistance is increasingly understood. Although there is still much to be learned, this improved understanding combined with rapid advances in medicinal chemistry focusing on structure-based drug design have resulted in a shift in the development of new agents away from traditional chemotherapy to more selective agents targeting key cellular pathways. Examples of “hot” new therapeutic targets include the B-cell receptor signaling pathway, PI3K/mTOR/AKT pathway, histone deacetylases (HDAC), regulators of apoptosis such as the BCL-2 family, the proteasome, and cell–cell interactions within the tumor environment. Many drugs that target specific agents in early clinical development have demonstrated activity in various subtypes of lymphoma and leukemia. Monoclonal and conjugated antibodies targeting cell surface proteins such as CD19, CD22, CD37, and different epitopes of CD20 have also shown promise in relapsed B-cell malignancies and are rapidly moving into efficacy studies. This review will focus on a few of the new nonantibody-based targeted agents in development, their respective pathways, and their activity in various B-cell malignancies.

B-cell malignancies represent a heterogeneous group of disorders with widely varying characteristics and clinical behavior. Historically, most patients with symptomatic disease received a combination of noncross-reactive genotoxic agents with the intent of achieving a durable remission and, in some cases, a cure. Although effective, many traditional regimens are also associated with considerable acute and long-term toxicities. The introduction of the first biologic targeted agent, the anti-CD20 monoclonal antibody rituximab, marked a turning point in the development of new drugs for these diseases and improved outcomes in nearly every B-cell disorder where it was employed. However, despite improvements in survival for many, the majority of patients continue to relapse following standard chemo-immunotherapy and more than 15,000 patients still die annually in the United States from B-cell cancers.

In the past several years, there has been remarkable progress understanding some of the key pathways that drive proliferation, survival, and resistance in lymphoma and leukemia. Advances in crystallography and protein spectroscopy have helped to identify active sites or “binding pockets” within specific biologic targets (Fig. 1). These advances, combined with structure-based drug design have allowed medicinal chemists to develop highly specific small-molecule inhibitors (Table 1).

B-CELL RECEPTOR PATHWAY

The B-cell receptor (BCR) is a transmembrane receptor protein that is critical in the selection and development of normal B-cells. Expression of a functional BCR is maintained throughout lymphoma progression. Signaling through the receptor pathway, either through antigen binding or from functional mutations, leads to activation of downstream MAP kinases and nuclear factor-kappa B (NF-κB) resulting in accelerated cell growth, proliferation, and survival. Selective knockdown of BCR components or its downstream kinases by RNA interference results in apoptosis in multiple B-cell lymphoma cell lines. Emerging evidence suggests that B-cell malignancies are dependent on constitutive activation of the pathway and that “chronic-active” BCR signaling is likely required for survival in subtypes of non-Hodgkin lymphoma (NHL) such as activated B-cell (ABC) type diffuse large B-cell lymphoma (DLBCL).

Bruton’s tyrosine kinase (BTK) and spleen tyrosine kinase (SYK) are proximal elements of the BCR pathway and play a key role in amplification of the downstream BCR signal. BTK is a member of the Tec family kinases and is largely restricted to B-lymphocytes. Loss of the BTK gene through mutation leads to the genetic immunodeficiency disease, X-linked agammaglobulinemia (XLA).

Ibrutinib (PCI-32765), an irreversible covalent inhibitor of BTK, inhibits proliferation and induces apoptosis in NHL.
cell lines and has been shown to inhibit BTK in animal models. A recent phase I study demonstrated efficacy across various relapsed/refractory B-cell malignancies. Responses were especially impressive in patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL), with more than 70% of patients demonstrating an objective response. The toxicity profile was favorable, and several patients remain on treatment beyond 2 years.¹ The activity in MCL and CLL was further confirmed by recently reported phase IB and II studies showing 66% and 67% objective responses in patients who relapsed, respectively.²,³ As expected, in patients with large-cell lymphoma, subtype tends to predict response. In a preliminary report, Wilson and colleagues reported significantly higher responses in patients with ABC compared with germinal center (GCB) DLBCL (40% vs. 5%; p = 0.0126).⁴ Interestingly, response rates appear to increase with prolonged drug exposure and in some patients with indolent disease, and nearly 12 months of therapy was required to attain a complete response (CR) in some patients.⁵ Early preclinical models suggest inhibition of BTK may alter cell–cell “cross-talk” and expression of chemokines such as CXCL12.⁶ These changes within the malignant microenvironment may partially explain the compartmental shift of malignant lymphocytes out of the node and into the peripheral blood, which has been observed in patients with CLL.

SYK is a tyrosine kinase that is another key component of B-cell receptor signaling pathway upstream of BTK. SYK inhibitors have been shown in vitro to induce apoptosis following drug exposure in primary and NHL cell lines.⁷ A study from Friedburg and colleagues with fostamatinib (FosD), an ATP-competitive inhibitor of SYK, in patients with relapsed hematologic malignancies demonstrated activity in a variety of B-cell malignancies. As with ibrutinib, the highest response was observed in patients with CLL (54%), with lower activity reported in follicular lymphoma (FL) (10%) and DLBCL (22%).⁸ One out of nine patients with MCL attained a response.⁹ Several other agents targeting BTK and SYK are in development, including CC292 and ONO-WG-307, and combination studies were recently started investigating the role of these new agents in multiple histologies.

### PI3K/MTOR PATHWAY

The oncogenic PI3K/AKT/mTOR pathway is essential for various cellular processes including cell growth, metabolism, and survival. Although mutations of PI3K or PTEN can lead to an oncogenic activation of PI3K/AKT/mTOR pathway, such mutations are rarely observed in lymphoid malignancies. Instead, activation of this pathway is frequently associated with constitutive activation of receptor pathways such as the BCR. The recent activity observed with several new agents targeting critical components of the pathway suggest that PI3K/mTOR inhibitors will likely have a future in the treatment of B-cell cancers.

#### PI3K Inhibition

Among the four isoforms of the class I PI3K subunit, p110-gamma and p110 delta are primarily expressed in leukocytes. Over-signaling of PI3K, primarily the delta isoform, has been observed in cell lines and primary cells of lymphoid malignancies. Inhibition of PI3K leads to cell death in several preclinical models, and similar to BTK inhibitors, these agents may also affect cell signaling and trafficking within the malignant microenvironment.⁹

GS1101 is an oral inhibitor of the delta isoform of PI3K. In a recent phase I study, 17 of 28 patients with indolent lymphoma,¹⁰ 11 of 18 patients with MCL,¹⁰ and 14 of 54 patients with CLL¹¹ experienced objective responses. As a single agent, GS1101 was tolerated in the majority of patients. Myelosuppression was minimal and transient transaminitis was observed in some patients. Preliminary results from combination studies of GS1101 with agents such as bendamustine and/or rituximab appear promising with response rates of 77% to 85%.¹² Phase II studies with GS1101 in several histologies including indolent NHL and CLL are ongoing.

IPI-145 is an oral dual inhibitor of the delta and gamma isoforms of PI3K. Preliminary results from an ongoing phase I study of patients with NHL and CLL demonstrated activity in several histologies. Complete inhibition of PI3K-delta was observed at early dose levels. Neutropenia and increased alanine aminotransferase (ALT) were the most common grade 3 and above treatment-associated adverse events. Among patients with aggressive or indolent B-cell, a 52% objective response rate was reported.¹³ Interestingly, two of six patients with T-cell lymphoma also reported an objective response.¹³

#### MTOR Inhibition

Mammalian target of rapamycin (mTOR) kinase is a downstream component of the PI3K/AKT pathway. Inhibition of mTOR has been shown to confer antiproliferative effects and apoptosis in various tumor types in vitro. The exact antitumor mechanism of mTOR inhibitor is yet to be elucidated, but may be because of induction of autophagy, antiangiogenesis, immunoregulation, and inhibition of translation of survival factors.

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**KEY POINTS**

- There is improved understanding of multiple processes and pathways that influence malignant B-cell proliferation, survival, and resistance.
- Recent advances have identified several key components of essential pathways that are valid targets for emerging therapeutics.
- Novel drugs in development targeting key cellular pathways and the malignant microenvironment appear active in various B-cell malignancies.
- Many new biologic agents are selective and have mild or unique toxicity profiles.
- Although impressive responses have been observed in various B-cell malignancies, integration of these active agents into rational drug combinations holds the most promise.

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Three mTOR inhibitors have been introduced to clinical development: CCI-779 (temsirolimus), RAD001 (everolimus), and AP23573 (ridaforolimus). Temsirolimus is a watersoluble specific inhibitor of the mTOR kinase and has been studied in the treatment of relapsed/refractory MCL and DLBCL. A phase II trial of single-agent temsirolimus at 250 mg/m² weekly dosing in 34 patients with relapsed MCL reported overall response rates (ORR) of 38% with one CR and 12 partial responses. The most common adverse events included thrombocytopenia, anemia, neutropenia, hyperglycemia, increased triglycerides, mucositis, and fatigue. In an attempt minimize toxicity, 25 mg/m² weekly dose was tested in a different study. The ORR was similar (41%) and severe thrombocytopenia was less common (100% vs. 39%). These results prompted a recent phase III trial of temsirolimus compared with investigator’s choice in patients with relapsed MCL. The higher doses in the temsirolimus arm (175 mg weekly for 3 weeks followed by 75 mg weekly) demonstrated an improved progression-free survival (PFS) compared with investigator’s choice and an improved ORR (22% vs. 2%, respectively). This drug also has shown activity in other NHLs with an ORR of 28% in aggressive B-cell lymphoma and 54% in FL.

A large phase II trial of everolimus at 10 mg daily in 145 patients with relapsed lymphoma, including 77 patients with aggressive non-Hodgkin lymphoma, has recently been reported. Responses were observed in patients with DLBCL (30%) and MCL (32%). The most common toxicity was cytopenia. This drug is currently investigated in a phase III study (PILLAR-2), comparing 1 year of maintenance everolimus with placebo for patients at high risk who achieve CR after R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)-based treatment for DLBCL. Ridaforolimus (also known as deforolimus) is an intravenous nonprodrug rapamycin analog. In a phase II trial in relapsed hematologic malignancies, response rates in CLL and MCL were 0% (0 of 8 patients) and 33% (3 partial responses in 9 patients). Both temsirolimus and everolimus have been associated with potential pulmonary toxicity, and follow-up studies will help determine the optimal management of these events.

**PROTEASOME INHIBITION**

The proteasome is the major extralysosomal mechanism for degrading intracellular protein and is responsible for the
regulation of protein homeostasis. The proteasome inhibitor bortezomib inhibits the activation of NF-kB by blocking the degradation of cytoplasmic IkBa and alters the expression of several survival and cell cycle regulatory proteins such as p21, p27, BCL-2, Bax, XIAP, survivin, and p53. Altered expression can lead to cell-cycle arrest and apoptosis in several tumor types, including lymphoma.

Bortezomib is currently approved by the Food and Drug Administration for the treatment of multiple myeloma (MM) and MCL. Its efficacy is well established in relapsed/refractory MCL with single-agent response rates ranging from 39% to 54%.21,22 Despite these impressive results, single agent bortezomib has only mild activity in other B-cell malignancies. Combining proteasome inhibition with conventional chemotherapy may improve efficacy. Preclinical models suggest that bortezomib can exert synergistic cytotoxicity when combined with chemotherapy or antibody therapy. A phase I/II study of bortezomib plus standard R-CHOP for untreated DLBCL and MCL has been reported. In patients with DLBCL, an ORR of 100% including CR of 86% was attained. In patients with MCL, an ORR and CR of 91% and 72%, respectively, was reported.23 Outcomes in patients with non-GCB DLBCL and GCB DLBCL were similar, suggesting bortezomib may improve traditionally inferior outcomes following R-CHOP in patients with non-GCB DLBCL. Combination therapy using bortezomib, bendamustine, and rituximab was tested in 73 patients with FL in a phase I/II study. In the 63 patients at the phase II dose (bendamustine 90 mg/m²), the overall response rate was 88% (including 53% CR). The treatment was well tolerated and myelosuppression (grade 3 or 4 neutropenia and thrombocytopenia) was observed in 25% and 14%, respectively).24 A similar ORR of 83% was reported in another study of this combination in patients with MCL or FL.8 Randomized studies combining bortezomib with bendamustine and rituximab in untreated MCL are underway. Carfilzomib, a new proteasome inhibitor, is also under clinical investigation for B-cell malignancies.

**APOPTOSIS-INDUCING PATHWAYS**

Overexpression of BCL-2 by various mechanisms including t(14;18) are frequently observed in B-cell cancers and play a role in resistance to apoptosis. Inhibition of BCL-2 family protein is a reasonable target of therapy, as inhibition of these proteins can induce normal caspase activation leading to cell killing. Several proteins are homologous to BCL2 (BCL-2 family proteins) and may be proapoptotic (such as BAX, BAK) or antiapoptotic (such as BCL-XL, BCL-w, MCL-1, BIM, twice daily). Complex interaction between these family proteins likely controls the fine balance between survival and cell death. Supported by the preclinical data suggesting that the inhibition of BCL-2 leads to apoptosis in cancer cells,
multiple agents targeting BCL-2 have been tested in various malignancies, mostly notably in CLL.

Oblimersen sodium is an antisense DNA molecule with sequence complementary to that of BCL2 mRNA. This drug has been tested in early phase clinical trials for CLL, showing modest activity by as a single agent (2 PR in 26 patients). A phase III study showed higher response rate when oblimersen is added to fludarabine-containing chemotherapy (17% vs. 7%), but 5-year overall survival was not significantly different (p = 0.87). Obatoclax is a small molecule that binds to essentially all BCL2 family proteins including BCL2, BCL-XL, and MCL-1, which has also shown only minimal activity in CLL as a single agent. Combination studies have been conducted with moderate activity. A study of obatoclax plus bortezomib demonstrated objective response in three of nine patients. In a phase I study of obatoclax with fludarabine and rituximab in patients with relapsed CLL, partial responses were observed in 54% of patients.

Novatoclax has a much higher affinity to BCL-2 proteins and was tested as a single agent in a phase II study, showing PRs in 10 of 46 lymphoid malignancies (22%). A follow-up study focusing on relapsed or refractory CLL in a heavily pretreated population showed nine of 29 patients achieving PR. Thrombocytopenia was common in these studies and is likely secondary to BCL-XL inhibition. ABT199 is a recently developed specific BCL-2 inhibitor that spares the BCL-XL. Interim results of a phase I study showed responses in eight of 15 patients, including six of six patients with MCL and one of two patients with DLBCL. Combination studies of ABT199 are currently underway.

TARGETING THE MICROENVIRONMENT
The malignant microenvironment is increasingly recognized as a key component in the development and persistence of B-cell malignancies and represents a new and exciting target for novel therapeutics. Past approaches to target the microenvironment through cytokine manipulation or vaccine therapy have resulted in only moderate success or considerable toxicity. Immunomodulatory drugs (IMiDs) are an emerging class of antineoplastic agents that likely work through modulation of the immune microenvironment. Although the exact mechanism is still under investigation, observed activity in B-cell cancers may be because of inhibition of angiogenesis, alteration of stromal cell–cell interactions and pro-tumor cytokines, and enhancement of immune cell function. A recent landmark study demonstrated that a critical component of the E3 ubiquitin ligase complex cereblon is a direct target of IMiDs. This finding may lead to further understanding of the mechanism of these agents, as cereblon has been implicated to play a role in cell signaling and cytokine secretion.

The parent drug of the class, thalidomide, has only minor single-agent activity in patients with recurrent or refractory B-cell lymphoma/leukemia. However, substantial antitumor activity has been observed when thalidomide was combined with rituximab in patients with relapsed or refractory disease. In a small phase II trial of 16 patients with refractory MCL, 81% and 31% of patients with relapsed MCL attained an objective response and CR, respectively.

Lenalidomide, a potent analog of thalidomide with increased immunomodulatory properties is currently approved for multiple myeloma and 5q-myelodysplastic syndrome. As a single agent it has activity in a broad spectrum of B-cell disorders such as CLL, indolent NHL, MCL, and DLBCL. Witzig and colleagues reported results with lenalidomide in patients with relapsed NHL, demonstrating an overall response of 18% in DLBCL and 40% in MCL. Based on these findings, a recent phase II study in heavily pretreated patients with MCL who were relapsed or refractory to bortezomib was conducted and demonstrated an overall response rate of 28% with a median duration of response of 16 months. Phase II studies of lenalidomide in aggressive lymphomas are complete and will be reported soon.

Although lenalidomide appears to have clear activity as monotherapy, some of the most promising results have emerged from combination trials. Preclinical studies suggest that combining lenalidomide with anti-CD20 therapy may be synergistic, with the potential to increase antibody-dependent cellular cytotoxicity (ADCC) through augmented natural killer (NK) cell activity. In addition, studies from Gribben and colleagues have demonstrated lenalidomide’s ability to repair dysfunctional immune synapses and increase T-cell recognition of primary CLL and FL cells. Phase II studies of lenalidomide and rituximab in relapsed MCL and indolent NHL have shown response rates of 57% and 83%, respectively. In a phase II study of patients with relapsed CLL, an objective response of 65%, including 67% in patients with 17p deletion, was reported by Farrajoli and colleagues.

The potential for combination was further emphasized by a recent randomized CALGB study comparing lenalidomide with lenalidomide plus rituximab in patients with relapsed FL. The ORR was 75% and 49% in the combination arm and lenalidomide single agent arm, respectively. Based on these and other early results M. D. Anderson Cancer Center conducted a phase II study of the combination in patients with indolent lymphoma. Objective responses were observed for 85% of patients, including 98% of patients with FL. The majority of remissions for patients with FL remain durable with a projected 3-year PFS of 81%. Toxicity was observed, but was manageable with supportive care in the majority of patients. Phase III studies comparing lenalidomide and rituximab with standard combination chemotherapy regimens are underway.

CONCLUSION
The identification of targetable pathways both within the malignant B-cell and the immune microenvironment represents a major leap forward in the development of therapy for patients with B-cell malignancies. However, despite the noteworthy activity observed in many new agents, the ideal regimen remains elusive, and most novel agents are still unable to induce complete responses in the majority of patients.
Further work is needed now to not only identify biomarkers of response and mechanism of resistance, but also to understand how to combine these agents in rational combinations. Although traditional regimens are still essential for most patients, the era of combination chemotherapy for many B-cell malignancies is ending. In the future, innovative strategies integrating biologic targeted agents into “chemotherapy-free” regimens will not only change the way we treat NHL, but have the potential to dramatically improve outcomes for patients with lymphoma and leukemia.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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References


LYMPHOMA AND PLASMA CELL DISORDERS

Multiple Myeloma: Advances in Diagnostics and Management

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Novel Approaches to Treatment of Double-Refractory Multiple Myeloma

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OVERVIEW

Multiple myeloma (MM) refractory to both proteasome inhibitors and immunomodulatory agents (IMiDs; double-refractory myeloma) has a poor prognosis. With the more frequent use of these agents as part of initial therapy, and then in the maintenance setting until disease progression, such drug resistance is an emerging problem of great significance. New therapeutic strategies are clearly needed for this patient population, including the development of more potent agents within existing antimyeloma drug classes, exploration of rational combinations of both novel and conventional drugs, and validation of new myeloma drug targets. Several approaches have shown substantial promise, including use of the second-generation proteasome inhibitor carfilzomib and the third-generation IMiD pomalidomide, which led to the recent regulatory approval of both agents. In addition, the kinesin-spindle protein KSP inhibitor ARRY-520 has shown activity as a first-in-class drug in myeloma therapeutics, whereas the histone deacetylase (HDAC) inhibitors vorinostat and panobinostat have demonstrated efficacy when used in rational combinations. This overview provides a summary of novel agents that have shown activity in double-refractory myeloma in recent phase II and III clinical trials, and a framework for future studies that will help to improve outcomes in this patient population.

The introduction of the proteasome inhibitor bortezomib and second-generation immunomodulator (IMiD) lenalidomide to the multiple myeloma (MM) therapeutic armamentarium has led to substantial improvements in patient outcomes over the last decade. Both agents now form the backbone of many preferred regimens in the up-front or relapsed settings, and they have contributed to a doubling in the average life expectancy for patients with myeloma.1,2 However, despite these novel therapies, MM remains an incurable disease, and resistance to bortezomib and lenalidomide is emerging with increasing frequency. For these patients with double-refractory disease, prognosis is poor, with a median overall survival (OS) and progression-free survival (PFS) of 9 months and 5 months, respectively.3 Improving the outcomes of patients in this setting therefore represents a substantial clinical challenge, and is an area of intense research focus. Although there is no standard treatment for these patients, several promising agents and strategies are currently under investigation. Notably, this has led to the recent U.S. Food and Drug Administration (FDA) approval of the second-generation proteasome inhibitor carfilzomib for patients who have been exposed to bortezomib and an IMiD, and whose disease was refractory to their last therapy. Likewise, the third-generation IMiD pomalidomide has just received regulatory approval for patients with refractory disease who have previously received treatment with bortezomib and lenalidomide. Other drugs such as histone deacetylase (HDAC) inhibitors and the kinesin-spindle protein (KSP) inhibitor ARRY-520 have also shown encouraging results in ongoing trials. This overview provides a summary of novel agents in development that have shown clinical activity in double-refractory MM, and may represent potential treatment strategies in this challenging disease subset.

CARFILZOMIB

Carfilzomib is a novel, highly selective epoxyketone proteasome inhibitor that irreversibly inhibits the chymotrypsin-like activity of the 20S proteasome.4 Its diminished off-target effects and lower incidence of peripheral neuropathy were demonstrated in early phase clinical trials. The efficacy of single-agent carfilzomib in patients with disease refractory to bortezomib and IMiD therapy was established in the PX-171-003-A1 study, a multicenter single-arm phase II trial.3 This study enrolled 266 patients who developed disease that had relapsed after two or more lines of therapy, and was refractory to the most recent treatment. All but one patient had received prior bortezomib, and every patient had received treatment with a different IMiD. Patients received single-agent carfilzomib for up to 12 cycles, and the primary end point was overall response rate (ORR) using the International
Myeloma Working Group (IMWG) criteria. After a median treatment duration of 3 months, ORR (≥ partial response [PR]) in 257 patients with assessable response was 24%, with one complete response (CR; 0.4%), 13 very good partial responses (VGPRs; 5%), and 47 PRs (18%; Table 1). Among 169 patients with disease refractory to both bortezomib and lenalidomide, ORR was 15% (median response duration, 7.8 months). Median OS was 15.4 months in the overall population, and 11.9 months in the double-refractory subgroup. Notably, response rates were not affected by unfavorable cytogenetic profiles. Overall, carfilzomib was well tolerated, and the most common grade 3 or 4 adverse events (AEs) were thrombocytopenia (29%) and anemia (24%), whereas only 12% reported treatment-emergent peripheral neuropathy. The positive results from this study ultimately led to the initial accelerated FDA approval of carfilzomib. A phase III clinical trial, which randomly assigned patients with relapsed MM that was refractory to all available therapy to receive carfilzomib or best supportive care, has completed enrollment and will provide additional insight into the role of this agent.6

POMALIDOMIDE
Pomalidomide is a third-generation IMiD with immunomodulatory, antiangiogenic, and direct antinmyeloma activity, and greater in vivo potency than its predecessors thalidomide and lenalidomide.7 The safety and promising efficacy of pomalidomide in double-refractory disease was initially reported by Richardson and colleagues in a phase I study in which 38 patients were exposed to four different dose levels.8 A maximum tolerated dose (MTD) was established at 4 mg daily for 21 of 28 days, and in 24 patients with both bortezomib- and lenalidomide-refractory disease, ORR was 25%, and CR rate was 4%.

Pomalidomide has been shown to be active against double-refractory MM in several subsequent phase II and III trials. The Intergroup Francophone du Myélome (IFM) randomly assigned 84 patients with relapsed/refractory MM to receive pomalidomide administered on day 1 through 21, or days 1 through 28 of a 28-day cycle, both with weekly dexamethasone.9 ORR and at least VGPR were 35% and 5%, respectively, in the 21-of-28-days arm, and 34% and 7%, respectively, in the continuous dose arm (Table 1). Of 64 patients with double-refractory disease, results were similar, with an ORR of 31%, PFS of 3.8 months, and OS of 13.8 months. Benefit was also seen in patients with adverse cytogenetics; ORR was 27% in 21 patients with deletion 17p and/or t(4;14). The Mayo Clinic group has also investigated the pomalidomide/dexamethasone combination in lenalidomide- and bortezomib-refractory MM as part of six sequential phase II trials comparing different pomalidomide dosing strategies.10 Two of the cohorts, each containing 35 patients, included only patients with disease refractory to both lenalidomide and bortezomib, who received either pomalidomide 2 mg daily (Cohort 3) or 4 mg daily (Cohort 4). ORR was similar in both groups at 26% (Cohort 3) and 29% (Cohort 4), and PFS was 6.4 months and 3.3 months, respectively (Table 1).

Additional evidence of the efficacy of pomalidomide and low-dose dexamethasone in double-refractory MM was shown in the MM-002 phase II study.11 A total of 113 patients, who had all received prior bortezomib and lenalidomide therapy, were enrolled onto the pomalidomide and low-dose dexamethasone arm of the trial; ORR was 30%, median PFS was 3.8 months, and median OS was 14.4 months (Table 1). Similar results were seen in the subgroup of 69 patients with bortezomib- and lenalidomide-refractory disease, in whom ORR was 28%, median PFS was 3.8 months, and median OS was 13.5 months. Recently, the results of the MM-003 phase III trial were presented, in which patients were randomly assigned 2:1 to receive pomalidomide and low-dose dexamethasone or single-agent high-dose dexamethasone.12 Final PFS analysis in 455 patients, all of whom received prior bortezomib and lenalidomide, demonstrated a significant increase in median PFS in the pomalidomide arm at 3.6 months compared to 1.8 months in the high-dose dexamethasone arm (p < 0.001; Table 1). At the interim analysis, median OS was not reached in the pomalidomide arm, whereas median OS in the high-dose dexamethasone arm was 7.8 months (p < 0.001). In 329 patients with double-refractory disease, median PFS in the pomalidomide arm was 3.2 months compared to 1.7 months in the high-dose dexamethasone arm (p < 0.001), and median OS was again not reached in the pomalidomide arm; median OS in the high-dose dexamethasone arm was 7.4 months (p < 0.001). On the basis of these results, the Data and Safety Monitoring Board (DSMB)
recommended immediate crossover of patients in Arm B to Arm A. Together, these findings support the use of pomalidomide and low-dose dexamethasone in double-refractory MM, and culminated in the recent FDA approval of pomalidomide for patients with disease refractory to their last therapy who had received prior bortezomib and lenalidomide.

Combinations of pomalidomide with antimyeloma agents other than dexamethasone are also being explored. One phase II study with pomalidomide, cyclophosphamide, and prednisone (PCP) has been reported by Palumbo and colleagues, in which 16 of 55 response-assessable patients had disease refractory to both bortezomib and lenalidomide. In these double-refractory patients, ORR after one cycle was 50%, with three patients achieving a VGPR or better (Table 1). Also, results from a recent multicenter phase I study using carfilzomib, pomalidomide, and dexamethasone (Car-Pom-d) were reported by Shah and colleagues. All 32 patients enrolled had lenalidomide-refractory disease, and all but two had bortezomib-refractory disease. Of 30 patients with assessable response, there were four VGPRs (13%) and 11 PRs (37%), corresponding to an ORR of 50%. Nonhematologic grade 3 and 4 AEs were rare; there were no instances of peripheral neuropathy. These studies highlight the feasibility and potential efficacy of combining pomalidomide with other novel drugs as a treatment strategy in patients with double-refractory disease, and enrollment of a larger phase II cohort in the latter is currently underway.

**HISTONE DEACETYLASE INHIBITORS**

Although proteasome inhibitors and IMiDs have garnered much of the recent attention in MM therapeutics, histone deacetylase (HDAC) inhibitors represent another novel drug class that may have potential activity in the double-refractory setting. HDAC inhibitors promote the acetylation of histone proteins, which decondenses chromatin to its active form and reverses the epigenetic silencing of transcription factors and tumor suppressor genes that regulate cell growth. Numerous nonhistone proteins such as p21, p53, and NF-κB have also been implicated as targets of HDAC inhibitors whose modulation promotes cell cycle arrest and apoptosis. Although HDAC inhibitors have demonstrated only modest activity as single-agents, more potent clinical activity has been observed when HDAC inhibitors are combined with other MM drugs. Perhaps the most promising combination is with bortezomib, as disruption of aggresome formation by HDAC inhibition, together with proteasome inhibition, leads to greater interference with protein turnover and induction of the misfolded protein response. Using this rationale, the pan-deacetylase inhibitor vorinostat was studied in combination with bortezomib in the VANTAGE 095 trial. All 143 patients enrolled onto this multicenter single-arm phase II study had bortezomib-refractory disease, and 87% had disease refractory to at least one IMiD. After a median treatment duration of four cycles, ORR was 17%, including 12% PR, 4% VGPR, and 1% CR (Table 1). In patients achieving a major response or better, median response duration was 6.3 months, PFS was 3.1 months, and median OS was 11.2 months. Common grade 3 or 4 AEs included thrombocytopenia (68%), anemia (38%), neutropenia (32%), and diarrhea (17%).

The synergistic activity of HDAC inhibitors with bortezomib in bortezomib-refractory disease is also being investigated with the pan-deacetylase inhibitor panobinostat in the PANORAMA 2 study. In this single-arm phase II trial, 55 patients with bortezomib-refractory disease who had also been exposed to prior IMiD therapy received treatment with bortezomib, panobinostat, and dexamethasone. Each cycle was repeated every 21 days for eight cycles, and patients achieving clinical benefit (defined as stable disease or better)
could continue with 6-week cycles by using a modified bortezomib schedule. At analysis after the first treatment phase, ORR was 31%, with three patients (5%) achieving a VGPR (Table 1). Notably, only one-third of patients completed all eight cycles of therapy, and the most frequent grade 3 or 4 AEs were thrombocytopenia (62%) and diarrhea (20%). A final analysis, which includes those patients who continued onto the second treatment phase, is pending.

Several other phase I and II trials studying the tolerability and efficacy of treatment regimens containing HDAC inhibitors are ongoing, and will provide additional insight into the optimal use of these agents in rational combinations with other conventional and novel drugs. The development of more selective HDAC inhibitors that minimize off-target toxicities is also likely needed for the potential of this therapeutic approach to be fully appreciated. The selective HDAC-6 inhibitorrocilinostat is one such promising example, and final results from an ongoing phase I/II study with monotherapy, and in combination with bortezomib/dexamethasone, are awaited.27

KSP INHIBITORS

Antimitotic agents have long been recognized and successfully used in cancer therapy across a variety of tumor subtypes. Many of these drugs target microtubule assembly and function, although lack of specificity in disrupting cellular transport processes often leads to dose-limiting toxicities, including peripheral neuropathy. KSP, part of a larger subfamily of kinesin-5 motor proteins, represents a novel antimitotic target with greater specificity toward actively dividing cells. These proteins are essential components of the early stages of mitosis in that they move apart overlapping microtubules, which ultimately leads to centromere separation and bipolar spindle formation.22,23

ARRY-520 is a potent, highly selective KSP inhibitor that has demonstrated single-agent activity in preclinical MM xenograft models, and phase I clinical studies in the relapsed and refractory setting.24,25 On the basis of these results, a phase II study with ARRY-520 was conducted by using ARRY-520 both as a single agent (Cohort 1) and in combination with low-dose dexamethasone (Cohort 2)26 because preclinical studies have suggested that ARRY-520 downregulates Mcl-1, a known dexamethasone resistance mechanism.27 Notably, all 18 patients in Cohort 2 had disease that was refractory to bortezomib and lenalidomide, and all but one had disease refractory to dexamethasone. After a median treatment time of 3.9 months, ORR rate was 22%, with four patients (22%) achieving a PR; median duration of response was 5.4 months. The most frequent grade 3 or 4 AEs included neutropenia (62%) and thrombocytopenia (57%), although these were generally reversible and not cumulative. Importantly, there was no association of peripheral neuropathy with ARRY-520 therapy. Cohort 1 contained a more modest number of patients with disease refractory to bortezomib (53%) and lenalidomide (75%), and of 32 patients with assessable response, ORR was 16%, with five PRs (16%). These data support further investigation of ARRY-520 in the double-refractory setting, and phase I studies evaluating the tolerability and efficacy of ARRY-520 in combination with other novel MM drugs such as bortezomib and carfilzomib are also ongoing.

CONCLUSION

Although the prognosis for MM refractory to lenalidomide and bortezomib therapy is poor, recent studies have highlighted several potentially effective strategies in this challenging disease subset. These have included the use of more potent analogs of existing myeloma drug classes, the development of rational combinations to overcome drug resistance, and the discovery of novel drug targets. Future work remains in establishing predictive biomarkers to help individualize therapy on the basis of an improved understanding of disease biology and emerging mechanisms of drug resistance, such as Cereblon depletion and Wnt/β-catenin-mediated CD44 overexpression in lenalidomide resistance, or insulin-like growth factor-1 (IGF-1) upregulation in bortezomib resistance.28-30 Together, these approaches will, we hope, continue to build on the improvement in outcomes seen in MM during the last decade, and result in longer intervals of disease control and even disease eradication.

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References


Update on the Initial Therapy of Multiple Myeloma

Donna Reece, MD

OVERVIEW

Advances in myeloma biology and the identification of new anti-myeloma agents have resulted in improved management of younger, transplant-eligible, and older patients. The first novel agents—thalidomide, bortezomib, and lenalidomide—have been integrated into induction therapy before autologous stem cell transplant (ASCT) as well as into first-line therapy in elderly individuals; phase III trials have established the superiority of these approaches in terms of better response rates, progression-free survival (PFS), and, in some studies, overall survival. With more experience, improvements in dosing have decreased the toxicity of these regimens. Before ASCT, four phase III studies have shown that bortezomib-based regimens confer better outcomes than older regimens. Posttransplant consolidation and maintenance strategies with novel agents provide additional benefit, particularly in terms of a longer PFS. In the elderly population, novel agents can be combined with melphalan plus prednisone (MP). MP plus thalidomide and MP plus bortezomib are commonly utilized, and the regimen of MP plus lenalidomide with lenalidomide maintenance (MPR + R) produces superior response rates and longer PFS compared with MP alone. Prolonged maintenance with bortezomib plus thalidomide also appears to extend PFS when given following combinations of MP plus bortezomib. Treatment of very elderly patients, however, remains challenging due to comorbidities and side effects. Lenalidomide plus weekly dexamethasone is also effective in elderly patients, and results of a trial comparing this regimen with MP plus thalidomide should be available soon. Finally, better methods of risk stratification and the availability of even newer drugs will allow future refinements in myeloma treatment.

In the previous decade, younger patients with newly diagnosed myeloma were typically treated with induction therapy based on high-dose dexamethasone (dex) (i.e., vincristine/doxorubicin/dexamethasone [VAD] or dex alone) followed by autologous stem cell transplantation (ASCT), whereas older individuals received 6–12 cycles of oral melphalan and prednisone (MP). Results from randomized trials indicated that an approach of VAD and a single ASCT produced an overall response rate (≥ partial remission [PR]) of 80% with up to 20% complete or nearly complete (CR/nCR) remission, a progression-free survival (PFS) rate of around 24 months, and an overall survival rate of 4–5 years. MP in older patients resulted in overall response rates on the order of 50% with few CR/nCRs; a PFS of approximately 12–15 months and an overall survival of 3–4 years could be anticipated.1

More recently, an improved understanding of the biology of myeloma and the identification of new drugs have improved the therapeutic approach to myeloma. Genomic techniques have provided insights into the different molecular subtypes of this disease with differing natural histories. In the clinic, application of the International Staging System (based on the serum levels of beta-2 microglobulin and albumin) and FISH cytogenetics has allowed the definition of different myeloma risk groups with readily available laboratory tests. Several investigators have reported that the presence of t(4;14), t(14;16) and deletion 17p identifies patients with a poorer outcome. More recently, both 1q gains, as well as deletions of 1p22 and 1p32, have been associated with an adverse prognosis in analyses of patients treated on Intergroupe Francophone du Myelome (IFM) studies involving ASCT.2,3

Following the introduction of the immunomodulatory derivatives (IMiDs) thalidomide and lenalidomide, and the first-in-class proteasome inhibitor bortezomib, a series of phase II and III studies in both younger and older patients with myeloma has evaluated the integration of these novel agents into first-line therapy. Other recent developments have included an appreciation of the toxicity of the older schedule of “pulse” dexamethasone (high-dose dex [HD-dex] = 40 mg/day for day 1 through 4, 9–12, and 17–20 of a 28-day cycle) and the benefit of low-dose dex = 40 mg/week (LD-dex).4 In addition, the incidence and severity of peripheral neuropathy associated with bortezomib can be reduced by weekly, rather than twice weekly, dosing as well as by the subcutaneous, rather than intravenous, route of administration.5,6

Finally, various maintenance strategies have been evaluated in both younger and older patients in an attempt to improve the duration of remission and overall survival.5–7

In Europe and Canada, a strategy that maintains the division of newly diagnosed patients into two categories—those who are designated for upfront ASCT and those who are transplant-ineligible on the basis of age and comorbidities—is still in place. In contrast, some U.S. specialists have...
recommended treating younger individuals, particularly those with standard-risk disease, as regimens based on novel agents for variable periods of time; ASCT is considered optional based on patient preference and other unknown factors. Some of these approaches advocate ASCT at the time of relapse. Although delayed ASCT may ultimately be shown to produce results comparable to first-line ASCT, phase III trials evaluating the two strategies have not yet been completed. Moreover, most reports describing the efficacy of 2-, 3-, or even 4-drug regimens include a mix of transplant and non-transplant patients, with a focus on response rates; information regarding longer term outcomes such as PFS is often limited and the contribution of ASCT difficult to assess. To more accurately ascertain the results of different therapeutic strategies, the current discussion will, therefore, emphasize the results of randomized trials in which the distinction between ASCT and nontransplant therapy is determined from the onset of study.

**MANAGEMENT OF TRANSPLANT-ELIGIBLE PATIENTS**

*Induction Therapy*

The most recent phase III induction studies have evaluated bortezomib-based combinations. Reported regimens have combined bortezomib with corticosteroids (BD), thalidomide (VTD), and/or doxorubicin (PAD). The number of cycles has varied, as has the use of single or tandem ASCT and post-transplant measures such as maintenance or consolidation, which makes the contribution of induction therapy per se more challenging (Table 1). Nevertheless, taken in aggregate, the median PFS after ASCT has increased from approximately 2 years with VAD or thalidomide + dex induction to 3 years when bortezomib is used (Table 2). A recent meta-analysis has also shown that bortezomib-based induction yields better response rates, PFS, and overall survival than older regimens such as VAD or thalidomide + dexamethasone. Of note, as bortezomib is associated with an increased risk of varicella zoster reactivation; antiviral prophylaxis should be used in all patients.

Several other 3- and 4-drug induction regimens have been reported in phase II trials, with no clear superiority of one particular regimen (Table 3). Three of the most commonly used regimens in community practice include: VRD (bortezomib + lenalidomide + dex), CVD or CYBor-D (cyclophosphamide + bortezomib + dex), and VTD (bortezomib + thalidomide + dex). Even though only the latter has been evaluated in randomized trials comparing it with thalidomide + dexamethasone, after induction with these regimens, at least 90% have entered ≥PR, with ≥very good PR (VGPR) rates in the range of 50% to 70% and CR/nCR rates of 25% to 50%. The rates of VGPR and CR/nCR usually increase further post-ASCT, which is important, as the achievement of such “deep” remissions correlates with improved outcomes for transplanted patients.

Newer, and potentially more potent proteasome inhibitors such as carfilzomib and ixazomib (MLN 9708) as well as the newer IMiD pomalidomide—all of which have been reported to have efficacy in some patients refractory to bortezomib and/or older IMiDs—will undoubtedly be evaluated earlier in the disease course in future clinical trials. Already, a phase I-II study of CRd, the combination of carfilzomib + lenalidomide + dex, has been reported in newly diagnosed patients, and a subsequent trial of CRd induction and consolidation is forthcoming. As well, a cooperative Dutch study has described a similar approach in which carfilzomib + thalidomide + dex is given as both pretransplant induction and post-transplant consolidation in newly diagnosed patients. The Mayo clinic recently reported a phase II study in which cyclophosphamide is added to CTD in a regimen referred to as CYCLONE as well (Table 2).

Although the inclusion of bortezomib, particularly in a 3-drug regimen, seems important for high-risk disease, as indicated by the recent integrated analysis of the four phase III studies of bortezomib induction described previously, the

**TABLE 1. Results of Bortezomib-Containing Pre-ASCT Induction Regimens Reported in Phase III Trials**

<table>
<thead>
<tr>
<th>Author</th>
<th>Induction Regimen</th>
<th>ASCT + Post-ASCT Therapy</th>
<th>≥PR</th>
<th>≥VGPR</th>
<th>≥CR/nCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harousseau et al.</td>
<td>Bortezomib + dex</td>
<td>1 or 2 (lenalidomide maintenance in some)</td>
<td>78%</td>
<td>38%</td>
<td>15%</td>
</tr>
<tr>
<td>Cavo et al.</td>
<td>VTD</td>
<td>2 + VTD consolidation + dex maintenance</td>
<td>92%</td>
<td>63%</td>
<td>31%</td>
</tr>
<tr>
<td>Sonneveld et al.</td>
<td>PAD</td>
<td>1 or 2 + bortezomib maintenance</td>
<td>83%</td>
<td>42%</td>
<td>15%</td>
</tr>
<tr>
<td>Rosinol et al.</td>
<td>VTD</td>
<td>1 + VT = bortezomib and thalidomide maintenance</td>
<td>82%</td>
<td>60%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; CR/nCR, complete remission/near CR; dex, dexamethasone; VTD, bortezomib/thalidomide/dexamethasone; PAD, bortezomib/doxorubicin/dexamethasone; PR, partial remission; VGPR, very good PR.

**KEYPOINTS:**

- Bortezomib-based induction regimens before ASCT produce better rates of response, PFS, and OS.
- Post ASCT measures involving novel agents improve PFS with a variable effect on overall survival.
- In elderly patients, the addition of a novel agent to melphalan and prednisone results in a better antimyeloma effect, but the incidence of grade 3/4 toxicity is relatively high.
- Lenalidomide plus weekly dexamethasone is also a promising regimen in elderly patients.
- Newer drugs such as carfilzomib are under evaluation in the first-line setting.
question of whether less intensive induction before ASCT is appropriate for standard-risk patients has not been prospectively addressed. In particular, the oral regimen lenalidomide + LD-dex, as first reported in the ECOG E4A03 trial comparing it with lenalidomide + HD-dex, produces reasonable overall response rates, albeit with comparatively lower CR/nCR rates, and is associated with excellent patient tolerance. Prolonged use can compromise, to some extent, blood stem cell mobilization and collection; stem cell collection is still usually possible by using combination approaches. Details regarding patient outcomes by risk stratification are not available from this study, although newer retrospective reports from the Mayo Clinic have suggested the utility of lenalidomide and LD-dex alone for induction. On balance, however, it seems prudent to avoid routine reduction in the intensity of induction therapy in transplant-eligible individuals until further supportive evidence is available.

Post-ASCT Therapy
The two main post-transplant measures include long-term maintenance, usually with either an IMiD or bortezomib as single agents, or consolidation therapy. Thalidomide maintenance has been evaluated in seven phase III trials in which the dose and duration of thalidomide varied, as did the use of concomitant corticosteroids. These trials consistently demonstrated a significantly better PFS—in the range of 6–12 months—in patients receiving thalidomide, with a variable effect on overall survival. A recent meta-analysis of these studies concluded that thalidomide as a single agent or in conjunction with corticosteroids improves both progression-free and overall survival rates. Toxocities such as peripheral neuropathy and thrombotic events were increased, not surprisingly, with thalidomide. These and other unpleasant side effects, in turn, negatively affect the quality of life, as highlighted in the recent analysis of the Canadian NCIC randomized study of thalidomide + prednisone compared with observation after ASCT.

On the other hand, maintenance with lenalidomide avoids many of the toxicities of thalidomide, although it is associated with the potential for myelosuppression. More recently, lenalidomide maintenance has been assessed in two phase III trials—the IFM and CALGB trials—in which patients were randomized post-ASCT to low dose lenalidomide or placebo until disease progression; the IFM trial also included 2 months of full-dose lenalidomide in all patients before beginning the assigned maintenance arm. The IFM study

### TABLE 2. Summary of Post-ASCT Outcomes in Phase III Trials Using Novel Agents

<table>
<thead>
<tr>
<th>Author</th>
<th>Post ASCT Response Rates</th>
<th>Median PFS</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harousseau et al.</td>
<td>68% VGPR/39% CR/nCR</td>
<td>36 mos</td>
<td>NYR 81% (3-yr)</td>
</tr>
<tr>
<td>Cavo et al.</td>
<td>89% VGPR/71% CR/nCR</td>
<td>N/A</td>
<td>NYR 68% (3-yr)</td>
</tr>
<tr>
<td>Sonneveld et al.</td>
<td>76% VGPR/49% CR/nCR</td>
<td>35 mos</td>
<td>NYR 61% (5-yr)</td>
</tr>
<tr>
<td>Rosinol et al.</td>
<td>N/A/46% VGPR/CR/nCR</td>
<td>56.2 mos</td>
<td>NYR 74% (4-yr)</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; CR/nCR, complete remission/near CR; mos, months; NYR, not year reached; VGPR, very good partial remission.

### TABLE 3. Summary of Selected 3- or 4-Drug Induction Regimens Reported in Phase I-II Trials

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Agents</th>
<th>N with ASCT</th>
<th>Post-Induction Response Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDD</td>
<td>Bortezomib + pegylated liposomal doxorubicin + dex</td>
<td>30/20</td>
<td>93%/63%/40%</td>
</tr>
<tr>
<td>VRD</td>
<td>Bortezomib + lenalidomide + dex</td>
<td>31/31</td>
<td>94%/62%/23%</td>
</tr>
<tr>
<td>RVDD</td>
<td>Lenalidomide + bortezomib + pegylated liposomal doxorubicin + dex</td>
<td>68/24</td>
<td>96%/57%/29%</td>
</tr>
<tr>
<td>VTD</td>
<td>Bortezomib + thalidomide + dex</td>
<td>49/48</td>
<td>96%/69%/44%</td>
</tr>
<tr>
<td>VTDC</td>
<td>Bortezomib + thalidomide + dex + cyclophosphamide</td>
<td>49/40</td>
<td>100%/69%/51%</td>
</tr>
<tr>
<td>CyBorD</td>
<td>Weekly oral cyclophosphamide + weekly bortezomib (15 mg/m² + dex)</td>
<td>83/83</td>
<td>97%/79%/N/A</td>
</tr>
<tr>
<td>CVDD</td>
<td>Cyclophosphamide + bortezomib + pegylated liposomal doxorubicin + dex</td>
<td>49/30</td>
<td>89%/69%/25%</td>
</tr>
<tr>
<td>RVD</td>
<td>Lenalidomide + bortezomib + dex vorinostat</td>
<td>30/10</td>
<td>100%/52%/32%</td>
</tr>
<tr>
<td>CRD</td>
<td>Carfilzomib + lenalidomide + dex</td>
<td>53/7</td>
<td>100%/88%/67%</td>
</tr>
<tr>
<td>CTD</td>
<td>Carfilzomib + thalidomide + dex</td>
<td>39/39</td>
<td>91%/61%/18%</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplantation; CR/nCR, complete remission/near CR; dex, dexamethasone; mos, months; N/A, not available; PR, partial remission; VGPR, very good PR.

* After 4 cycles.
** After ≥4 cycles.
found a significant prolongation of PFS from 23 to 41 months (p < 0.001), whereas the CALGB trial described a significantly longer time to progression from 27 to 46 months, in the lenalidomide arm (p < 0.001).30,31 The latter study also reported a survival benefit (p = 0.03).31 Lenalidomide maintenance was generally well-tolerated, although a small but consistent increase in the risk of secondary malignancies has been observed with this agent.30,32 Some groups are now advocating the use of lenalidomide maintenance for a shorter, finite period of time (i.e., 1–3 years) in an effort to reduce this risk, although it is currently uncertain whether the same benefit in terms of PFS and survival will be preserved. The introduction of better methods to assay minimal residual disease post-ASCT, such as narrow multiparameter flow cytometry or molecular studies, may help direct the optimal use of maintenance therapy in the future.

The term “consolidation” does not have a standard definition in myeloma but, as in acute leukemia, usually refers to moderately intensive combination therapy given for several cycles after recovery from ASCT. The Arkansas group was with first to report the use of consolidation, which has been a major feature of all of their Total Therapy trials.32 Outside of Arkansas, the Italian cooperative group led by Cavo and colleagues has described excellent results with VTD induction, tandem transplantation, and VTD consolidation followed by maintenance with dexamethasone alone, without a novel agent.33 Advantages of consolidation compared with long-term maintenance therapy include a finite period of treatment and, potentially, a lower and more predictable cost. It is not known whether the risk of secondary malignancies will be decreased.

The CTN trial (Stamina Trial; BMT-CTN0702) that evaluates different post-transplant strategies will hopefully delineate the optimal approach in the future. In this phase III trial, patients receive induction with RVD followed by ASCT; thereafter, patients are randomized either directly to lenalidomide maintenance for 3 years, to a second ASCT followed by lenalidomide maintenance, or to RVD consolidation and lenalidomide maintenance. This trial has completed accrual, and the results are awaited with considerable interest.

In the interim, many centers like the author’s institution, Princess Margaret Hospital, consider some method of risk stratification for transplant-eligible patients. Given Princess Margaret Hospital’s current Canadian resources, they use weekly CyBorD induction, anticipating a 90% to 95% overall response rate and 45% to 50% CR/nCR rate pre-ASCT.17 This is followed by ASCT with melphalan 200 mg/m². High-risk patients’ with (4;14), (14;16) and/or del 17p or plasma cell leukemia undergo a second ASCT; all patients then received lenalidomide maintenance. Of note, a recent single-center report described a similar approach and observed that high-risk patients undergoing tandem transplantation had outcomes similar to standard-risk patients undergoing a single ASCT.34 In the future, consolidation with a 3-drug combination, analogous to the approach of Cavo and colleagues, would ideally be integrated into therapy, particularly in the high-risk setting. Regardless of the choice of induction and post-ASCT regimens, the goal should be a median PFS of 3 or more years, in keeping with the results of the phase III trials discussed above.

**TREATMENT OF TRANSPLANT-INELIGIBLE PATIENTS**

In non-ASCT candidates, the two main approaches to improve results have included: (1) the addition of a novel agent (thalidomide, bortezomib, or lenalidomide) to the MP regimen; (2) the continuous use of an IMiD—without an alkylating agent—and dexamethasone.1

MP has been compared with MPT in six randomized studies, all of which demonstrated an improvement in PFS to approximately 24 months years, compared with MP, which had a PFS of 14–16 months.35,36 Survival outcomes were more variable, but a recent meta-analysis of these trials, including a total of 1685 patients, confirmed a superior 1-year response rate, PFS, and overall survival with MPT.35 On the other hand, grade 3 or 4 toxicity occurred in 45% to 50% of patients, with a considerably higher risk of both peripheral neuropathy and venous thromboembolism,36 the latter of which requires thromboprophylaxis.37 In addition, benefit was most apparent for patients younger than age 65. An appreciation of the effect of poor performance status on outcomes has been recognized, and dose adjustments in very elderly patients (>75 years) and more vulnerable individuals has been proposed.38

VMP (= bortezomib + MP) is the other MP-containing regimen that is commonly used in elderly patients. The VISTA trial demonstrated a substantial improvement in response rates, PFS and overall survival with VMP compared with MP. Similar to MPT, the PFS was 24 months with VMP. However, grade 3–4 toxicities were also noted in a high proportion of patients.39 Peripheral neuropathy was not uncommon, although modifications of the regimen, in which bortezomib is given once rather than twice per week, have decreased the incidence of this side effect without compromising the antitumor effect;40 the use of subcutaneous bortezomib is anticipated to improve patient tolerance as well.6

The use of prolonged maintenance in subsequent trials, either as VT (bortezomib + thalidomide) or VP (bortezomib + prednisone), has been reported to extend PFS even further than 2 years in patients initially treated with VMP, VTP, or VMPT, but no significant survival improvement has been realized in either of the two trials exploring this strategy.6,40 Third, lenalidomide has been combined with MP in MM015 study reported by Palumbo and colleagues. This study compared three treatment arms: MP compared with MPR (MP + lenalidomide) compared with MPR-R (MPR followed by lenalidomide maintenance until disease progression). MPR-R produced a significant prolongation of PFS over MP (p < 0.001), although no significant benefit in overall survival was observed.41 Just as in the post-ASCT setting, MPR-R was associated with a small, but measureable, increase in the incidence of secondary cancers.42 Additionally, studies of VMP and MPR-R, noted inferior outcomes in patients over the age of 75 years.41

Historically, the first continuous IMiD and corticosteroid regimen used in older patients with myeloma was

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**References:**

1. DONNA REECE

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thalidomide + HD dex. However, this regimen produces excessive toxicity and has been replaced by the combination of lenalidomide + weekly dex, which is better tolerated. As shown by Rajkumar and colleagues in the ECOG E4A03 trial, lenalidomide and LD-dex induces remission in approximately 70% of patients, with a median PFS of about 2 years. This regimen is widely used in the United States, and its efficacy and benignity in an older population will hopefully be illustrated by the results of the MM010 trial, which has completed accrual but has not yet been reported. This large phase III study randomized newly diagnosed patients ≥ 65 years of age to a standard regimen of MPT compared with lenalidomide and LD dex until myeloma progression compared with lenalidomide and LD dex for a fixed period of 18 months.

In practice, MPT, VMP, and lenalidomide + LD-dex can each be considered for older patients with myeloma, with the choice based on a variety of disease-related and patient-related factors. Although data are limited regarding the optimal therapy for high-risk patients, particularly those with adverse cytogenetics, many experts recommend a bortezomib-containing regimen in such individuals. Mateos and colleagues has published the results of VMP-based regimes and noted that those with t(4;14) and del 17p have better outcomes with VMP than MP, although the results are less favorable than in the setting of standard-risk disease.

Given the comorbidities of many older patients with myeloma, the selection of the best approach for those very elderly (>75 years of age) or very frail patients may be challenging. In this population, specific dose reductions have been recommended for the agents in the VMP, MPR, and len + dex regimens, as well as for MPT as mentioned above.

Newer regimens with less morbidity are also being explored for patients ineligible for ASCT. For example, the combination of weekly oral cyclophosphamide + dexamethasone with carfilzomib has recently been reported to produce ≥ PR in 91% of elderly patients without significant neuropathy and with relatively few grade 3/4 toxicities; equivalent results in patients below and above the age of 75 years have been described. Trials of 3-drug regimens in which MP is combined with ixazomib and which the monoclonal antibody elotuzumab is combined with len + LD-dex are also in progress in an effort to improve therapeutic options for older individuals with myeloma.

**Disclosures of Potential Conflicts of Interest**

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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**References**


This article reviews the most relevant techniques currently used for the evaluation of patients with multiple myeloma. Although bone marrow morphologic examination and electrophoretic analysis of the monoclonal paraprotein and conventional x-rays remain the “gold standard” techniques for fast, accurate, and cost-effective diagnosis, other assays such as molecular cytogenetics, immunophenotyping, MRI, and PET-CT may contribute to a better assessment of patients with myeloma. Here, we will discuss not only the contribution of each technique to differential diagnosis of monoclonal gammopathies, but also the value of each parameter for determining prognosis and for monitoring treatment efficacy. In addition, possible technical pitfalls inherent to each technique will be analyzed.

Diagnosis of multiple myeloma (MM) requires the examination of bone marrow showing plasma cell infiltration, detection, and quantification of monoclonal protein in the serum or urine and evidence of end-organ damage (i.e., hypercalcemia, renal insufficiency, anemia, or bone lesions).1,2 Diagnostic assays have three main objectives: to contribute to the diagnosis and differential diagnosis of monoclonal gammopathies, to yield information about prognostic factors in order to facilitate the therapeutic decision-making process, and to provide appropriate tools to monitor treatment efficacy. It should be noted that many of the laboratory parameters contribute to more than one objective. In this review we have grouped the different diagnostic and prognostic assays into five areas: protein analysis, morphology, immunophenotyping, genetics and cytogenetics, and imaging techniques (i.e., MRI, PET/CT). An overview of diagnostic tools is provided in Table 1.

PROTEIN ANALYSIS
Measurement of the serum and urine monoclonal immunoglobulin (MC) has been a mainstay in the treatment of patients with multiple myeloma (MM). Agarose gel electrophoresis or capillary zone electrophoresis of serum and urine is preferred to screen for the presence of MC, but quantification of monoclonal protein in the serum or urine (i.e., hypercalcemia, renal insufficiency, anemia, or bone lesions).1,2 Diagnostic assays have three main objectives: to contribute to the diagnosis and differential diagnosis of monoclonal gammopathies, to yield information about prognostic factors in order to facilitate the therapeutic decision-making process, and to provide appropriate tools to monitor treatment efficacy. It should be noted that many of the laboratory parameters contribute to more than one objective. In this review we have grouped the different diagnostic and prognostic assays into five areas: protein analysis, morphology, immunophenotyping, genetics and cytogenetics, and imaging techniques (i.e., MRI, PET/CT). An overview of diagnostic tools is provided in Table 1.

Measurement of the serum and urine monoclonal immunoglobulin (MC) has been a mainstay in the treatment of patients with multiple myeloma (MM). Agarose gel electrophoresis or capillary zone electrophoresis of serum and urine is preferred to screen for the presence of MC, but quantification of serum immunoglobulins (particularly those uninvolved) by nephelometry should also be performed.1 Bence-Jones or immunoglobulin D (IgD) myeloma should be suspected in the absence of serum MC but severe hypogammaglobulinemia.5 Once the MC is detected, the heavy and light chain isotypes must be identified by immuno fixation. If negative for IgG, IgA, and IgM but positive for kappa or lambda, an immuno fixation for IgD or IgE should be performed.5 Twenty-four–hour urine collection is mandatory to assess the total amount of protein excreted. An aliquot must be concentrated (150 to 200 fold) for electrophoresis (detection of monoclonal light chain) and immunofixation (isotype identification). The lowest detected level of M-protein by electrophoresis ranges between 0.2 g/L and 0.6 g/L, whereas for serum immunofixation it ranges between 0.12 g/L and 0.25 g/L. According to the International Myeloma Working Group,2 a serum MC of 3 g/dL or greater distinguishes patients with smoldering myeloma from patients with monoclonal gammopathy of undetermined significance (MGUS), but it is not a requisite to define symptomatic disease. The size of the MC does not have prognostic influence in MM.4 During the past decade the measurement of serum immunoglobulin-free light chains (FLC) has become part of routine clinical testing. An abnormal serum FLC ratio indicates the presence of clonality in approximately one-third of patients with MGUS and in 90% or greater of those patients with smoldering and symptomatic myeloma (including light chain disease).5 The assay is particularly indicated for the treatment (diagnosis and follow-up) of patients with nonsecretory and oligosecretory myeloma, as well as amyloidosis, but measurement of serum FLC levels does not obviate the need for 24-hour urine studies.1,5 Noteworthy, a highly abnormal serum FLC ratio predicts for shorter time to progression in patients with MGUS and smoldering myeloma, as well as for inferior survival rates for patients with active myeloma.5

The variation in the size of the MC by electrophoresis is the major criterion to define response to treatment in myeloma. Complete response (CR) criteria requires (among others) negative immuno fixation of serum and urine, and stringent
CR requires the CR criteria plus a normal serum FLC ratio. Achievement of CR is now considered one of the strongest prognostic markers in myeloma, both in the transplant and nontransplant settings. The stringent CR criteria has failed to unequivocally demonstrate a superior prognostic value compared with conventional CR, which might be partially explained by the presence of false-positive results driven by oligoclonal expansions after therapy. This particular drawback could be overcome with a novel assay that separately identifies the different light chain types of each immunoglobulin class (that is, IgG-kappa, IgG-lambda, IgA-kappa, and IgA-lambda), therefore capable of quantitating involved and uninvolved immunoglobulins (e.g., IgG-lambda, IgA-kappa, and IgA-lambda for a patient with IgG-kappa disease). Recent studies have shown that the new heavy/light chain assay provides additional prognostic information in MGUS and active myeloma; however, it should be noted that the major contribution for prognostication comes precisely from the quantification of the uninvolved immunoglobulins, thereby highlighting the importance of initial polyclonal immunoglobulin suppression and later recovery to identify patients with MGUS who have higher risk of progression or increased likelihood of long-term survival in active myeloma, respectively.

**KEY POINTS**

- Conventional morphology, protein electrophoresis, and skeletal survey remain the standard of care in the diagnosis and treatment of patients with myeloma, but novel cellular, serologic, and imaging assays have found their way into the clinic.
- Serum-free light chain and the new heavy/light chain assays are particularly valuable for diagnosis and follow-up of oligosecretory myelomas; however, these are not currently a substitute for the 24-hour urine assay.
- Fluorescence in situ hybridization (FISH) analysis on purified plasma cells is mandatory for patient risk stratification and should only be repeated at relapse/progression for those patients initially classified as genetic standard risk.
- Flow cytometry immunophenotyping and allele-specific oligonucleotide polymerase chain reaction have contributed to the evaluation of minimal residual disease (MRD), which translated into definition of high-quality responses (immunophenotypic and molecular remission) associated with longer survival and with the possibility of monitoring consolidation and maintenance therapies.
- Novel imaging techniques (e.g., MRI or PET/CT) have progressively been incorporated into routine practice and might become a new standard in the future, particularly for identification of occult bone disease in smoldering myeloma and to exclude extramedullary disease for definition of complete response outside of the bone marrow.

### TABLE 1. Most Relevant Techniques Currently Used for the Evaluation of Patients with Multiple Myeloma

<table>
<thead>
<tr>
<th>Protein Analysis</th>
<th>Screening and quantification of serum and urine immunoglobulins.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrophoresis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Immunofixation</strong></td>
<td>Characterization of heavy- and light-chain isotypes. Confirmation of CR.</td>
</tr>
<tr>
<td><strong>Serum-Free Light Chains</strong></td>
<td>Particularly indicated for the management of patients with nonsescretory and oligosecretory myeloma. Do not replace 24-h urine analysis. Confirmation of stringent CR.</td>
</tr>
<tr>
<td><strong>Serum-Heavy Light Chains</strong></td>
<td>Allows simultaneous quantification of involved and uninvolved immunoglobulins.</td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Bone Marrow Aspirate</strong></td>
<td>Quantification and morphologic characterization of plasma cells.</td>
</tr>
<tr>
<td><strong>Trephine Biopsy</strong></td>
<td>Particularly indicated for patients with suspected myeloma and low marrow plasmacytosis.</td>
</tr>
<tr>
<td><strong>Immunophenotyping</strong></td>
<td>Determines the degree of clonality (which is associated with higher risk of transformation in MGUS and smoldering myeloma patients) through the balance between normal and clonal plasma cells. The latter are identified by their aberrant phenotypes, which are also informative for MRD monitoring.</td>
</tr>
<tr>
<td><strong>Genetics and Cytogenetics</strong></td>
<td>Cytogenetics-typically evaluated by FISH on purified plasma cells–has become one of the most important prognostic factors, and is considered mandatory for all patients with newly diagnosed myeloma. The presence of t(14;14), t(14;16) and/or del(17p) currently defines high-risk disease.</td>
</tr>
<tr>
<td><strong>Imaging Studies</strong></td>
<td></td>
</tr>
<tr>
<td><strong>X-ray</strong></td>
<td>Gold standard for baseline evaluation of bone disease.</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>Mandatory in selected cases (e.g., presumed diagnosis of solitary plasmacytoma).</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>When MRI is unavailable for assessment of the spine, or to clarify the extent of soft tissues.</td>
</tr>
<tr>
<td><strong>PET/CT</strong></td>
<td>Not to be used routinely. May be useful to evaluate MRD outside the bone marrow.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CR, complete response; FISH, fluorescence in situ hybridization; MGUS, monoclonal gammopathy of undetermined significance; MRD, minimal residual disease.

The urine M-protein should also be monitored during follow-up, even in patients without urinary excretion of para-protein at diagnosis, because there are cases with light chain escape as the only sign of relapse. Albumin quantitation is important for staging, and the most accurate assay is nephelometry because electrophoresis might overestimate albumin concentration if there is a high MC.

**MORPHOLOGY**

The estimation of bone marrow plasma cell infiltration is a major criterion for the diagnosis and differential diagnosis of
MM and other plasma cell dyscrasias (e.g., solitary plasmacytoma). Recent consensus from the International Myeloma Working Group support that a patient with suspected MM should undergo a unilateral bone marrow aspirate (May-Grünwald Giemsa stained smears) and/or biopsy, and the diagnosis is confirmed when 10% or greater of plasma cells are detected. The use of bone marrow biopsies is probably a more accurate method (through CD138 staining) for evaluation of plasma cell infiltration because cytomorphology is more vulnerable to the heterogeneous distribution of plasma cells in the bone marrow, and the percentage of plasma cells may substantially vary depending on site of sample aspiration. This phenomenon could also help to explain the inconsistency of plasma cell quantification as a prognostic factor in symptomatic patients. However, for the definition of CR, morphologic assessment is mandatory and requires the presence of less than 5% of plasma cells. Immunoperoxidase staining, immunofluorescence, or flow cytometry immunophenotyping of the bone marrow aspirate can be used to establish the clonality of plasma cells; however, this is not a standard procedure.

In contrast with other hematologic malignancies, little attention in MM is paid to the morphologic characteristics of plasma cells (e.g., mature, intermediate, immature, plasmablasts).

**IMMUNOPHENOTYPING**

The multiparameter nature of flow cytometry allows the detection of clonal plasma cells through their aberrant phenotypes rather than by light chain restriction. Aberrant phenotypes include: typically underexpression of CD19, CD27, CD38, CD45, and/or CD81; overexpression of CD28 and/or CD56; and asynchronous expression of CD117. The degree of clonality assessed by immunophenotyping (i.e., the balance between malignant and residual normal plasma cells) has become particularly relevant to the identification of patients with MGUS or smoldering myeloma who are at different risk of progression into symptomatic disease—higher risk for patients in whom almost all plasma cells are clonal (greater than 95%). In addition, immunophenotyping identifies prognostic-associated antigenic profiles (e.g., CD19*, CD28*, CD81*, or CD117* being associated with inferior outcome) as well as patient-specific phenotypic profiles informative for minimal residual disease (MRD) monitoring.

The CR rates have substantially improved with up-front treatment with novel agents and high-dose therapy followed by autologous stem cell transplantation; overall survival rates have also substantially improved for patients with myeloma. However, only a minor fraction of patients actually achieves long-term disease control (more than 10 years of disease-free survival), which underlies the persistence of MRD undetectable by conventional serologic and cytomorphologic techniques. The need for bone marrow confirmation of CR has been discussed, but important data showing that up to 14% of patients with immunofixation-negative CR might have 5% or greater of plasma cells in the marrow confirms the need for its evaluation. However, in contrast with acute leukemias, conventional morphologic methods are generally not able to distinguish normal from clonal plasma cells. Moreover, the value of immunohistochemistry or immunofluorescence is rather limited in this setting because of the recovery of normal plasma cells after therapy that precludes the use of low-sensitive techniques. The unique features of multiparameter flow cytometry immunophenotyping, applicable to 90% or greater of patients and with a sensitivity to detect one or more tumor cells out of 10,000 normal cells render this an attractive approach for patient follow-up. From a clinical point of view, achieving an immunophenotypic CR (no residual aberrant plasma cells with a sensitivity limit of 10^-4) predict for extended survival in younger patients undergoing intensive therapy and elderly patients treated with novel agents. Moreover, and similar to the paradigm in other hematologic malignancies (e.g., acute lymphoblastic leukemia, chronic myeloid leukemia, and acute promyelocytic leukemia), risk assessment combining baseline evaluation through (cyto)genetics and MRD monitoring following up-front treatment provides accurate patient stratification—identifying those at risk of showing unsustained CR. Pitfalls of conventional flow cytometry include its lack of standardization and the need for experienced personnel. The EuroFlow Consortium is trying to overcome these drawbacks; moreover, the evolution from four-color into multidimensional flow cytometry with eight or more colors is increasing the specificity and sensitivity of MRD assessments. Regarding molecular polymerase chain reaction techniques, these are well standardized and are suitable for MRD monitoring, with several small studies showing the clinical significance of achieving a molecular CR. However, highly sensitive molecular approaches (10^-5 to 10^-6) rely on the design of allele-specific oligonucleotides, which are time and labor consuming, relatively expensive, and require quality DNA not only in post-treatment samples but also at baseline. The estimated applicability of this approach is approximately 70% in myeloma. Some aspects of current molecular approaches have the potential to be overcome by novel high-throughput gene sequencing, which already showed impressive results in acute lymphoblastic leukemia. It should be noted that MRD negativity (either by immunophenotypic or molecular techniques), even with a sensitivity of 10^-5 or higher, does not necessarily mean complete tumor eradication, particularly in a disease typically characterized by patchy marrow infiltration and extramedullary involvement. Therefore, to have a positive MRD result is a negative prognostic factor, but a negative MRD is not always associated with a favorable outcome. Nonetheless, there is an increasing interest in MRD monitoring as a tool for risk-adapted treatment, particularly in the consolidation and maintenance settings.
GENETICS AND CYTOGENETICS

As in other hematologic malignancies, cytogenetics has become one of the most important prognostic factors for MM. The advent of high-throughput methodologies for genomic analysis has greatly increased the variety of available technologies for investigating genetic abnormalities. Thus, modern whole-genome techniques such as comparative genomic hybridization, mapping arrays based on single nucleotide polymorphisms, and gene expression profiling have been added to the techniques of classical karyotyping and molecular cytogenetics based on fluorescence approaches. Nowadays, cytogenetic evaluation is mandatory in all patients with newly diagnosed MM and should always include interphase fluorescence in situ hybridization (FISH) in purified plasma cells or in combination with immunofluorescent detection of light chain-restricted plasma cells (cIg-FISH). Cytogenetic abnormalities in MM can be classified in two main groups: translocations involving immunoglobulin heavy-chain locus (IGH) and genomic imbalances. Patients can have one or more of these abnormalities, and in general, over time, there is accumulation of new cytogenetic abnormalities.

IGH translocations are detectable in approximately 40% of patients. There is a notable diversity of chromosomal partners involved in IGH translocations. The most recurrently involved loci are 11q13 (CCND1) in 15%, 4p16 (FGFR3/MMSET) in 15%, and 16q23 (MAF) in 5% of cases. Several groups have demonstrated that t(4;14) is associated with poor survival. Patients with t(4;14) treated with either conventional or intensive chemotherapy display shorter event-free survival and overall survival times, but recent studies show that it may be possible to almost completely overcome the poor prognostic effect of t(4;14) using bortezomib-based regimens. However, recent analysis suggest that patients with t(4;14) make up a heterogeneous group. Thus, the Intergroupe Francophone du Myéloïde (IFM) discriminated a subset of these patients (approximately 45%) with both low beta2-microglobulin and high hemoglobin diagnosis who are experiencing prolonged survival after tandem transplant, thus benefitting from high-dose therapy. This heterogeneity has also been reported by the Arkansas group using the 70 gene-expression model, which enables a clear separation of two groups of patients with different overall survival. Regarding t(14;16), controversial results (because of its low frequency) have been reported using autologous transplant: the IFM did not confirm the poor prognostic value of t(14;16) in patients receiving a tandem-autologous transplantation approach, whereas a recent study from the MRC Myeloma IX trial showed a shorter survival time among patients with t(14;16) who were treated with autologous transplant.

MM is characterized by the frequent occurrence of chromosomal imbalances including gains and losses that lead to the classification into hyperdiploid and nonhyperdiploid subgroups, the former having a better prognosis. Several studies have shown that 1q gains is selected as an important and independent poor prognostic factor, although there are also series that have failed to confirm this. Monosomy 13/13q deletions (present in approximately 50% of patients) have been associated with short survival in almost all large series of patients treated with both conventional and high-dose therapy. However, this adverse prognosis come from its close association with other high-risk genetic features such as t(4;14), which harbors monosomy 13 in 80% of patients with MM. In fact, the Rb deletion on its own is not a negative prognostic factor. Although deletion of 17p, which includes the p53 locus, is less frequent in MM (occurring in approximately 10% of patients), it remains a strong prognostic factor that has been associated with a negative effect on survival in different treatment contexts. Extramedullary disease, which is commonly related to more aggressive disease, has a higher prevalence of 17p deletion.

Most of the genetic studies show a close association among chromosome abnormalities in MM. Recently, it has been shown that the cosegregation of multiple adverse genetic lesions confers the worst clinical prognosis. On the contrary, a recent study showed that the presence of trisomies in patients with high-risk cytogenetic abnormalities can almost fully abrogate the adverse prognostic effect of the additional abnormalities on MM survival.

There is general consensus that the same genetic abnormalities characteristic of poor prognosis at diagnosis may suggest poor outcome if detected at the time of relapse. Therefore, although routine genetic analysis should be confined to diagnostic myeloma samples, it should be carried out at relapse in those cases initially classified as genetic standard-risk, with the goal of identifying high-risk genetic features associated with adverse prognosis not present at diagnosis time. Finally, because the sensitivity limit of FISH assay is 10−2, it is not recommended for MRD analysis.

IMAGING STUDIES

Bone disease is the hallmark of MM, with up to 90% of patients developing osteolytic lesions during the course of their disease. Imaging is therefore mandatory in patients’ initial work-up, and bone disease distinguishes active treatment-requiring myeloma. Conventional skeletal survey has been considered during the past 4 decades as the gold standard for baseline evaluation of bone disease. A total of 13 plain radiographs should be performed including anteroposterior and lateral of skull, spine (cervical, thoracic, and lumbar) femora and humeri, plus posteroanterior of chest (focus on ribs and scapula) and pelvis. Special attention should be paid to lesions at risk of impeding fracture. Almost 80% of patients with symptomatic myeloma will have radiologic evidence of skeletal involvement, but the technique lacks specificity (discrimination of benign causes of osteopenia) and sensitivity, because lytic lesions are only evident if greater than 30% of bone substance has been lost.

MRI is the most sensitive noninvasive imaging technique for detection of bone involvement in the spine. It also provides relevant information on the extent and nature of soft tissue disease and on the pattern of marrow infiltration (i.e.,...
normal, focal, variegated, or diffuse). MRI is mandatory in (1) presumed diagnosis of solitary plasmocytoma; (2) symptomatic patients for a detailed evaluation of a painful area of the skeleton to look for a soft-tissue mass arising from a bone lesion; (3) suspicion of cord compression; and (4) before kyphoplastia. 1 An MRI is recommended for patients with smoldering myeloma because it can detect occult lesions, which predict for faster progression to symptomatic disease. 29 It is also recommended for patients with nonsecretory myeloma (for diagnosis and follow-up) and for patients with a vertebral collapse in the context of osteoporosis. Osteoporosis with compression fracture requires extensive evaluation by MRI. If a malignant lesion is detected, then the patient has symptomatic disease and requires antimaloma treatment. Noteworthy, bone fracture may be the sequel of osteoporosis (particularly in elderly white women), and other criteria such as anemia or renal impairment should be considered to diagnose symptomatic myeloma. Occasionally, an MRI-assisted CT-guided biopsy of the collapsed vertebra is needed to make the diagnosis. 1 High numbers of focal lesions (more than seven) or a diffuse MRI pattern are considered as adverse prognostic factors in patients with symptomatic myeloma. 10

CT scanning is more sensitive and faster than conventional skeletal survey, but the radiation dose delivered can be up to 3 times higher. Whole-body low-dose CT has recently been investigated, and it may be an alternative for patients for whom MRI is contraindicated. 30 Similarly, CT scan should also be considered when MRI is unavailable for assessment of the spine or to clarify the extent of soft tissues. It is also valuable to clarify lytic lesion in the ribs, sternum, and scapulae, as well as to assist planning of radiotherapy or surgery.

The use of PET/CT is not recommended outside of clinical trials, although it may be informative regarding patients with elevated lactate dehydrogenase, Bence Jones protein escape, and rapidly recurrent disease with no marrow involvement, as well as for patients with suspected extramedullary myeloma. Recent studies showed an independent prognostic value of baseline fluorodeoxyglucose-PET/CT evaluation and of fluorodeoxyglucose suppression before and after high-dose therapy. 31 Accordingly PET/CT may be useful to evaluate MRD outside of the bone marrow and to predict long-term outcomes.

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LYMPHOMA AND PLASMA CELL DISORDERS

State-of-the-Art Updates and Controversies in Lymphoma Therapy

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LIMITED-STAGE HODGKIN LYMPHOMA: OPTIMAL CHEMOTHERAPY AND THE ROLE OF RADIOThERAPY

Nancy L. Bartlett, MD

OVERVIEW

Approximately 90% of patients with early-stage Hodgkin lymphoma (HL) will be cured with first-line therapy. Chemotherapy alone or combined-modality therapy are both acceptable standard treatment options for nonbulky early-stage HL. Combined-modality therapy is associated with more serious late effects and, in at least one study, showed inferior survival rates compared with chemotherapy alone. Modern radiotherapy fields and doses are likely to result in fewer complications, but given the common involvement of the mediastinum in HL, complete avoidance of the heart, lungs, and breasts in the radiotherapy field is unlikely. In patients receiving chemotherapy alone, four to six cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD), with fewer cycles being given to those with an early complete remission, is recommended. Three cycles of ABVD may be adequate in those with an early negative PET, but these results have been published only in abstract form. Current standards for combined-modality therapy include two cycles of ABVD and 20 Gy of involved field radiotherapy in those with a favorable risk profile and four cycles of ABVD plus 30 Gy for unfavorable HL in early-stage patients. Standard of care for bulky early-stage HL remains combined-modality therapy. Whether an interim PET will allow selection of patients with nonbulky HL who will benefit most from consolidative radiotherapy is still under investigation.

The question of whether chemotherapy alone or combined-modality therapy (CMT) represents the optimal approach for early-stage classical HL has been debated for more than two decades, including most recently at the 2012 annual meeting of the American Society of Hematology. Current guidelines and recommendations continue to support either approach in the treatment of nonbulky early-stage HL. The recent publication of the 12-year follow-up of a randomized trial of ABVD alone compared with radiation-based therapy in limited-stage HL showed for the first time a survival advantage in the chemotherapy-alone arm, despite an inferior progression-free survival (PFS), and has rekindled the debate. In addition, the recently presented preliminary results of the phase III United Kingdom RAPID and European Organisation for Research and Treatment of Cancer (EORTC) H10 trials evaluating chemotherapy alone compared with CMT provide important new data for consideration.

Balancing efficacy with long-term toxicity in early-stage HL has proven to be an extraordinary challenge, primarily related to the significant delay of more than 10 years, and in many cases 30 years, between HL therapy and its associated complications. Evaluating alterations in therapy requires decades of follow-up to determine whether new approaches have indeed accomplished the goal of decreased long-term toxicity. Dissecting the late effects of chemotherapy compared with radiation when a large percentage of patients receive both modalities presents an additional hurdle. Finally, currently undefined potential host factors in patients with HL, such as subtle immune deficiencies or genetic susceptibilities to cancer, continue to represent potential explanations for at least a portion of the second malignancies. Despite these obstacles, continued discussion regarding optimal therapy of early-stage HL is warranted as additional phase III data becomes available.

LATE COMPLICATIONS OF THERAPY

Central to the discussion of chemotherapy alone compared with CMT is a brief review of the potential serious long-term complications of treatment. Potential late complications of current regimens are difficult to assess, given the modifications of both radiation techniques and chemotherapy agents over time. Abandonment of the MOPP (mechlorethamine, vincristine, procarbazine, prednisone) regimen and alkylating agents in the primary therapy of HL has virtually eliminated the incidence of secondary acute leukemia related to primary therapy, except in those receiving escalated (esc) BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen and alkylating agents in the primary therapy of HL has virtually eliminated the incidence of secondary acute leukemia related to primary therapy, except in those receiving escalated (esc) BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). Even with the alkylator-dense escBEACOPP regimen, reducing the number of cycles resulted in many fewer cases of acute leukemia.
The transition from extended field radiotherapy to combined-modality therapy with chemotherapy and involved field radiotherapy (IFRT) in the 1990s was the first step aimed at curbing radiation-related toxicities. Retrospective studies demonstrate a significant reduction in second breast cancers in women treated with mediastinal radiotherapy (RT) compared with mantle RT (hazard ratio [HR] 2.7, 95% CI: 1.1 to 6.9), and a breast in patients receiving IFRT compared with extended field radiotherapy (HR = 0.04). In a population-based study of second cancers occurring up to 30 years after treatment in HL survivors, women treated in their twenties had the highest relative risk compared with an age matched control population (24.3% vs. 4.5% at 30 years). Of concern, there was no difference in the incidence of solid tumors in patients treated between 1970 to 1984 and 1985 to 1996, despite the likelihood that patients received more limited doses and fields of RT in the second era. In addition, the relative risk of second solid cancers was also increased after chemotherapy alone, perhaps associated with the increased risk of lung and bladder cancers associated with alkylating agents. A British national cohort study of 5,002 women treated with RT for HL reported a standardized incidence ratio of 5 for breast cancer risk and a remarkable standardized incidence ratio of 47 for those treated at age 14. Risk remained high more than 40 years after treatment. The risk of lung cancer is also substantially increased after both RT and chemotherapy for HL, most commonly in smokers, but not exclusively. Smoking increases the risk of lung cancer more than 20-fold in HL survivors and appears multiplicative, not additive, in combination with RT.

Reducing the dose and field of RT and eliminating alkylating agents from primary therapy will likely result in fewer second cancers, but it not clear that there is a “safe and effective” dose of RT. The German Hodgkin Study Group (GHSG) HD10 and HD11 trials, which compared limited chemotherapy combined with 20 or 30 Gy IFRT in early-stage HL, reported a 3.7% to 4.6% incidence of second malignancy at a median follow-up of 7.5 years with no difference in the incidence of second malignancies or deaths caused by second cancers in those receiving 20 Gy versus 30 Gy.

In addition to second cancers, cardiovascular and cerebrovascular diseases are common causes of premature death in HL survivors. Compared with population-based reference rates, Aleman et al. reported a 2- to 7-fold increased risk of myocardial infarction (MI), angina, congestive heart failure (CHF), and valvular disorders in HL survivors treated with mediastinal RT. Anthracyclines significantly added to the risk of CHF and valvular disorders with a 25-year cumulative incidence of CHF after mediastinal RT and anthracyclines of 7.9%. Swerdlow et al. found a standardized mortality ratio (SMR) of 2.5 for fatal MI in HL survivors. Risks were independently increased for patients treated with RT, anthracyclines, or vincristine. Risk was particularly high for patients receiving ABVD chemotherapy (SMR 9.5), including those who received ABVD but no mediastinal RT (SMR 7.8). Hodgson et al. recently showed a significant increase in cardiac-related hospitalizations in patients treated with ABVD alone compared with the general population, with a 10-year risk of cardiac-related hospitalization of 5.5% compared with 2.2% expected in the general population.

After a median follow-up of 14.7 years for 1,279 patients treated with mediastinal RT, the 20-year cumulative incidence of cardiac events was 16%. Patients treated with neck and mediastinal RT had a 30-year cumulative incidence of stroke or transient ischemic attack of 7%, representing a two- and-a-half-fold increase over a control population.

When weighing the risks and benefits of various treatment approaches it is critical to take into account the site(s) of disease, patient’s age and gender, family history of cancer and cardiovascular disease, smoking history, and the presence of additional cardiovascular risk factors such as diabetes, hypertension, hypercholesterolemia, and obesity.

**KEY POINTS**

- Chemotherapy alone cures nearly 90% of patients with nonbulky HL, but is associated with a slightly higher relapse rate than combined-modality therapy.
- In the combined-modality approach to early-stage HL, the number of cycles of chemotherapy (two to four) and dose of radiotherapy (20 to 30 Gy) are dictated by the risk stratification group.
- Interim and end-of-treatment PET scans may help guide the decision of when to use radiotherapy.
- Patients with bulky disease should receive combined-modality therapy with four to six cycles of ABVD followed by IRRT.
- Late effects are more common with combined-modality therapy and may result in inferior overall-survival rates compared with chemotherapy alone. Modern radiotherapy techniques are likely to result in fewer long-term complications.

**RISK STRATIFICATION**

Comparing results of trials and discussing treatment recommendations for early-stage HL continues to be complicated by the lack of a uniform risk stratification system (Table 1). Current trials in North America differentiate treatment approaches based only on the presence or absence of bulky disease, with bulk defined as a mediastinal mass ratio (MMR) of more than 1/3 or a lymph node mass larger than 10 cm. The GHSG defines an unfavorable presentation as having any one of the following characteristics: an extranodal site of disease, patient’s age and gender, family history of cancer and cardiovascular disease, smoking history, and the presence of additional cardiovascular risk factors such as diabetes, hypertension, hypercholesterolemia, and obesity.
studies with comparable characteristics may provide more accurate comparisons. Ideally, a universal prognostic index should be developed and incorporated into all early-stage trials.

**NONBULKY, EARLY-STAGE HODGKIN LYMPHOMA**

Approximately 60% of patients with newly diagnosed HL will have stage I or II disease and the vast majority will be classified as nonbulky. Given the excellent prognosis of early-stage nonbulky HL, efforts to minimize therapy in HL have focused primarily on this group. The standard of care options for both CMT and chemotherapy alone, as well as the ongoing studies that may influence future treatment recommendations, are discussed below.

The objective of the GHSG HD10 and HD11 trials was to minimize the dose and field of RT, as well as the number of cycles of chemotherapy, but not to eliminate RT entirely. Results of these studies represent the current standard of care for CMT in early-stage HL. HD10, for patients with a “favorable” presentation by GHSG criteria, randomly assigned 1,370 patients to one of four groups: four cycles of ABVD plus 30 Gy IFRT; four cycles of ABVD plus 20 Gy IFRT; two cycles of ABVD plus 30 Gy IFRT; or two cycles ABVD plus 20 Gy RT. In this favorable subset, two cycles of ABVD plus 20 Gy of IFRT was equivalent to all other approaches and was associated with a 5-year freedom from treatment failure of 91% and overall survival (OS) of 97%. Patients with unfavorable results were enrolled on the HD11 trial (1,395 patients) and were randomly assigned to one of four groups: four cycles of ABVD plus 30 Gy IFRT; four cycles of ABVD plus 20 Gy IFRT; four cycles of standard BEACOPP plus 30 Gy IFRT; or four cycles of standard BEACOPP plus 20 Gy IFRT. Outcomes were superior for those receiving 30 Gy compared to 20 Gy, but the use of standard dose BEACOPP did not improve outcomes. At 5 years, the freedom from treatment failure was 85% and OS 95% for patients treated with four cycles of ABVD plus 30 Gy. Importantly and often misunderstood in the general oncology community, the number of cycles of ABVD (two vs. four) and the dose of RT (20 Gy vs. 30 Gy) should reflect the appropriate GHSG risk stratification.

In an effort to determine whether the use of chemotherapy alone resulted in a survival disadvantage for patients with early-stage HL, the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and Eastern Cooperative Oncology Group (ECOG) conducted a study (HD.6) of 405 patients with nonbulky stage I-IIA HL comparing ABVD alone with subtotal nodal irradiation (STNI), with or without ABVD. All patients in the ABVD-alone arm received four to six cycles of ABVD depending on computed tomography (CT) response following cycle two. In patients assigned to STNI, those with an unfavorable risk profile (Table 1) received two cycles of ABVD plus STNI, and those with a favorable risk profile received STNI alone. The 12-year PFS was 87% in the chemotherapy-alone arm compared with 92% in the RT arm (p = 0.05), but the 12-year OS favored the patients receiving ABVD alone; 94% compared with 87% (p = 0.04). In the ABVD-alone arm, there were 12 deaths (six caused by HL, four caused by second cancers, and two caused by cardiac events). In the RT arm, there were 24 deaths (four caused by HL, 10 caused by second cancers, two caused by cardiac events, three related to infection, and five from other causes). Importantly, 12-year follow-up does not yet reflect the striking increase in second malignancies and cardiovascular disease that begins approximately 15 to 20 years after initial therapy with extended field RT, raising the concern that the survival curves will continue to separate with longer follow-up. Applicability of results of the CMT arm are limited by the use of STNI, an outdated approach that likely holds significantly increased risk of late toxicity compared with modern limited-RT fields. However, two important end points of this study are still highly relevant to current therapy. First, this study represents the largest prospective series of nonbulky, early-stage HL patients treated with ABVD alone providing a reliable estimate of long-term PFS with this approach. Second, this study helps addresses the number of cycles of chemotherapy for patients treated with ABVD alone. All patients were assessed by CT following two cycles of

| TABLE 1. Limited-Stage Hodgkin Lymphoma Risk Groups in Current Trials |
|-----------------|-----------------|-----------------|-----------------|
| **North America** | **EORTC** | **GHSG** | **NCIC HD.6** |
| **Unfavorable:** | | | |
| Age ≥ 50 | Any extranodal sites | Age ≥ 40 |
| MMR > 1/3 | MMR > 1/3 | Mixed cellularity or lymphocyte-deplete histology |
| Sites > 10 cm | | | |
| ≥ 4 nodal sites | ≥ 3 nodal sites | ≥ 4 sites |
| ESR ≥ 50 if asymptomatic or ≥ 30 if symptomatic | ESR ≥ 50 if asymptomatic or ≥ 30 if symptomatic | ESR ≥ 50 |
| **Favorable:** | | | |
| No risk factors | | | |

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; GHSG, German Hodgkin Study Group; NCIC, National Cancer Institutes of Canada; MMR, mediastinal mass ratio; ESR, erythrocyte sedimentation rate.
ABVD. Sixty-nine of 196 (35%) patients treated with ABVD alone achieved complete response (CR) after two cycles. For patients who achieved CR by CT after two cycles, the 5-year PFS was 95% compared with 81% for patients who did not achieve CR after two cycles (Fig. 1). This data suggests that for patients with limited-stage, nonbulky HL who achieve a CR by CT after two cycles of ABVD, a total of four cycles is adequate.

In an attempt to more precisely compare HD.6 with HD10 and HD11 because of differences in eligibility, staging, end points, and follow-up duration, investigators performed an individual patient-data comparison of the ABVD-alone arm of HD.6 with the two cycles of ABVD plus 20 Gy IFRT arm of HD10 and the four cycles of ABVD plus 30 Gy IFRT arm of HD11.23 Patients were included in this analysis if eligible for HD.6 and either HD10 or HD11. 406 patients were analyzed and time to progression (HR 0.44, 95% CI 0.24–0.78) and PFS (HR 0.71, 0.42–1.18) but not OS trended to being superior in patients treated with CMT (Table 2). For patients achieving a CR by CT after two cycles of ABVD, there was no improvement in outcome with RT. However, in patients who did not achieve a CR by CT after two cycles of ABVD, RT appears to improve PFS. At 8-years follow-up, there were 17 deaths (4.2%) in the 406 HD10/HD11 patients (five from HL and 12 from other causes) and nine (4.9%) in the 182 HD.6 patients (four from HL and five from other causes).

Several large European and North American trials are now evaluating interim PET-directed therapy in patients with early-stage HL, with the goal of minimizing chemotherapy cycles as well as avoiding or limiting RT. In the United Kingdom RAPID trial, patients with nonbulky stage I-IIA HL received three cycles of ABVD followed by a PET/CT.4 Patients with a negative scan (PET-) were randomized to IFRT or observation. All patients with a positive interim PET (PET+) scan received one additional cycle of ABVD and IFRT. Scans were considered “positive” if the London Deauville visual scale score was 3 or higher.26 602 patients were randomly assigned: 33% were stage I and 67% were stage II; 68% were favorable by GHSG criteria and 63% were favorable by EORTC criteria. 75% of patients (420/565) had a negative interim PET and were randomly assigned to IFRT (209 patients) or observation (211 patients). At a median follow-up of 48.6 months from randomization, PET+ patients (145/565) had an excellent 3-year PFS of 85.9% and OS of 93.9%. PET- patients randomly assigned to observation had a 3-year PFS of 90.7% compared with 94.5% for those randomly assigned to IFRT (CI: −10.7% to 1.4%) and 3-year OS rates of 99.5% versus 97%, respectively. 25 of 209 PET- patients assigned to IFRT did not receive the RT. For PET- patients, the 3-year PFS for the 184/209 patients who received IFRT according to protocol assignment was 97% compared with 90.7% for those randomized to observation (p = 0.03). Of the seven deaths in the IFRT arm, five occurred in patients who never received RT. Universal application of these trial results will require strict adherence to the London Deauville criteria used in the trial. Outcomes for PET- patients treated with three cycles of ABVD with or without RT were excellent, but because of the lower limit of the confidence interval of −10.7%, the trial does not rule out an advantage in PFS with the use of IFRT. Importantly, even the PET+ patients had an excellent outcome when treated with four cycles of ABVD and IFRT, arguing against altering chemotherapy regimens on the basis of the interim PET.

Interim analysis of the phase III H10 (EORTC/LYSA/FIL) trial, which accrued 1,137 patients with newly diagnosed stage I or II classical HL, were recently presented.3 Patients were randomly assigned to PET-directed or standard therapy with modest variations in the schema for favorable compared to unfavorable patients by EORTC criteria (Fig. 2). All patients received two cycles of ABVD followed by a PET scan. In the PET-directed group, patients with a negative interim PET (PET-) received from two to four more cycles of ABVD whereas patients with a positive interim PET (PET+) received two cycles of escalated BEACOPP and 30 Gy INRT (involved node RT). Patients on the standard arm received from one to two more cycles of ABVD and 30 Gy INRT re-

![FIG 1. Freedom from disease progression for patients achieving CR/CRu after two cycles of ABVD compared with those who did not achieve CR/CRu after two cycles. Copyright 2012, N Engl J Med.3 Reprinted with permission.](image-url)

### TABLE 2. Comparison of GHSG HD10/HD11 and NCIC HD.6

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HD10/11 CMT</th>
<th>HD.6 ABVD</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-yr progression-free survival</td>
<td>89%</td>
<td>86%</td>
<td>0.71</td>
</tr>
<tr>
<td>CR by CT after C2</td>
<td>87%</td>
<td>95%</td>
<td>2.8</td>
</tr>
<tr>
<td>Non-CR by CT after C2</td>
<td>88%</td>
<td>74%</td>
<td>0.35</td>
</tr>
<tr>
<td>8-yr overall survival</td>
<td>95%</td>
<td>95%</td>
<td>1.09</td>
</tr>
<tr>
<td>8-yr time to progression</td>
<td>93%</td>
<td>87%</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Abbreviations: GHSG, German Hodgkin Study Group; NCIC, National Cancer Institute of Canada; CMT, combined modality therapy; CR, complete response.
**BULKY, EARLY-STAGE HODGKIN LYMPHOMA**

The standard treatment for bulky early-stage HL outside the setting of a clinical trial remains CMT in most countries. Unfortunately, bulky mediastinal disease is most common in young women, the very population in which mediastinal RT holds the highest risk secondary to RT-induced breast cancers. Given the lower incidence of bulky HL, conducting randomized trials to evaluate the role of RT may not be feasible. Patients with bulky disease are represented in the unfavorable GHSG and EORTC early-stage studies, but will likely represent too small a group to perform subset analyses. The recent intergroup trial E2496 included 268 patients with stage I/II bulky HL of 854 total patients; patients were randomly assigned to ABVD or Stanford V. Patients on the ABVD arm with bulky mediastinal disease received from six to eight cycles of ABVD and modified IFRT (36 Gy) while patients on the Stanford V arm received modified IFRT (36 Gy) to sites larger than 5 cm in maximum transverse dimension at diagnosis plus spleen if involved on CT. For bulky patients on both arms, the 5-year failure-free survival and OS were 82% and 94%, respectively, with no difference between arms. Trials investigating the elimination or reduction of RT in this patient population should be compared with this data.

There is scant data regarding PET-directed therapy in limited-stage, bulky HL. A Canadian study of patients with residual abnormalities on CT scan after treatment used end of chemotherapy PET scans to guide consolidative RT. Patients with positive end of chemotherapy PET scans received consolidative RT but patients with negative end of chemotherapy PET scans received no further therapy. There was no difference in 3-year time to progression between the patients with bulky disease and those without bulky disease (86% vs. 91%, p = 0.71). Patients (160) in an Italian study of radiotherapy compared with observation for bulky disease (defined as at least 5 cm, median size 9 cm) and a negative end of chemotherapy PET showed an increase in relapses at 40 months in the patients who did not receive RT (14% vs. 4%).

Two additional studies may provide additional insight into the number of cycles of chemotherapy needed in those who achieve an early CR by PET/CT and are treated with chemotherapy only. First, the ongoing GHSG HD16 trial, which includes only patients with favorable stage I-II HL according to the GHSG criteria, randomly assigns patients to standard therapy with two cycles of ABVD and 20 Gy IFRT compared with an experimental arm, in which patients are stratified by interim PET following two cycles of ABVD: PET-positive patients receive 20 Gy IFRT while PET-negative patients receive no further treatment. The second study, CALGB 50604, recently completed accrual with enrollment at 162 patients with nonbulky stage I-II HL. All patients received two cycles of ABVD followed by an interim PET/CT scan. PET negative patients received two more cycles of ABVD while PET positive patients received two cycles of escBEACOPP plus IFRT.

Regardless of the interim PET scan result. In the favorable arms (444 patients), the 1-year PFS was 100% in the RT group compared with 94.5% in the PET- patients not receiving RT; ten patients relapsed (one in the standard arm and nine in the PET-directed arm). In the unfavorable arms (693 patients), the 1-year PFS was 97.3% in the RT group compared with 94.7% (no RT); 23 patients relapsed (seven in the standard arm and 16 in the PET-directed arm). On the basis of the study stopping rules, this study was discontinued early because of the difference in relapse rates between the consolidative RT and observation arms. The question remains whether these small differences in PFS in favor of RT warrant the use of even limited RT in all patients without a proven survival benefit.

CONCLUSION

Chemotherapy alone cures 85% to 90% of patients with nonbulky HL with long-term survival rates of close to 95% expected. Preliminary results of the RAPID and EORTC H10 studies show that CMT results in a 4% to 6% improvement in 1- and 2-year PFS rates over chemotherapy alone, even in the most favorable subset of patients who achieve an early CR by PET. This early disadvantage in PFS with chemotherapy alone is extremely unlikely to translate into a decreased overall survival. In fact, as was seen in the NCIC CTG/ECOG HD.6 trial, avoiding RT as initial therapy for nonbulky early-stage HL may be associated with improved survivals caused by fewer late effects. Efforts to decrease dose and fields of RT will likely result in fewer longer-term complications; however, because mediastinal nodes are involved in the majority of patients with HL, most patients will continue to have at
least modest exposure to the heart, lungs, and breasts regardless of efforts to administer only involved field or even involved nodal RT. For all patients with initial bulky disease or those with nonbulky disease but a positive early or end of treatment PET, consolidative RT (30 Gy) is indicated.

The optimal number of cycles of ABVD chemotherapy in the combined modality setting is from two to four depending on the GHSG risk group. As few as three cycles may be adequate when using chemotherapy only, if an early interim PET is negative, however this data has not yet been published. Outside the setting of a clinical trial, from four to six cycles of ABVD is appropriate. There is no clear role for more intensive chemotherapy such as BEACOPP in the initial treatment of early-stage HL. Whether all or part of the bleomycin doses can be safely eliminated from the ABVD regimen is under study in the setting of advanced stage HL, as well as in early-stage disease in the setting of CMT. Hopefully, limiting the number of cycles of ABVD will result in less late cardiac complications. The addition of new agents such as brentuximab vedotin into first-line therapy may result in higher cure rates with fewer complications when compared with ABVD or CMT.

Disclosures of Potential Conflicts of Interest

References


