One of the major efforts to improve the results of intensive therapy and autologous stem cell transplantation (ASCT) in multiple myeloma involves the integration of novel agents into the transplantation sequence. This can include their administration before, during, and after the transplantation procedure. Several phase 2 and 3 studies have evaluated the use of novel agents as part of induction therapy before transplantation to produce higher response rates and progression-free survival (PFS). Similarly, posttransplantation maintenance—or consolidation—with these agents consistently improves PFS. Survival benefits have been more difficult to demonstrate, although one trial using bortezomib before and after transplantation and a second using lenalidomide as maintenance have shown significantly longer survival times. This article reviews the different regimens used with ASCT, with an emphasis on randomized trials.

Introduction
High-dose chemotherapy and autologous stem cell transplantation (ASCT) has been an integral component of first-line therapy for younger multiple myeloma patients for more than 2 decades. For many years, this approach involved induction therapy with high-dose dexamethasone-based therapy—either VAD (vincristine, doxorubicin, and dexamethasone) or dexamethasone alone (dex)—followed by stem cell collection, high-dose melphalan, and ASCT. Data from randomized trials comparing ASCT with conventional chemotherapy demonstrated a significant benefit to ASCT in terms of progression-free survival (PFS) and, in some studies, overall survival (OS). Typically, a PFS of ~ 2 years and OS of 4-5 years can be anticipated with such an approach.1

Several prognostic factors for outcome after ASCT have been examined. The International Staging System (ISS), which uses the β2-microglobulin and albumin levels, is applicable to stem cell transplantation recipients. In addition, FISH cytogenetics have identified the presence of t(4;14) and del17p (p53 deletion) as adverse prognostic factors; patients with these abnormalities have a median PFS of only 8-9 months and a median OS of < 2 years with a single stem cell transplantation using older techniques.2 Newer prognostic systems using gene-expression profiling and proliferative indices have also been developed. These prognostic tools can identify the ~ 15% of newly diagnosed patients who succumb to their disease within 2 years, even when more modern transplantation regimens are used.3 Another prognostic factor for outcome, although not available at diagnosis, is the achievement of a high-grade remission post-ASCT. The achievement of complete remission (CR), near CR (nCR) (same as CR except for persistent immunofixation positivity), and/or very good partial remission (VGPR; ≥ 90% reduction in serum monoclonal protein) have each been associated with better PFS and OS in several analyses, although CR may be the most important of these.4,5 Using even more sensitive measures to detect minimal residual disease, such as multiparameter flow cytometry of BM, 2 groups have found that minimal residual disease negativity was the most important correlate of long-term PFS and OS, surpassing even immunofixation negativity in electrophoresis studies in one large Spanish study.6,7

More recently, highly efficacious novel agents, such as the immunomodulatory derivatives (IMiDs) thalidomide and lenalidomide and the proteasome inhibitor bortezomib, have been discovered and were initially used in relapsed and refractory patients. Many studies integrating these agents earlier in the disease course and in conjunction with ASCT have now been conducted and include their use in the following settings: (1) in pretransplantation induction therapy; (2) during the high-dose therapy itself; and (3) as posttransplantation measures such as “maintenance” and “consolidation” therapy. The next section focuses on the use of newer measures before and after the actual transplantation procedure, with an emphasis on the results of phase 3 studies.

Pre-ASCT induction therapy
Because numerous studies have noted that patients achieving CR, nCR, and/or VGPR after transplantation have longer remissions and survival times than those with lesser responses, it has been hypothesized that the achievement of such high-grade responses before ASCT would increase the number of patients in this favorable state after the procedure and would in turn confer a better PFS and OS. Numerous phase 2/3 trials of induction regimens capable of inducing high CR, nCR, and VGPR rates have been published, some of which are listed in Table 1.8-13 These trials have combined bortezomib and dexamethasone with conventional cytotoxic agents such as cyclophosphamide11,12 or pegylated liposomal doxorubicin,8 the novel agent lenalidomide,9,11 or both.10,11 They include the EVOLUTION trial, which is a phase 2 randomized trial comparing 4 different combinations, in which the combinations of bortezomib and dexamethasone with either lenalidomide or cyclophosphamide, but not both, yielded the best results with an acceptable toxicity profile (Table 1).11 The initial phase 1/2 study combining lenalidomide, bortezomib, and dexamethasone (RVD), conducted by the Dana-Farber group, produced an overall response rate of 100%, with a VGPR rate of 76% and a CR/nCR rate of 40%.9

One factor that complicates the interpretation of these trials is the lack of a standardized approach with respect to ASCT. Specifically, after several cycles, patients have the option of undergoing elective ASCT or remaining on all or some of the drugs in induction, a
Table 1. Results of phase 1/2 trials of 3- and 4-drug combination induction regimens in multiple myeloma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>ASCT, n</th>
<th>Response after 4 cycles ≥ PR/VGPR/nCR + CR, %</th>
<th>Best response ≥ PR/VGPR/nCR + CR, %</th>
<th>Response post-ASCT ≥ PR/VGPR/nCR + CR, %</th>
<th>PFS, % All patients</th>
<th>ASCT patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDD</td>
<td>40</td>
<td>30</td>
<td>85/57/37 (after 6 cycles)</td>
<td>97/77/57</td>
<td>92.5% (12 mo)</td>
<td>97.5% (12 mo)</td>
<td>75% (18 mo)</td>
</tr>
<tr>
<td>VD</td>
<td>66</td>
<td>28</td>
<td>75/5/6 (all)</td>
<td>100/67/40</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CR only.

Table 2. Phase 3 trials of novel induction regimens before ASCT

<table>
<thead>
<tr>
<th>Study/author</th>
<th>N</th>
<th>Induction regimen</th>
<th>ASCT, no</th>
<th>Consolidation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAG/Macro</td>
<td>204</td>
<td>thal + dex</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOVON-50/Lokhorst</td>
<td>536</td>
<td>VAD</td>
<td>1</td>
<td></td>
<td>thal</td>
</tr>
<tr>
<td>IFM 2005-02/Harousseau</td>
<td>482</td>
<td>TAD</td>
<td>1 or 2</td>
<td>Some patients entered into lenalidomide maintenance trial 2005-02</td>
<td>IFN</td>
</tr>
<tr>
<td>HOVON-65/GMMG-HD4/Sonneveld</td>
<td>613</td>
<td>BD or VAD</td>
<td>1 or 2</td>
<td>thal 50 mg/d</td>
<td></td>
</tr>
<tr>
<td>GIMEMA MMY-3006/Cavo</td>
<td>447</td>
<td>PAD</td>
<td>2</td>
<td>VTD</td>
<td>B 1.3 mg/m² q 2 weeks</td>
</tr>
<tr>
<td>PETHHEMA/GEM05MEN0S65/Rosinol</td>
<td>306</td>
<td>thal + dex</td>
<td>1</td>
<td>thal + dex</td>
<td></td>
</tr>
<tr>
<td>IFM 2007-02/Moreau</td>
<td>199</td>
<td>thal + dex</td>
<td>1</td>
<td>VBMCP/VBAD/B</td>
<td></td>
</tr>
</tbody>
</table>

Several large phase 3 trials comparing novel combinations with older induction regimens followed by ASCT in all patients have now been reported. However, it can still be difficult to isolate the impact of novel induction regimens on the posttransplantation outcome, particularly OS, because many trials also include maintenance and/or consolidation measures post-ASCT. In addition, effective salvage therapies are usually available after disease progression in the control arm, and therefore OS may also be extended in these patients. Table 2 lists the design of several key phase 3 trials evaluating the following novel induction regimens followed by ASCT: thalidomide + dex (thal + dex) by the MAG group,14 thalidomide + Adriamycin + dex (TAD) in the HOVON-50 trial,15 bortezomib + dexamethasone (BD) in the IFM 2005-01 trial,16 bortezomib + Adriamycin + dexamethasone (PAD) in the Dutch/German HOVON MM-65/GMMG-HD4 trial,17 bortezomib + thalidomide + dexamethasone (VTD) in the Italian GIMEMA trial,18 VBMCP/VBAD/B (vincristine + carmustine + melphalan + cyclophosphamide + prednisone/vincristine + carmustine + doxorubicin + dexamethasone/bortezomib) in the 3-arm Spanish PETHHEMA/GEM05MEN0S65 trial,19 and lower-dose bortezomib + thal + dex (vTD) in the IFM 2007-02 trial.20 The comparator was VAD in the first 3 trials, thal + dex in the Italian trial by Cavo et al, and BD in the most recently conducted IFM trial by Moreau et al. The results are summarized in Table 3. Although, as mentioned above, the use of posttransplantation therapy complicates the interpretation of the role of induction therapy, the post-ASCT CR/nCR and ≥ VGPR rates are unprecedented at 30%-60% and 60%-85%, respectively, and the median PFS in these trials is significantly higher than in the control arm and is in the range of 3 years. Despite these favorable findings, the only trial to demonstrate a statistically significant improvement in OS using novel agents in conjunction with ASCT is the HOVON MM-65/GMMG-HD4 study, in which bortezomib was used both before and after ASCT.17

Table 2. Phase 3 trials of novel induction regimens before ASCT

<table>
<thead>
<tr>
<th>Study/author</th>
<th>N</th>
<th>Induction regimen</th>
<th>ASCT, no</th>
<th>Consolidation</th>
<th>Maintenance</th>
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<td></td>
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<td>1</td>
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<td></td>
</tr>
</tbody>
</table>
Several of these studies reported details about subset analysis. First, in the IFM 2005-01 trial, a significant advantage was observed in patients with ISS stage II-III disease who received BD versus VAD before ASCT.16 Second, improvements in PFS and OS were observed in the patients with t(4;14) who were given BD.21 The results of t(4;14) patients in this and other studies is illustrated in Table 4. Taken in aggregate, the outcomes of patients with this cytogenetic abnormality fared better with the use of a bortezomib-based induction regimen versus VAD, but the results were still less favorable than in patients without t(4;14).2,21-25 One explanation for the inferior results using alkylating agents—including high-dose melphalan—in this t(4;14) subgroup has been proposed by Scottsdale Mayo Clinic group. They found that the MMSET dysregulation that characterizes many t(4;14) patients results in aberrant responses to DNA-damaging agents such as melphalan.26 An ongoing Canadian phase 2 trial in newly diagnosed patients with t(4;14) is based on bortezomib combination therapy administered for 1 year, followed by dexamethasone maintenance without planned ASCT. Interim results indicate that the median PFS is ~2 years, which compares favorably with the results of ASCT programs in t(4;14) disease.27

Table 4. Results of ASCT trials in myeloma patients with t(4;14)

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Type of study</th>
<th>N</th>
<th>Induction</th>
<th>ASCT, no</th>
<th>Consolidation/maintenance</th>
<th>PFS, mo</th>
<th>OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang/20042</td>
<td>Case series</td>
<td>16</td>
<td>VAD or dex</td>
<td>1</td>
<td>±thalidomide maintenance</td>
<td>9.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Gertz/200522</td>
<td>Case series</td>
<td>26</td>
<td>N/A</td>
<td>1</td>
<td>N/A</td>
<td>8.2</td>
<td>18.3</td>
</tr>
<tr>
<td>Moreau/200723</td>
<td>IFM tandem transplantation trials 99-02, 99-03, and 99-04</td>
<td>100</td>
<td>VAD</td>
<td>2</td>
<td>±thalidomide maintenance in low-risk patients on IFM 99-02 trial</td>
<td>21</td>
<td>41.4</td>
</tr>
<tr>
<td>Avet-Loiseau/201021</td>
<td>Phase 3 and case series</td>
<td>106</td>
<td>BD</td>
<td>1 or 2</td>
<td>±lenalidomide maintenance for ~30% of patients on IFM 2005-02 trial</td>
<td>28</td>
<td>63% (4 y)</td>
</tr>
<tr>
<td>Cavo/201024</td>
<td>Phase 3</td>
<td>110*</td>
<td>VTD</td>
<td>2</td>
<td>VTD consolidation/dex maintenance thal + dex</td>
<td>69% (3 y)</td>
<td></td>
</tr>
<tr>
<td>Goldschmidt/201025</td>
<td>Phase 3</td>
<td>38</td>
<td>PAD</td>
<td>2</td>
<td>B maintenance thalidomide maintenance</td>
<td>36</td>
<td>76% (3 y)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VAD</td>
<td>2</td>
<td>thalidomide maintenance</td>
<td>18</td>
<td>39% (3 y)</td>
</tr>
</tbody>
</table>

*Includes t(4;14) patients with and without del 17p.
and highly convenient first-line regimen, does not significantly compromise stem cell collection as long as patients are mobilized with chemotherapy and hematopoietic growth factors, and produces a high overall response rate after 4 cycles.

The other noteworthy approach to induction before ASCT includes the Total Therapy programs developed by the University of Arkansas myeloma group, although they have not been compared with less intensive transplantation approaches in randomized trials. In the Total Therapy 2 trial, newly diagnosed patients were treated with 2 cycles of D-PACE (dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide), followed by tandem ASCT, further D-PACE consolidation and maintenance with IFN for 1 year, and dexamethasone until progression. These patients were randomized to either thalidomide throughout the entire program, or to no thalidomide. Remission rates before and after ASCT were higher in the thalidomide group, and PFS was significantly longer in this arm. Although this advantage did not translate into a survival benefit for the thalidomide arm due to a shorter survival after myeloma progression, longer follow-up revealed that higher-risk patients (those with cytogenetic abnormalities by metaphase karyotyping) had a significant survival benefit with thalidomide. The next study from this group, Total Therapy 3, builds on this experience by incorporating bortezomib, thalidomide, and dexamethasone (VTD) as VTD-PACE given before and after tandem ASCT. With this approach, the response rate, PFS, and OS have improved further in newly diagnosed patients with low-risk disease as defined by gene-expression profiling. Nevertheless, as mentioned above, ~15% of patients experience early treatment failure and death; optimal treatment of this subset remains challenging and will be the target of future cooperative trials.

Our own group at Princess Margaret Hospital has selected the 3-drug bortezomib regimen CyBoRd weekly as the pre-ASCT induction regimen, consisting of weekly bortezomib 1.5 mg/m² on days 1, 8, 15, and 22 of a 28-day schedule, along with weekly oral cyclophosphamide 300 mg/m² and dexamethasone, the latter initially in a pulse fashion for cycles 1 and 2, and then weekly for cycles 3 and 4. Advantages include the lower incidence of toxicity (peripheral neuropathy and thrombocytopenia) and improved patient convenience compared with biweekly bortezomib. The cost and remission rates, including a CR/nCR rate of almost 50% after 4 cycles, compare favorably with other 3-drug bortezomib-containing regimens that contain an IMiD. However, despite the high remission rates pre-ASCT in all subgroups, it is insufficient, in the absent of post-ASCT measures, to confer a longer advantage in PFS or OS in high-risk subgroups such as t(4;14).

In summary, all of the regimens above establish the superiority of regimens containing novel agents in terms of achieving higher response rates, including CR/nCR rates, after induction therapy. Thalidomide-based regimens such as thal + dex and TAD are associated with the usual toxicities seen with this ImiD—peripheral neuropathy, constipation, fatigue, and increased risk of venous thromboembolism—and produce responses on the lower end of the spectrum. In addition, a benefit on post-ASCT status has not been established. The highest response rates are observed using 3-drug regimens, particularly those containing both bortezomib and an IMiD, and the RVD combination developed by the Dana Farber group has been selected as the test arm of several large cooperative group trials. Bortezomib-associated peripheral neuropathy, which may be painful, can occur when this drug is part of induction. The use of less intensive bortezomib dosing, either as 1.0 mg/m² biweekly doses in the vTD regimen or 1.5 mg/m² weekly doses in the CyBoRd regimen, appears to decrease the chance of grade 3 or 4 neuropathy without compromising response rates, but only the former combination has been evaluated in a randomized fashion. In addition, antiviral prophylaxis against herpes zoster is required during induction with bortezomib to avoid the risk of reactivation during therapy.

Post-ASCT therapy

A myeloma consensus panel recently defined maintenance therapy as any treatment administered after the completion of induction therapy in patients whose disease is either responsive or nonprogressive at that time, with the goal of prolonging survival. Earlier ASCT studies used less potent agents such as corticosteroids or IFN-α with variable results and, particularly with IFN-α, toxicity concerns. The availability of more effective novel agents has generated a renewed interest in maintenance therapy in this disease, and several phase 3 trials have now been reported.

The concept of post-ASCT consolidation therapy was initially introduced into myeloma treatment as part of the Total Therapy programs developed by Dr. Barlogie at the University of Arkansas and, similar to acute leukemia therapy, referred to the administration of additional courses of intensive chemotherapy after induction, ideally after the patient had achieved a CR. However, the definition of consolidation is not standardized in myeloma, and the difference between consolidation and maintenance is not always clear. Regardless, the goal of consolidation therapy in myeloma is to improve the depth and length of posttransplantation response. Maintenance therapy

IMiDs

The IMiDs thalidomide and lenalidomide have been the most frequently studied maintenance drugs, given their ease of oral administration and established antmyeloma efficacy. Table 5 summarizes the 7 randomized trials of post-ASCT thalidomide maintenance. These studies differ with respect to induction regimen used, use of single or tandem transplantation before maintenance, dose and duration of thalidomide, concomitant use of corticosteroids, and comparator arm. Despite these differences, thalidomide maintenance was consistently associated with a longer PFS, although the benefit on OS was variable.

In addition to the PFS benefit, several observations are evident from these trials. First, in some instances, thalidomide improved the depth of response and therefore functioned as a therapeutic agent, rather than simply providing a stabilizing effect on the myeloma burden. Second, because none of these trials mandated therapy for progressive myeloma, the possibility that heterogeneity in such treatment influenced survival outcomes has been raised. For example, a statistical exercise performed using the British MRC IX dataset, in which patients of all ages were randomized to either thalidomide or no therapy after induction therapy (which included ASCT in the younger patients), demonstrated a significantly longer survival in patients given thalidomide maintenance if they subsequently had access to novel agents at the time of myeloma progression, but not in those who were treated only with further thalidomide or older cytotoxic agents. Other phase 3 trials, including the Therapy 2 trial, the HOVON-50 trial, and the NCIC trial (Table 3), have attributed the absence of a survival advantage to a shorter life expectancy after relapse in patients who received thalidomide maintenance. The NCIC trial recorded the treatment administered at the time of disease progression and found
similar access to lenalidomide and bortezomib in both arms of the study. Despite this, the OS was still not significantly improved in the thalidomide arm (not yet reached versus 5 years in the thalidomide plus prednisone vs observation arm, respectively, at a median follow-up of 4 years; hazard ratio 1.29 [95% confidence interval 0.89-1.88]; *P = .188*).36 This finding raises the possibility that the myeloma cell population might be intrinsically more resistant after exposure to maintenance therapy.

Several investigators have tried to identify the patient subgroups most likely to benefit from maintenance thalidomide. In a post-hoc analysis of the IFM 9502 trial, Attal et al determined that the beneficial effect of maintenance therapy was limited to patients who had achieved VGPR and whose myeloma cells lacked the cytogenetic abnormality del13q by FISH. This trial excluded patients with del13q.32

More recently, lenalidomide maintenance therapy has been studied, and 2 randomized trials comparing low doses of lenalidomide (10-15 mg/d) with placebo after ASCT have completed accrual: the CALGB-100104 trial in North America and the IFM 2005-02 study in France.37,38 The induction regimens were not specified in these studies, and the French trial included some patients who had undergone tandem ASCT. In addition, the IFM trial administered the full therapeutic dose of lenalidomide (25 mg) for 2 months as consolidation to all patients shortly after ASCT and before randomization to the lower maintenance dose, whereas the CALGB study simply commenced maintenance lenalidomide at a dose of 10-15 mg on days 60-90 post-ASCT.37,38 Both of these trials reported an aggressively multiphase program, later described a significantly better survival in the thalidomide arm in patients considered high-risk due to the presence of cytogenetic abnormalities defined by conventional karyotyping.30,31 Due to the varied criteria used to subclassify patients, a definitive conclusion about the optimal use of thalidomide maintenance remains uncertain.

Despite the longer PFS with thalidomide maintenance, this approach has not gained uniform acceptance outside of clinical trials due in large part to the toxicity of this drug. Peripheral neuropathy, sedation, and constipation are common, and rashes and an increased risk of venous thromboembolism may also occur. These side effects lead to a reduction in quality-of-life parameters and premature discontinuation even when low doses are used. In practical terms, patients can usually tolerate the drug < 1 or 2 years before side effects become prohibitive.15,35,36

| Table 5. Post-transplantation maintenance therapy with IMiDs |
|-----------------|------------------|------------------|------------------|------------------|------------------|
| **Induction therapy** | Daily maintenance dose, mg | Comparator | Duration of maintenance | CR rate, % | PFS/EFS, % | OS, % |
| **Thalidomide trials** |  |  |  |  |  |  |
| Attal/200632 (IFM 95-02) | N | VAD | thal 400 | thal - | thal+ | Obs | Until prog | 67 55 | 52 36 | 87 77 |
| Spencer/200633 (Australia) | N/A | thal 200 + prednisolone | dex | thal - | thal+ | Prednisolone | 12 mo | 63 40 | 42 23 | 86 75 |
| Maiolino/200834 (Brazil) | N/A | thal 200 + dex | dex | thal - | thal+ | thal 100 | 12 mo | 42 25 | (median F/U 15 mo) | 65 74 |
| Barlogie/200630 (Total therapy 2) | N/A | thal 400 | No thal | thal - | thal+ | IFN | Until prog | 62 43 | 62 43 | 57 44 |
| Morgan/201035 (MRC IX) | N/A | thal 100 | Obs | thal - | thal+ | Obs | Until prog | N/A | N/A | N/A |
| Lokhorst/201015 (HOVON-50) | N/A | thal 50 | IFN | thal - | thal+ | IFN | Until prog | 31 23 | 34 22 | 73 60 |
| Stewart/201024 (NCIC MY.10) | N/A | thal 200 + prednisone | Obs | thal - | thal+ | Obs | 48 mo | N/A | N/A | 32 14 |
| **Lenalidomide trials** |  |  |  |  |  |  |
| Attal/201037 (IFM 2005-02) | N | VAD or BD | len 25 days | len 25 days | len 25 days | len 25 days | Until prog | 23 | 25 | 42.3 | 21.8 | 81 81 |
| McCarthy/201038 (CALGB 100104) | N | len 32% | len 10–15 | len 10–15 | len 10–15 | len 10–15 | Placebo | N/A | N/A | 42 24 | 81 81 |

EFS indicates event-free survival; F/U, follow-up; N/A = not available; obs, observation; prog, progression.

Hematology 2011 201
excellent PFS rate of 42 months in the lenalidomide arm, with a
significant survival benefit now observed in the CALGB study in the
most recent analysis presented at the International Myeloma Work-
shop in 2011.\textsuperscript{39} Toxicity was acceptable and only 6% of patients in
the IFM trial and 13% in the CALGB trial discontinued lenalido-
mide maintenance early, before myeloma progression, in contrast to
the experience with thalidomide. Neutropenia was the most com-
mon side effect noted, but febrile neutropenia was rare.\textsuperscript{37,38}

An unexpected finding from the lenalidomide maintenance trials
was a modest increase in the incidence of secondary cancers,
including secondary myelodysplastic syndromes (MDS) and/or
acute myelogenous leukemia (AML): \( \sim 6.5\% \) in both studies
compared with 1.6%-2.6% in the placebo groups for all tumor
types.\textsuperscript{37,38} Intense investigation regarding the risk of secondary
cancers in recipients of lenalidomide in various disease settings has
ensued. Interpretation of the risk is complicated by the recent
recognition that new primary malignancies, particularly MDS/
AML, occur with increased frequency in plasma cell disorders
such as monoclonal gammopathy of undetermined significance in
the absence of cytotoxic/genotoxic therapy. In addition to a
suspected intrinsic risk of second cancers in this disease,
antimyeloma drugs other than lenalidomide may predispose to
secondary malignancies. In this regard, the IFM maintenance
study identified prior exposure to the DCEP (dexamethasone,
cyclophosphamide, etoposide, and cisplatin) regimen as an adverse
prognostic factor for the development of secondary malignancies
while on lenalidomide. This regimen is, fortunately, unlikely to be
used commonly in the future before ASCT, because it did not confer
any improvement in posttransplantation outcome when evaluated in
an IFM phase 3 trial. Moreover, other alkylating agent regimens
used more often in myeloma therapy have long been known to be
associated with a low but measurable risk of MDS/AML and,
because myeloma patients live longer due to improved therapy,
this risk is likely to become more apparent. It appears that the risk of
secondary cancers in patients treated with lenalidomide is quite
small and is likely counterbalanced by the strong antimyeloma
efficacy of this drug when used in the maintenance setting.

The risk of secondary cancers when novel agents other than
lenalidomide are used for maintenance after ASCT has not been
rigorously evaluated, but appears to be low. For example, the NCIC
trial reported only 1 fatal secondary cancer in the thalidomide plus
prednisone maintenance arm (0.6%) versus 2 in the observation arm
(1.2%).\textsuperscript{38} One other potential advantage of thalidomide over lenalido-
mide maintenance therapy is the anticipation that more therapeutic
options will be available when relapse eventually occurs. Thalido-
mide-treated patients will likely subsequently benefit from both
lenalidomide- and bortezomib-based regimens, because even pa-
tients refractory to thalidomide have been shown to have satisfac-
tory remission rates and remission durations with lenalidomide.
Although the data are limited, the converse may not be true,
because, in our experience, patients progressing on lenalidomide
who are subsequently treated with thalidomide usually experience
minimal benefit. Avoiding the most effective agent in the hopes of
maximizing options for relapse is not a common approach in any
malignancy, however, and has not been formally tested as a
treatment strategy in well-designed trials. In addition, it will be
important to determine whether patients given lenalidomide mainte-
nance will respond to increasing the dose of lenalidomide to the
usual therapeutic dose and adding dexamethasone at the time of
myeloma progression.

\textbf{Bortezomib}

The HOVON-65/GMMG-HD4 trial described above (Table 2) was
the first to report results using posttransplantation bortezomib
maintenance. In this study, bortezomib 1.3 mg/m\textsuperscript{2} was given every
2 weeks for 2 years after PAD induction and 1 or 2 transplantations.
All outcomes were significantly better than the arm with VAD
induction and low-dose thalidomide maintenance 50 mg daily. After
ASCT, 57% of the patients randomized to bortezomib maintenance
started the drug; 27% required dose reductions and 9% discontinued
bortezomib due to toxicity. In the thalidomide arm, 67% of
post-ASCT patients randomized to thalidomide maintenance started
the drug, but 31% discontinued thalidomide due to toxic effects.
Multivariate analysis showed that bortezomib treatment was a
significant variable for OS.\textsuperscript{17}

\textbf{Consolidation therapy}

The use of consolidation therapy after ASCT has been evaluated in
3 recent phase 3 trials. The Italian trial by Cavo et al, which has
yielded some of the best outcomes of a transplantation program to
date, used the VTD regimen, which was also given for induction,
for 2 cycles after transplantation as a consolidation measure. The
control arm was given thal + dex without bortezomib for 2
months.\textsuperscript{17} As discussed above, the IFM 2005-02 trial designated
the use of single-agent lenalidomide given at the full therapeutic
daily dose of 25 mg for 2 cycles as a consolidation rather a mainten-
ance phase of treatment, followed by the lower maintenance dose
of lenalidomide until progression.\textsuperscript{37} The Nordic Myeloma Study
Group randomized ASCT patients at 3 months to either consolida-
tion with single-agent bortezomib administered biweekly in a
21-day cycle for 3 cycles, followed by a weekly dosing on days 1, 8,
and 15 of a 28-day cycle for 4 additional cycles or no therapy.\textsuperscript{40}
The use of bortezomib resulted in a rate of \( \geq VGPR \) of 70% compared
with 50% in the arm without consolidation \((P = .01)\); the PFS was
also improved, at 27 months from the time of randomization versus
20 months in the no-treatment group \((P = .02)\). The 2-year OS was
90\% in both groups.\textsuperscript{40}

These studies of post-ASCT maintenance and/or consolidation
indicate that the administration of each novel agent can delay
disease progression, although an OS benefit has not always been
realized. Currently, the superiority of any one particular post-ASCT
strategy using novel agents has not been established with absolute
certainty, although the phase 3 trials of lenalidomide maintenance
compared with placebo have demonstrated the longest PFS after
ASCT reported to date: \( > 3.5 \) years. The ongoing Clinical Trials
Network (CTN) trial in the United States will help to clarify the
benefit of different posttransplantation treatments, because it random-
izes patients after ASCT to proceed directly to lenalidomide
maintenance versus undergoing a second ASCT followed by
lenalidomide maintenance versus consolidation with RVD followed
by lenalidomide maintenance. Until further information is available,
the selection of the preferred approach will likely depend on issues
of toxicity and patient/physician preference. In the future, informa-
tion regarding efficacy in different disease subgroups and concerns
regarding long-term outcomes, such as secondary malignancies and
options for treatment for eventual relapse, will likely influence
post-ASCT management.

\textbf{Summary and conclusions}

Unlike many other hematologic malignancies, several new anti-
myeloma drugs have been introduced and have shown efficacy in phase
2/3 trials when integrated before and after ASCT. This favorable
situation, however, has produced uncertainty for hematologists regarding the best approach to select for transplant-eligible myeloma patients. In the absence of consistent and reproducible survival benefits with a given approach, the physician has considerable flexibility in choosing induction and maintenance/consolidation regimens, but should be guided by expectations of a 70%-80% high-grade remission rate (ie, ≥ VGPR) after ASCT and a median posttransplantation PFS of at least 3 years. Based on the available data, albeit limited, patients with t(4;14), and likely also those with other poor prognostic factors such as high ISS score and/or plasma cell leukemia, should receive bortezomib-based regimens at least for induction. To date, the best reported results with respect to PFS have used novel agents in induction followed by lenalidomide as maintenance after ASCT, and the ongoing CTN trial will help to determine the contribution of a second ASCT or consolidation therapy to lenalidomide maintenance. Further information is required to clarify issues regarding the management of posttransplant relapse in patients exposed to the 2 most potent novel agents, bortezomib and lenalidomide, as part of first-line therapy, as well as to evaluate the risk of late untoward effects such as secondary malignancies as myeloma patients experience longer survival times. Innovative measures will be needed to improve the outcome of the 15% of patients with very high-risk features at diagnosis, such as del17p and/or unfavorable gene-expression profiling results.

Disclosures
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Correspondence
Donna E. Reece, MD, Princess Margaret Hospital, 610 University Ave, Toronto, Ontario M5G 2M9 Canada; Phone: (416) 946-2824; Fax: (416) 946-6546; e-mail: donna.reece@uhn.on.ca.

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