

## Treatment of Myeloma: Cure vs Control

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Although not often openly acknowledged, “cure vs control” is the dominant philosophical difference behind many of the strategies, trials, and debates related to the management of myeloma. Should we treat patients with myeloma with multidrug, multitransplant combinations with the goal of potentially curing a subset of patients, recognizing that the risk of adverse events and effect on quality of life will be substantial? Or should we address myeloma as a chronic incurable condition with the goal of disease control, using the least toxic regimens, emphasizing a balance between efficacy and quality of life, and reserving more aggressive therapy for later?

To be sure, if cure were known to be possible (with a reasonable probability) in myeloma, it would undoubtedly be the preferred therapeutic goal of most patients and physicians. But this is not the case. Myeloma is generally not considered a curable disease; however, new definitions of cure have been suggested, including *operational cure*, which is defined as a sustained complete response (CR) for a prolonged period.<sup>1,2</sup> Cure vs control is debated because the strategies currently being tested are not truly curative but rather are intended to maximize response rates in the hope that they will translate into an operational cure for a subset of patients.

For decades, the treatment of myeloma was restricted to conventional chemotherapy with alkylators and corticosteroids, and the question of cure vs control never arose. The response rate with alkylators and corticosteroids was only about 50%, and CR<sup>3,4</sup> was rare. Cure was never a goal of therapy because it was assumed to be unattainable. Instead, the goal was to control the disease as much as possible, providing the best quality of life to the patient for the longest duration by judicious, intermittent use of the 2 available classes of active chemotherapeutic agents.

In the 1990s, high-dose therapy with autologous stem cell transplant (ASCT) became part of standard practice

when it was found to prolong survival compared with conventional chemotherapy.<sup>5-7</sup> Subsequently, bisphosphonates were found to be effective in decreasing the incidence of bone lesions.<sup>8,9</sup> In the past decade, thalidomide,<sup>10</sup> bortezomib,<sup>11-13</sup> and lenalidomide<sup>14,15</sup> emerged as effective agents for the treatment of myeloma, producing spectacular results in combination with other known agents in terms of response rate, CR rate, progression-free survival (PFS), and (more recently) overall survival. Numerous combinations have been developed, resulting in a veritable alphabet soup of clinical trials,<sup>16</sup> and drug combinations are vying with each other for the highest response rate (and prominence).<sup>17,18</sup> The results obtained with new combinations have indeed been remarkable and have prompted a relatively new philosophy of treating myeloma with the goal of potential cure rather than disease control. These philosophical differences underpin the various clinically relevant debates regarding myeloma currently confronting patients and physicians. In fact, it is not uncommon to find that well-meaning investigators interpret the same clinical trial data in opposite ways because they ascribe to different philosophies (cure vs control).<sup>19</sup> Although this commentary focuses on myeloma, the cure-vs-control debate may be relevant to other similar chronic malignant and nonmalignant disorders.<sup>20-28</sup>

### COMPLETE RESPONSE

If cure is the goal, then CR is the critical first step. High CR rates require greater intensity of therapy. Although overall survival is usually better in patients who achieve CR than in those who do not, this could be more a reflection of underlying disease biology, with CR functioning as a prognostic marker for those with inherently favorable disease biology. It is far from clear whether increasing or intensifying therapy for patients without CR until such status is achieved actually prolongs overall survival. In other words, although the achievement of CR is a favorable prognostic factor, modifying therapeutic strategy with the sole purpose of achieving CR in a patient who is otherwise responding well to therapy is of unproven value.

The following 6 important caveats concerning CR should be kept in mind.<sup>29</sup> First, CR is a surrogate marker for *improved overall survival* and as such is the means to a goal, not the ultimate goal. Second, in clinical trials, CR is often but not consistently associated with better overall

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survival.<sup>30-33</sup> Third, trying to achieve the highest CR rate may cause harm because overall survival is a composite end point based not just on efficacy but on safety as well. High CR rates frequently require more aggressive, more toxic therapy. Fourth, a small monoclonal protein (minimal residual disease) is not in itself clinically important and is commonly present in the general population in the form of monoclonal gammopathy of undetermined significance.<sup>34-36</sup> In many patients, reduction of myeloma to a state similar to monoclonal gammopathy of undetermined significance (near-CR or very good partial response) may be all that is required for best long-term survival. Fifth, CR in myeloma, unlike CR in large cell lymphoma, reflects profound tumor reduction but not elimination of the clone and thus is not a true surrogate for cure. Finally, myeloma may not be a single disease cytogenetically<sup>37-42</sup>; achievement of a CR seems particularly important in the 15% of patients with high-risk myeloma, whereas survival is similar in patients without high-risk features who have and have not achieved CR.

For those who embrace cure as the goal of therapy, these caveats aside, CR is a desirable and important first step. For those who favor treating myeloma as a chronic disease with the goal of disease control, CR remains just as desirable but is not the goal.

#### COMBINATION VS SEQUENTIAL THERAPY

As the number of active chemotherapeutic agents has increased, so too has the number of studies evaluating the efficacy and safety of various combinations of these agents. Several comparative trials of 2-drug vs 3-drug combinations (eg, lenalidomide-dexamethasone vs bortezomib-lenalidomide-dexamethasone) are being conducted. In these trials, the 3-drug combination in all likelihood will produce a higher CR rate and PFS compared with the 2-drug regimen. However, the effect on overall survival is often not clear. Patients who receive a 2-drug regimen as initial therapy still have the third drug available for relapse, whereas those who receive the 3-drug regimen do not. Those who are treated with the 2-drug regimen will likely endure fewer adverse events. If cure is the goal, then the best chance for eradicating all malignant cells is early in the disease course with the best available multidrug combination. If disease control is the favored approach because cure is not considered to be possible with currently available drugs, then starting with the 2-drug combination makes sense, reserving the third agent for relapse. Clearly, trials testing 2-drug vs 3-drug combinations should have overall survival as the primary end point. However, such is often not the case because the required sample size is too large. As a result, decisions are usually made on the basis of one's underlying bias in the cure-vs-control debate.

#### AUTOLOGOUS STEM CELL TRANSPLANT

Currently, the most important question for patients with myeloma is whether ASCT as initial therapy is still needed with the availability of several new active antimyeloma drugs. Autologous stem cell transplant is remarkably safe and can be done on an outpatient basis in 40% of patients.<sup>43</sup> It improves CR rates and prolongs median overall survival in myeloma by approximately 12 months.<sup>5,7,44,45</sup> Given the promising results obtained with a single ASCT, double (tandem) ASCT was investigated. With double ASCT, patients receive a second ASCT shortly after recovery from the first procedure.<sup>6,46</sup> A French randomized trial found significantly better survival in recipients of double vs single ASCT.<sup>47</sup> Results of ASCT can be further improved by incorporating new active chemotherapeutic agents into the transplant strategy, resulting in extraordinarily high CR rates, PFS, and survival. If cure is the goal, double ASCT incorporating novel chemotherapeutic agents before, during, and after ASCT is the ideal therapeutic regimen.<sup>48</sup>

In contrast, impressive results can be obtained with a strategy of long-term oral therapy, with consideration to patient preference regarding the timing (early vs at the time of relapse) and number (1 vs 2) of transplants.<sup>49</sup> If disease control is the goal, then it is desirable to have a treatment algorithm that takes into account patients' needs, goals, and attitudes toward overall survival vs quality of life. Physicians who choose this approach look to supporting data from 3 randomized trials showing that survival is similar whether ASCT is done early (immediately after induction therapy) or delayed (at the time of first relapse),<sup>32,50,51</sup> as well as to trials that have not shown a clear overall survival advantage with double ASCT.<sup>52-54</sup> Physicians who prefer this approach also use as supporting evidence a Spanish randomized trial in which patients who responded to induction therapy had similar overall survival and PFS with either ASCT or continued chemotherapy,<sup>55</sup> suggesting that patients with disease refractory to induction therapy benefit the most from ASCT.<sup>56,57</sup>

#### ALLOGENEIC TRANSPLANT

Only a small percentage of patients with myeloma meet the eligibility requirements for allogeneic transplant: appropriate age, availability of a human leukocyte antigen-matched sibling donor, and adequate organ function.<sup>58</sup> The high treatment-related mortality, mainly related to graft-vs-host disease, has made conventional allogeneic transplants unacceptable for most patients with myeloma, even though it is currently the only potentially curative approach. Several recent trials have been conducted using ASCT followed by a reduced-intensity ASCT (nonmyeloablative or mini-allogeneic transplant).<sup>59</sup> The main concerns with this approach are relatively high early mortality and morbidity;

treatment-related mortality is approximately 15%, and there is a high risk of acute and chronic graft-vs-host disease. Further clinical trials have resulted in conflicting results.<sup>60,61</sup> For those who favor a curative approach, the data available and the potential for cure are sufficient to justify this therapy outside of a clinical trial setting in high-risk patients. In contrast, for others this form of therapy cannot be justified outside of a clinical trial until further data are available.

### CURE OR CONTROL?

The cure-vs-control debate colors the approach to the treatment of smoldering (asymptomatic) disease, duration of therapy, choice of drugs, and many other clinical decisions in myeloma. It also substantially affects the interpretation of study results and the approach to the care of patients with myeloma.

So, should it be cure or control in myeloma? In the setting of designing and conducting clinical trials, *both* strategies should be explored simultaneously. Some patients desire a potentially curative approach and are not greatly concerned about the risk of adverse events, whereas others think quality of life is more important than overall survival and are unwilling to risk their quality of life for a potential cure. Having clinical trials available to cater to both types of patients is important. For example, the Mayo Clinic myeloma group is currently pursuing an approach with single-agent lenalidomide as initial therapy for myeloma with other drugs added as needed, with an emphasis on quality of life and disease control. At the same time, we are testing a multidrug combination strategy with 4 active agents in the attempt to develop a curative “myeloma CHOP (cyclophosphamide-hydroxydaunomycin [doxorubicin]-vincristine [Oncovin]-prednisone)” regimen; the CHOP regimen has been used successfully to cure large cell lymphoma. Thankfully, many centers have a similar selection of trials targeting both options.

Outside of a clinical trial setting, I prefer disease control as the treatment goal, except in selected high-risk patients in whom an aggressive approach to achieving CR may be the only route to long-term survival.<sup>62-65</sup> The disease control approach involves targeting very good partial response (minimal residual disease) rather than CR as a goal; using limited, less intense therapy first and moving to more aggressive approaches as need arises (sequential approach); allowing patients to help determine the timing and number of transplants (patient choice); and avoiding allogeneic transplant. Although cure is the ultimate goal of our long-term research, we need more data from randomized trials before resorting to highly intense therapy that is more toxic and unlikely to lead to a cure outside the setting of a clinical trial. On this one point, proponents of both cure and control can agree.

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