Please summarize the concept of “cure versus control” in myeloma.
This is a very important subject. Myeloma is a devastating and complicated disease that is still not curable. All of us who treat myeloma patients recognize the gravity of the situation. If we had treatments for myeloma with a reasonable probability of cure and acceptable toxicity, there would not be a cure-vs-control debate. All of us would surely choose cure. But the available treatment options, while excellent, fall far short of being curative. Therefore we must weigh the pros and cons of cure versus control treatment strategies. Cure-vs-control is the key philosophical point of debate among physicians and patients about the management of myeloma. Unlike certain hematologic malignancies, such as large cell lymphoma, myeloma cannot be cured as traditionally defined, at least for the vast majority of patients. So, should we treat myeloma patients aggressively in an attempt to potentially cure the disease, knowing that this is unlikely and that aggressive therapies come with the risk of adverse events and substantially decreased quality of life? Or, should we treat myeloma as an incurable but chronic, manageable condition with the goal of controlling the disease for as long as possible, balancing efficacy and quality of life?
The cure approach involves multi-agent therapy applied in combination early
in the disease course with a goal of achieving a complete response (CR), and then sustaining it. The control approach involves administering treatments in a sequential approach with a goal of preventing disease progression rather than CR, but emphasizing low toxicity and quality of life. On the one hand, proponents of a curative approach generally feel that therapies that work in high-risk disease tend to work even better in low-risk disease and therefore should be used for all patients with myeloma. On the other hand, proponents of the control approach employ an individualized, risk-adapted approach, targeting CR for high-risk patients with aggressive therapy, and a sequential, gentler therapy for low-risk patients with an emphasis on avoiding serious toxicity (such as neuropathy) at all costs since low-risk patients are destined to live an average of 7-10 or more years regardless of what the sequence of treatment is.

The cure-vs-control debate has an impact on most clinical decisions in both symptomatic and asymptomatic myeloma, including choice of drugs and intensity and duration of therapy. It also colors our interpretation of clinical trial results, with well-meaning investigators interpreting the same clinical trial data in opposite ways depending on whether they subscribe to the cure or control philosophy as they approach the care of patients with myeloma. Interestingly, the journal Nature recently published an article which called for a change of strategy in the war on cancer. The author makes the point that trying to control the disease may prove to be a better plan biologically than striving to cure it. He draws a parallel with agriculturalists who have abandoned efforts to eliminate invasive species, and now apply insecticides only when infestation exceeds some threshold level, with the goal of producing a sustainable and satisfactory crop.

**What is the background of this debate?**

Before the introduction of high-dose therapy with autologous stem cell
transplant (ASCT) in the 1990s, the goal was to control myeloma as much as possible, providing the best quality of life to the patient for the longest duration by use of the available chemotherapeutic agents. Subsequently, bisphosphonates were found to be effective in decreasing the incidence of bone lesions. In the past decade, three novel agents (thalidomide, bortezomib, and lenalidomide) emerged as effective anti-myeloma drugs, producing remarkable results in numerous treatment regimens in terms of CR rate, progression-free survival (PFS), time-to-progression (TTP), and overall survival (OS). We expect upcoming newer drugs, like pomalidomide and carfilzomib, to improve on these outcomes. These results have prompted a new philosophy of treating myeloma with the goal of potential cure rather than disease control.

Some groups such as the Mayo Clinic myeloma group are pursuing both strategies in clinical trials, allowing patient choice. For example, we are 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 4-drug combination strategy in a separate trial in an attempt to develop a curative regimen for myeloma.

Please share the logic of each approach.

If cure is the goal, then CR is the logical first step, and maintaining the CR is the second step. The best time to attempt to achieve a CR is early in the disease course. Moreover, administering the best treatments early on will provide a greater chance at success. Trying to achieve and maintain the highest CR rate requires more intense, more toxic therapy. However, many side effects are reversible, and many patients are willing to accept high toxicity rates in exchange for the possibility of longer life. It must be kept in mind that although OS is usually better in patients who achieve CR than in those who do
not, this could be more a reflection of some patients having inherently more favorable disease prognosis. It is still unclear whether intensifying therapy with the sole purpose of achieving CR for patients who are otherwise responding well to therapy actually prolongs OS. In addition, there are many problems with our definitions of CR; in myeloma, unlike in other cancers, CR really reflects profound disease reduction, but not elimination, and thus is not a surrogate for true cure (unlike diseases such as large cell lymphoma, where the majority of patients achieving CR are cured).

If control is the goal, CR becomes a desirable event, but it is not the goal. In many myeloma patients, reduction of the disease to a state similar to that of monoclonal gammopathy of undetermined significance (MGUS) by achieving very good partial response (VGPR) may be all that is required for best long-term survival. The logic of the control approach is that not everyone needs to be subjected to the toxicity of aggressive therapy, and that drugs administered sequentially with a goal of optimal quality of life will result in equally long duration of life for low-risk patients with lower morbidity. The control approach recognizes that myeloma is a marathon, not a sprint, and that preserving options for later is important.

**Is there a conclusion to be drawn from interpretation of available clinical trials data?**

I think that there are three big factors that are of concern. They are: 1) Overestimating the clinical benefit of endpoints like PFS and TTP; 2) Overestimating the value of a CR; and 3) Considering and treating myeloma as if it were acute leukemia. These factors are affecting the way in which clinical trials are interpreted and ultimately are affecting the way in which patients are treated clinically.

The metrics for a new drug going through the clinical trials process in order to receive FDA approval differ from the metrics that need to be applied to
non-regulatory trials, where the goal is to determine the place of that new drug in the overall treatment strategy. Although with the best of intentions, it is not unusual for pharmaceutical companies, researchers, and practicing clinicians to lose sight of this. And most patients and caregivers do not have the training to correctly process statistical terminology or clinical trial data.

In regulatory clinical trials, endpoints such as PFS and TTP are meaningful because they often suggest clinical benefit, and since the drug being tested is not approved, patients in the control arm (and patients at large) do not have the option of getting the drug later on in the disease course. In contrast, in non-regulatory trials, PFS and TTP do not carry the same value because patients in the control arm do have the option of getting the same drug later. Thus, in most non-regulatory studies, prolonged PFS or TTP does not necessarily imply clinical benefit (which would be prolonged OS or patient-reported improvement in quality of life). In these situations, PFS or TTP in the control arm must ideally be measured at second relapse, after the patient has failed use of the experimental treatment in question that was administered at first relapse.

The ultimate goal of our therapy should be improved OS. The problem is OS data in regulatory clinical trials is impractical because the required sample size is too large and the duration of follow-up needed is too long, and it would significantly delay the FDA approval of a drug that might be quite useful to myeloma patients.

**Where is your position in the cure-vs-control debate?**

The answer to this question depends on what kind of myeloma we are talking about. Outside of a clinical trial setting, I suggest a risk-adapted approach.

In high-risk patients – about 15% to 25% of the myeloma population – an aggressive approach to achieving CR may be the only route to long-term survival. We use cytogenetic abnormalities to identify these high-risk patients.
These patients should consider: 1) a multi-drug regimen, including bortezomib early in the disease course; 2) CR as a treatment goal; and 3) routine maintenance therapy.

In standard-risk patients – about 75% of the myeloma population – I favor a control approach. In clinical trials before the introduction of novel agents, patients under the age of 65 lived an average of 7 to 10 years, and the current availability of novel agents will increase their survival further. For low-risk patients, my approach involves:

1) Using non-neurotoxic initial therapy such as lenalidomide plus low-dose dexamethasone (Rd), and avoiding bortezomib except if patients have renal failure or need urgent control of disease. My rationale is to avoid the risk of neurotoxicity (which can be severe) in low-risk patients when there is no OS data indicating that using bortezomib early rather than later at first relapse improves survival compared with Rd

2) Targeting VGPR rather than CR as a goal, using treatments at the minimal effective dose with a sequential approach of less intense therapy first and more aggressive approaches only when the need arises

3) Allowing patients to decide between early versus delayed transplant, and

4) Employing maintenance therapy primarily in patients who have failed to achieve a VGPR or better.

In clinical trials, of course, we need to continue the search for a cure, and we need to explore both the cure and control strategies. The treatment algorithm must also take into account patients’ needs, goals, and attitudes toward prolonged survival versus a better quality of life. Some patients prefer a potentially curative approach despite the risk of adverse events; others think that quality of life is more important than a potential cure. MT