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December 10, 2011 * Vol. 33 * No. 23

oncology-times.com

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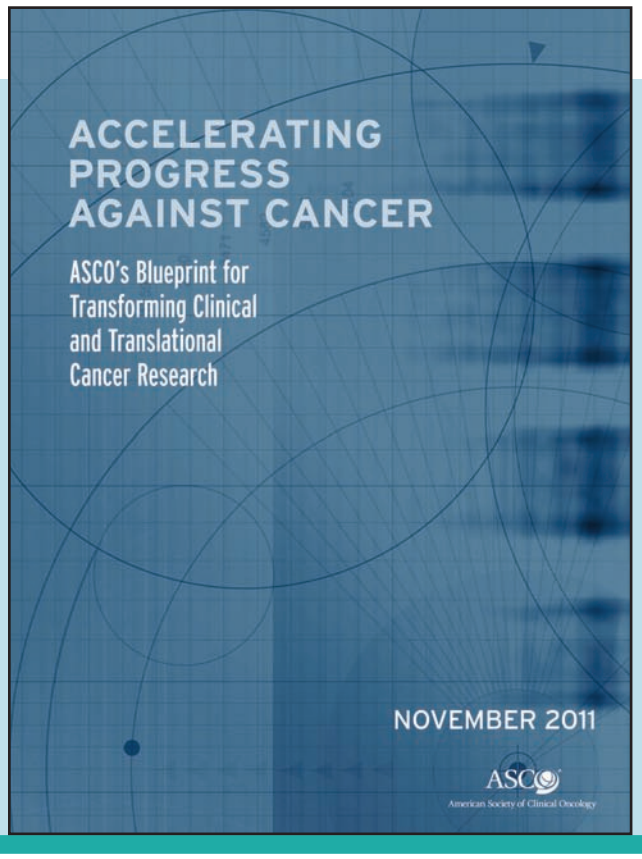


## New 'Blueprint' from ASCO Aims to Transform Cancer Research Based on Cutting-Edge Science

BY PEGGY EASTMAN

The report makes the following four cases for action: (1) Investments in cancer research have already saved and improved many lives; (2) Cancer science is in a period of revolutionary change; (3) Clinical cancer research and patient care could be vastly more targeted, more efficient, and more effective; and (4) With recent advances, it is not unrealistic to imagine that over the next decade, clinicians will increasingly be able to choose therapies that target the characteristics of each cancer and each patient.

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**Myeloma: Is Allogeneic Transplant Still Justified for High-Risk Patients?** p.18

**LEE KRUG: How Do I Treat Patients with Malignant Pleural Mesothelioma?** p.25


**Institute of Medicine Panel Focuses on Role of Obesity in Cancer Survivorship** p.33

[ ALSO ]



PERIODICALS

# Sergio Giralt: Allogeneic Transplant Remains Justified for High-Risk Multiple Myeloma Patients


BY MARK FUERST

NEW YORK CITY—Allogeneic stem cell transplantation (SCT) remains a valid option for patients with high-risk multiple myeloma, as well as for younger patients with standard risk with very aggressive disease.

"For patients with standard-risk myeloma, treatment has improved so much that the risk-versus-benefit ratio needs to be balanced," Sergio Giralt, MD, Chief of the Adult Bone Marrow Transplant Service at Memorial Sloan-Kettering Cancer Center, said in an interview here at the Lymphoma & Myeloma 2011 meeting.

"In very young patients with very aggressive disease, you may consider an allogeneic transplant for long-term disease control. But the availability of a donor is not a reason to do an allogeneic transplant."

Oncologists frequently see multiple myeloma patients in their practice who have achieved a stringent complete response (CR) after receiving several cycles of combination therapy, such as bortezomib plus thalidomide plus dexamethasone, followed by an autologous SCT. "These patients ask, 'Can I be cured? What is my life expectancy? Will my disease come back?'" Dr. Giralt said in his presentation at the meeting. "There is a chance these patients will be cured, but more likely the disease will come back and will be more difficult to control due to clonal evolution, and will be more difficult to control with chemotherapy."

The question for these patients is "would replacement of their bone marrow with the bone marrow and immune system of someone else be able to achieve long-term disease control? That is, can I do SCT and exploit the graft-versus-myeloma [GvM] effect that will prevent the disease from coming back. Is the risk of the procedure worth the benefit?"

"There is a sign that patients who develop GvHD have lower risk of relapse in this group of patients, but if we look at auto-allo transplants, a significant number of patients are still dying of multiple myeloma. Despite getting donor cells, these cells can escape immune surveillance."

## Bar Has Changed

Dr. Giralt noted that the bar for treatment of these patients has changed. "Traditionally we have been telling patients that high-dose chemotherapy and one autotransplant leads to an average remission rate of about 40% for around two to three years, with a progression rate of 90%. Only one-third of these patients would achieve a CR and stay in CR 10 years down the road. That data is no longer valid today. Some patients will live long enough to die of something else."

Clinical studies show where the bar for treatment stands today. Standard therapy for multiple myeloma patients includes induction therapy and lenalidomide maintenance for those who are not progressing.

SERGIO GIRALT, MD: "Traditionally we have been telling patients that high-dose chemotherapy and one autotransplant leads to an average remission of about 40% for around two to three years, with a progression rate of 90%. Only one-third of these patients would achieve a CR and stay in CR 10 years down the road. That data is no longer valid today. Some patients will live long enough to die of something else."

Patients who receive lenalidomide have a remission duration of approximately four years, compared with only about two years for those receiving placebo in clinical trials. "With standard therapy and one autologous transplant followed by maintenance, the average remission duration is four years. Survival data from clinical trials show that 80 to 90 percent of patients are alive at four years," Dr. Giralt said.

The goal of therapy is for the patient to achieve a complete response, which is a surrogate for long-term disease control. "Previously, patients who received allogeneic SCT with myeloablation therapy had a 30% mortality rate, which is high. With reduced intensity transplants, the mortality rate is down to 10-15%," said Dr. Giralt, noting that data from the University of Arkansas using a third tandem transplant using intensive induction following normal therapy show a reduction in the relapse rate.

New trials have compared allogeneic SCT versus autologous transplant in the upfront setting. "This is the question we face the most in the clinic," said Dr. Giralt. "A 55-year-old today has an expected lifespan of 30 years. To say to a patient you have a seven-year lifespan, which is twice as high as it would have been 20 years ago, is still not that good."

He cited a North American trial (BMT-CTN 0102) that compared tandem autologous transplant with or without maintenance therapy (auto-auto) versus single autologous transplant followed by HLA-matched sibling non-myeloablative allogeneic transplant (auto-allo) for patients with standard-risk multiple myeloma.

The main groups compared had standard-risk disease and either had no sibling donor (436 patients auto-auto) or had an HLA-identifiable donor (189 patients auto-allo). This study was designed to evaluate patients with standard-risk disease who had no deletion 13 identified by conventional cytogenetics and a beta 2 microglobulin (B2M) of less than 4 mg/mL at diagnosis.

## Tendency to Refer Only High-Risk Patients to Clinical Trials

There is a tendency for oncologists to refer only high-risk patients to clinical trials, Dr. Giralt said: "In the community, we send only our worst-risk patients to a clinical trial. We don't want good-risk patients assigned to allogeneic transplant. Unfortunately, we still have one-quarter of patients referred to transplantation when B2M has not been done at diagnosis."

However, this is changing: "More patients are having a full workup as recommended by National Comprehensive Cancer Network guidelines," he said, adding that a proper workup involves tests of bone marrow, cytogenetics, and fluorescence in situ hybridization.

The results of the North American trial show that therapy failed for the same number of patients, about 15%, Dr. Giralt noted. The trial did not meet the primary endpoint – three-year progression-free survival (PFS) – which was similar in both groups (46% auto-auto, 43% auto-allo). Overall survival also was similar (80% auto-auto, 77% auto-allo).

"More patients are now having a full workup as recommended by NCCN guidelines; a proper workup involves tests of bone marrow, cytogenetics, and FISH."

A limitation in the study, though, he said, was that 30% of patients in the auto-auto arm who were randomized to receive thalidomide/dexamethasone refused to take the drugs. "They refused due to prior exposure to thalidomide and its side effects.

Thalidomide maintenance was not considered acceptable by the patients in this trial."

The trial did demonstrate a GvM effect. Relapse rates were slightly higher, but the difference was not enough to overcome a higher transplant-related mortality in the auto-allo arm (12%) compared with the auto-auto arm (4%). The non-relapse mortality rates are acceptable but need to be improved upon, he said. "If we could exploit the GvM effect without decreasing the non-relapse mortality rate, we would have an instrument that could reduce the relapse rate by 50%."

The cumulative incidence of chronic graft-vs-host disease (GvHD) after allogeneic transplant was 54% at two years, he said. Chronic GvHD has an impact on disease progression and relapse for patients with standard-risk disease. Those who had no GvHD in the first 12 months had a higher incidence of disease progression at three years (42%) compared with those who did have a GvHD effect (20%).

## High-Risk Patients

Regarding high-risk patients, Dr. Giralt said that for patients who show deletion 13 by conventional cytogenetics or a high B2M, there was no improvement in either progression-free or overall survival. "There is a sign that patients who develop GvHD have lower risk of relapse in this group of patients, but if we look at auto-allo transplants, a significant number of patients are still dying of multiple myeloma. Despite getting donor cells, these cells can escape immune surveillance."

Dr. Giralt cited a recent study by a Nordic group that reported longer follow-up on a trial comparing tandem autologous/reduced intensity conditioning allogeneic SCT versus autologous transplantation (*Bjorkstrand B et al: JCO 2011;29:3016-3022*). The 357 patients in the trial received conventional modern induction high-dose therapy and were assigned to transplant or no transplant depending on the availability of an HLA-identical sibling.

"The bottom-line result showed as with the American trial, that the relapse rate decreased, but the researchers saw a significant benefit in PFS, and may be starting to show an overall survival benefit late in the course of the disease," Dr. Giralt said. "Survival was way below 60%, which when compared with modern autologous transplantation with maintenance seems to be significantly inferior." The non-relapse mortality was similar to the North American trial, about 12%.

> "In very young patients with very aggressive disease, you may consider an allogeneic transplant for long-term disease control. But the availability of a donor is not a reason to do an allogeneic transplant."

"As we think about recommending transplantation to all patients with standard-risk disease, we need to recognize that we have to reduce the risk of non-relapse mortality," he said. "What we really need is a better way to define disease burden. If we could see the disease burden the same way we do in chronic myeloid leukemia using polymerase chain reaction, we could see that the tumor burden was increasing over time or that the tumor burden fell below a certain threshold that we knew maintenance therapy could not reduce, and we could then recommend aggressive therapy."

In summary, Dr. Giralt said, "current results with both autologous and allogeneic SCT justify the following patterns of care: in standard practice allogeneic SCT can be offered to patients with high-risk disease, or younger patients with standard risk disease who are highly motivated and well-informed. Allogeneic SCT as consolidation of a first remission should preferentially be performed under the auspices of a clinical trial. Autologous SCT remains the most reasonable consolidative therapy for myeloma patients today."

He added that approximately 15 to 20 percent of patients who receive a salvage allogeneic transplant achieve long-term disease control as long as they have increased clinical remission. "This is a reasonable strategy that should be performed in the context of a clinical trial," he said.

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## →MYELOMA ALLOGENEIC

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### Morton Coleman: Allogeneic Not Routine

Morton Coleman, MD, Director of the Center for Lymphoma and Myeloma at Weill Cornell Medical College, commented on Dr. Giralt's presentation by saying that allogeneic transplant should be relegated only to a clinical trial or to young patients at high risk who are fully informed of the risks and benefits.

"This is not a routine procedure. The data do not show any genuine benefit using myeloablation or non-myeloablation allogeneic transplant. This is only for a subset of patients who are young with a poor prognosis."

### Brian Durie: Balance Toxicity and Efficacy

And Brian Durie, MD, Chairman of the Board of the International Myeloma Foundation and the International Myeloma Working Group and an attending physician at Cedars-Sinai Samuel Oschin Cancer Center in Los Angeles, said, "Myeloma treatment starts before the patient has myeloma with smoldering disease. How should we treat a high-risk patient? Once identified, 50% will progress within two years."

The goal for low-risk patients is to extend survival and avoid unnecessary treatment, he continued. "We can't move away from early autologous transplant yet, because good-risk patients who receive a transplant early do amazingly well."

The role of double transplant, which is not yet a standard of care, may be best as consolidation for patients who do not attain very good partial response to induction therapy, he added. "The main thing is to balance toxicity and efficacy with what the physician thinks is best and what the patient wants to do when it comes to transplant."

### In Summary

Dr. Giralt summarized his view as follows, that current results with both autologous and allogeneic SCT justify the following patterns of care:

- In standard practice allogeneic SCT can be offered to patients with high-risk disease, or younger patients with standard-risk disease who are highly motivated and well-informed.
- Allogeneic SCT as consolidation of a first remission should preferentially be performed under the auspices of a clinical trial.
- Autologous SCT remains the most reasonable consolidative therapy for myeloma patients today.