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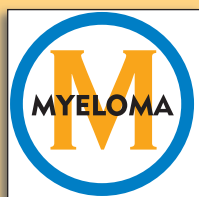
THE NEWS CENTER FOR THE CANCER CARE TEAM



Crisis in Cancer Research Funding

At AACR Meeting, Many Express Alarm at Budget Cuts, Saying This Is Not Just a Case of 'Been There Before But Bounced Back'

Page 15



Myeloma: In Surprise Finding, Plasma Exchange Found Not

Helpful for Patients with Kidney Failure

Also: NCCN Tweaks Myeloma Guidelines, Suggesting Watching Smoldering Form

Page 8

SIMONE'S ONCOPINION: Leadership of the FDA

Page 3



CMS Demonstration Projects:

Lessons Learned Point Way to Future Directions for High-Quality Cancer Care; and How the 2006 Version Aims to Expedite Data Collection

Page 6



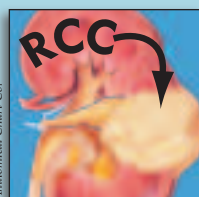
Highlights from the 2006 Prostate Cancer Symposium:

(1) Treatment by 'High-Volume' Prostate Cancer Surgeons Results in Better Outcomes; (2) The Racial Gap in Prostate Cancer; (3) Virus Linked to Development of Prostate Cancer; (4) Alendronate May Prevent Bone Loss in Patients on Anti-Androgens; (5) Brachytherapy Equal to High-Dose External-Beam RT for Early Disease; (6) Drug Holidays Effective for Some Prostate Cancer Patients; (7) Adjuvant RT May Be More Effective than Salvage for Stage III/IV; (8) and Vitamin D May Lower Risk of Thromboembolic Events

Page 47



- Strategy Found to Overcome Doxorubicin Resistance . . . 24
- Gastric Cancer: Ethnic Disparities in Outcome Confirmed . . . 25
- Advanced Laryngeal Cancer: Single Cycle of Induction Chemo May Select Patients for Laryngectomy . . . 28
- Salinosporamide A, 2nd-Generation Proteasome Inhibitor, May Be Alternative to Bortezomib . . 34
- Rectal Cancer: Adequate Delivery of RT Has Impact on Relapse Rate . . . 35



Partial Nephrectomy Underused, Study Shows; Also Update on

Screening & Treatment for Early Renal Cancer

Page 40

DEPARTMENTS

EYE ON WASHINGTON

SHOP TALK

JOURNAL SCAN

TURRISI TAKES ON THE MOVIES

POETRY BY CAREGIVERS

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H
NEWS CENTER
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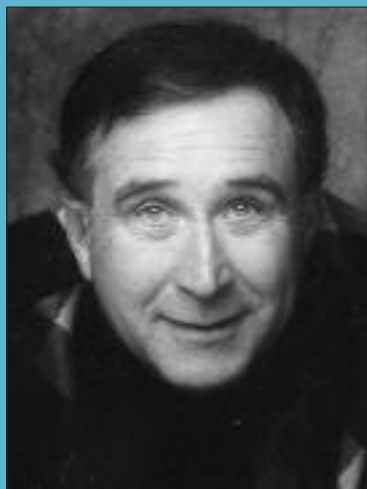
Myeloma Study: In Surprise Finding, Plasma Exchange Found Not Helpful for Myeloma Patients with Kidney Failure

By Devon Schuyler

Two sets of management guidelines endorse the use of plasma exchange in patients who have kidney failure associated with myeloma. But according to a recent study by the Canadian Apheresis Group, there's no evidence that plasma exchange benefits these patients.

"This is the most powerful paper to date, and it doesn't support the use of plasma exchange for the average myeloma patient with renal failure," said Morie A. Gertz, MD, Chairman of the Division of Hematology at the Mayo Clinic, who wrote an accompanying editorial. He said that he was surprised by the results because all of the prior literature had suggested an advantage, and because it was logical to believe that plasma exchange would be beneficial.

The lead author of the study (*Ann Intern Med* 2005;143:777-784), William F. Clark, MD, Professor of Medicine at the University of Western Ontario, also said he was surprised, explaining that



William F. Clark, MD, predicted that the guidelines would soon be revised to no longer recommend plasma exchange. Plasma exchange, he noted, is not completely benign and can produce a short-term increase in the risk of infection. It also costs money—money that could be reallocated to more effective therapies, he said. "We can take that money, which is probably about \$5,000 per patient, and put it towards better treatment." Also, revising the guidelines would make it easier for researchers to enroll patients in randomized controlled trials and determine with greater certainty the role of plasma exchange in myeloma. He said that when the 2003 Myeloma Foundation guidelines came out, enrollment in his own study dropped off sharply.

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he and his coinvestigators undertook the study thinking that the treatment would be beneficial, based on the results of two prior small, randomized controlled trials.

So, why the negative result? Dr. Clark said one possible explanation is that treatments have greatly improved over the past few years. In particular, he cited the use of dexamethasone and more-rapid initiation of chemotherapy and rehydration.

"When patients are identified immediately and treated rapidly, they're much more likely to recover their renal function," he said. As a result, plasma exchange may become unnecessary.

Of course, there may be another reason the results didn't match up: The current study could have failed to detect a true benefit.

Study Started Before Immunoglobulin-Free Light Chain Assays Were Routine

Dr. Clark said that because his study was small and had a wide 95% confidence interval, the possibility of even a large benefit couldn't be ruled out. In addition, new studies might find that certain subgroups of patients might benefit from the procedure, such as those with the highest levels of light chains. (The idea behind plasma exchange is to treat kidney damage by reducing serum levels of light chains, which are often elevated in people with myeloma.) He explained that the study was undertaken before immunoglobulin-free light chain assays become routinely available.

'Lot of Open Questions'

"The study leaves a lot of open questions," said Brian G. M. Durie, MD, who led the panel of scientific advisors that drafted the International Myeloma Foundation guidelines. Dr. Durie is the Director of Research and Myeloma Programs at Cedars-Sinai Comprehensive Cancer Center in Los Angeles.

He said it remains unclear how the levels of the IgG and IgA light chains might affect results, and what the optimal number of plasma exchange procedures might be.

Dr. Durie offered another possible explanation for the lack of a demonstrated benefit in this study: that a high level of light chains was not responsible for the kidney failure. He said that the type of light chain might be more important than the level—something that only future studies can determine.

104 Patients at 14 Centers in Canada

The study, which took place at 14 medical centers in Canada, included 104 people between the ages of 18 and 81 who had newly diagnosed multiple myeloma and progressive acute kidney failure. Patients were eligible for the study if a bone marrow aspirate showed more than 10% plasma cells and a monoclonal light chain in their urine, plasma, or kidney tissue.

Patients were randomized to either a control group or a plasma exchange group and were then treated in an unblinded manner. People in both groups received standard chemotherapy with either melphalan plus prednisone or vincristine-doxorubicin-dexamethasone. Those in the plasma exchange group also had five to seven plasma exchange procedures within the first 10 days of the study.

Seven patients withdrew from the study, leaving 97 for the analysis. The primary outcome was a composite that encompassed death, dialysis dependence, and severely reduced kidney function, defined as a glomerular filtration rate of less than 0.29 mL/min per 1.73 m².

This composite outcome occurred in 58% of the patients in the plasma



Brian G. M. Durie, MD, who led the panel of scientific advisors that drafted the International Myeloma Foundation guidelines, said he's not ready to give up on plasma exchange. "I don't think the guidelines were too strong," he said. "The problem is that they don't give much guidance. We need to clarify them." He said the next update of the guidelines, now in the works, will likely emphasize that plasmapheresis should be carefully considered on a case-by-case basis, and should be administered only by an experienced team, and will include a discussion of the results by Dr. Clark et al.

exchange group and 69% of those in the control group—a difference of 11%, but one that was not statistically significant (95% CI of -8% to 29%; $p = 0.36$). The survival rate also was comparable for the two groups, with about a third of the patients in both groups dying by six months.

Recommendations Based on Two Trials

Just two previous randomized trials had evaluated the effect of plasma exchange in people with multiple myeloma complicated by acute kidney failure. The first trial included 21 participants, and the second, 29.

Based on these and other studies, the International Myeloma Foundation concluded in 2003 that plasma exchange can be "at times be critically important" to improving kidney function in these patients.

The American Association of Blood Banks and the American Society for Apheresis also endorsed the procedure in a 2003 review.

Dr. Clark predicted that the guidelines would soon be revised to no longer recommend plasma exchange. He pointed out that plasma exchange is

(continued on page 10)

Two sets of management guidelines endorse the use of plasma exchange in patients who have kidney failure associated with myeloma. But the new study by the Canadian Apheresis Group found that there is no evidence that plasma exchange benefits these patients.

NCCN Tweaks Guidelines for Myeloma; Suggest Watching Smoldering Form

By Ed Susman

HOLLYWOOD, FL—Sometimes diagnosing a disease correctly may lead to a treatment in which the observation becomes the treatment of choice. That's the case for patients with Stage

1 multiple myeloma, at least according to new guidelines from the National Comprehensive Cancer Network (NCCN), the 19-institution consortium that has been writing treatment algorithm since 1996.

"Primary treatment of systemic, smoldering, or Stage 1 myeloma is

observation," said Seema Singhal, MD, Professor of Medicine and Director of the Multiple Myeloma Program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, speaking here at the NCCN's 11th Annual Conference. "The panel expanded this recommendation to include

the time interval of three to six months."

The guidelines indicate that people identified with the smoldering type of multiple myeloma may have disease without symptoms for many years. "These patients have low concentrations of M-protein—the marker of disease progression—and bone marrow infiltration with 10% to 20% of plasma cells; however, they do not have anemia, renal failure, hypercalcemia, or bone lesions," Dr. Singhal said.

Patients diagnosed with Durie-Salmon Stage 1 myeloma also have low M-protein without much anemia, hypercalcemia, or bone disease, and

Plasma Exchange

continued from page 8

not a completely benign procedure; it can produce a short-term increase in the risk of infection when used in people with myeloma.

The procedure also costs money—money that could be reallocated to more effective therapies, he said. "We can take that money, which is probably about \$5,000 per patient, and hopefully put it towards better treatment for those patients."

"This is the most powerful paper to date, and it doesn't support the use of plasma exchange for the average myeloma patient with renal failure."

Finally, revising the guidelines would make it easier for researchers to enroll patients in randomized controlled trials and determine with greater certainty the role of plasma exchange in myeloma. Dr. Clark said that when the 2003 Myeloma Foundation guidelines came out, enrollment in his own study dropped off sharply.

Still, Dr. Durie said he's not ready to give up on plasma exchange. "I don't think the guidelines were too strong," he said. "The problem is that they don't give much guidance. We need to clarify them."

He said that the next update of the guidelines, which is in the works, will likely emphasize that plasmapheresis should be carefully considered on a case-by-case basis, and that it should be administered only by an experienced team. The revised guidelines, he said, will include a discussion of the results by Dr. Clark and his colleagues. 