



NOVEL AGENTS IN MYELOMA: AN EXCITING SAGA by Morton Coleman, MD

An exciting page in the annals of cancer therapy has been unfolding recently with the development of novel agents for the treatment of multiple myeloma. Less than a decade ago, myeloma therapy was in the doldrums, and had been that way for years. Other than bisphosphonates, basic therapy consisted of alkylating agents in all their various guises, although oral melphalan and to a lesser degree, cyclophosphamide were the mainstays of treatment. Combining alkylating agents into a triple therapy combination had been considered a step forward by some, but, in actuality, represented simply more intense therapy. Steroids, particularly high dose dexamethasone, were helpful, but the contribution of vincristine and doxorubicin in the classic VAD program was marginal. Autologous transplantation, employing mostly high dose alkylating agents, for younger patients was and still remains the gold standard therapy, but its impact over conventional chemotherapy is modest and it does not represent curative therapy. Further, it is not applicable to a large cohort of patients, the elderly, who predominate in this disease. Median survival for active myeloma a decade ago ranged from three to five years.

In the late 1990's, an assemblage of a determined and insistent wife of a heavily pretreated myeloma patient, a receptive

and innovative group of physicians in Arkansas, and a biotech company came together to provide the first major breakthrough in years. Thalidomide, the infamous drug used as a sedative in pregnant women responsible for shortened or truncated limbs in newborns, was tried in myeloma for its putative anti-angiogenic properties based on the observation that the more aggressive or advanced the myeloma, the greater the vascularity. As is almost universal in cancer therapy, end-stage, refractory, or previously treated patients were the initial recipients of this novel therapy. Indeed almost all of the patients had received extensive treatment and had limited marrow reserve. Despite these severe drawbacks, thalidomide produced responses in approximately a third of patients although some of the responses were minor (the myeloma immunoglobulin levels declined by less than half). Thalidomide though was particularly useful here because it is minimally myelosuppressive. Subsequently several groups, including ourselves at Cornell, observed that the addition of steroids greatly augmented the therapeutic effect of thalidomide in previously treated patients enhancing both the quality and amount of the responses. Successful responses occurred in well over

half the patients. Our program at Cornell gave thalidomide only in low dose, dexamethasone once weekly, and added clarithromycin. Responses approached ninety percent. Whether the enhanced response in our program reflected differences in patient selection (one of many problems in comparing Phase II results), the effect of clarithromycin on the myeloma or the metabolism of the other two drugs, or the use of once weekly high dose dexamethasone is unclear. Once weekly high dose (referred to as "low dose") dexamethasone though

has been proven superior to the "classical" Barlogie method of spaced four continuous days of high dose dexamethasone. While steroids combined with thalidomide greatly augmented the response, there is no such thing in life as a free lunch. So was the situation here. The steroids also ratcheted up the toxicity. Indeed the major impediment to the long term use of thalidomide has been neuropathy which invariably occurs in almost all individuals receiving the combination. The neuropathy does not resolve easily even with cessation of the

continued on page 2

Donations to Cancer Research & Treatment Fund

With the recent news regarding the severe drop in the stock market and the Madoff scandal, we at CR&T want to assure all our donors and friends that our organization has always invested, and will continue to invest its assets conservatively. With this philosophy, our assets are invested in money market accounts, mutual funds and US Treasury obligations. CR&T financial records are audited on an annual basis by certified public accountants.

While many charities have been hit hard by the stock market drop and the Madoff fraud, we are pleased to report that we are quite solvent and continue to maintain our current and projected commitments.

We will continue to be efficient and effective and accountable to all our donors. We are grateful for your contributions made so generously over the years.

NOVEL AGENTS IN MYELOMA

continued from cover

drugs. In addition, we, and subsequently others, observed that the combination was associated with an extraordinarily high incidence of thrombosis and sudden death. Reasoning that thalidomide may produce vascular injury if it is truly antiangiogenic, low dose aspirin was inaugurated by us and proved successful notwithstanding the reported lack of efficacy of aspirin in "slow flow" venous thrombosis, a frequently reported phenomenon with thalidomide-dexamethasone. Heparin and warfarin have also been effective, but low dose warfarin may not be adequate.

As a natural sequence in testing, the Mayo Clinic headed up a cooperative group study pitting thalidomide and dexamethasone in a randomized trial against dexamethasone alone in newly diagnosed patients destined for autologous transplantation. The combination is, in some ways, ideal since neither medicine of the combination was myelosuppressive. The combination indeed proved superior to dexamethasone alone producing statistically superior responses (70% versus 50%) but at a cost of greater toxicity, primarily thrombotic events. Unfortunately antithrombotic measures were not employed in the study.

Following the remarkable success of thalidomide, two novel agents, bortezomib and lenalidomide, followed in relatively rapid succession. Lenalidomide, an IMiD (immunomodulatory drug) reportedly more potent than thalidomide, was introduced in 2006. Again treatment was first tried in previously treated patients. As with thalidomide, approximately a third of patients responded. Two concurrent randomized studies, one spearheaded in North America by the M.D. Anderson group and one in Europe, Australia and Israel, tested lenalidomide and dexamethasone against dexamethasone in previously treated patients. Combined dexamethasone and lenalidomide was superior and produced responses, as with thalidomide, in approximately half of patients. Once data of the combinations efficacy were established in previously treated patients, newly diagnosed patients were studied. Responses in at least 90% of the patients were produced. In addition, depending on the nuances of the combination (such as the addition of clarithromycin or the use of weekly dexamethasone) or response criteria used, i.e., strict complete remissions, complete remissions, near complete responses, or very good par-

tial responses (all connoting at least a greater than ninety percent reduction in immunoglobulin), up to 40% of patients had nearly a complete reduction of the myeloma spike. These responses represented a significant achievement since responses of this magnitude were rarely seen with conventional chemotherapy, and were equal to or superior to transplantation. Data suggest that these major responses may translate into enhanced survival. Remarkably thrombosis was less problematic with the prophylactic use of antithrombotic agents; however, thrombosis was seen when the antithrombotic agent and lenalidomide were discontinued simultaneously. Apparently any damage to the endothelium is more longstanding that the antithrombotic effects of aspirin, for instance, which usually abates in about ten days.

Bortezomib, another novel agent, entered the market in 2003 with a mechanism of action thought to be entirely different from the IMiDs. Putatively bortezomib inhibits proteasome activity allowing inhibition of NF-kappa B, a substance with many nefarious activities once it enters the nucleus. Other mechanisms though may be operative. Nevertheless similar to the results with thalidomide and lenalidomide, responses in previously treated patients hovered around a third. Adding steroids clearly enhanced the efficacy of bortezomib. When used in previously untreated patients, with augmentation by necessary steroids, responses similar to the IMiDs were obtained. Nearly 90% of patients responded, again with major responses. In a large randomized study headed by the Dana Farber in Boston, bortezomib when tested against dexamethasone was clearly superior and showed an actual enhancement in survival. Bortezomib, like thalidomide, produces neuropathy, although the neuropathy is clearly different from thalidomide and is more rapidly reversible. Like lenalidomide, there is some myelosuppression, primarily thrombocytopenia, but generally less than with lenalidomide. The IMiDs are taken orally, bortezomib is given intravenously. Bortezomib though need not be given on a continuous basis once a major response has occurred and been sustained.

Given the different mechanisms of action, the novel agents have been combined, but because of overlapping toxicity, doses may require attenuation. For instance, thalidomide has been combined with bortezomib but suffers from overlapping neurologic toxicity. Bortezomib and lenalidomide are also being combined, but do have some overlapping

hematologic toxicity. A thalidomide and lenalidomide combination represents another possible combination due to the relative lack of overlapping toxicity. Whether such a combination will have an additive or synergetic impact remains to be seen, since there are insufficient data to indicate that resistance to one will not impart resistance to the other. The preliminary responses though to combinations of the IMiDs with bortezomib in previously treated patients look remarkably impressive. Now that doses have been finalized, it is only a matter of time before results of the combinations will be forthcoming in both treated and newly diagnosed patients.

The group in Los Angeles, as well as the Europeans, the Italians and French in particular, took a different tack. They combined novel agents with chemotherapy, and showed enhanced efficacy to chemotherapy alone. The Italians have shown that thalidomide combined with melphalan was clearly superior to melphalan alone. The French have shown in newly diagnosed elderly that thalidomide and melphalan combined were clearly superior to melphalan alone or to a reduced intensity autologous transplantation. Meanwhile the group formerly at the Cleveland Clinic showed that pegylated liposomal doxorubicin was effective in myeloma despite what appears to be marginal activity of standard doxorubicin. The group in North Carolina, having done pioneering work with bortezomib, noted excellent results combining bortezomib with liposomal doxorubicin. Dr. Harousseau, leading a French cooperative group compared combined bortezomib and liposomal doxorubicin to bortezomib alone in previously treated patients. The results with the combination were superior in just about every parameter measured. It is now apparent that combinations of novel agents with themselves, steroids and/or chemotherapy are superior to a novel agent, steroids, or chemotherapy alone and probably represent true synergism.

A question often posed is which novel agent is superior and which should be used initially. In point of fact, the data would suggest they are all of relatively equal efficacy, and that the selection of the particular agent should be based on the necessities presented by the patient. Does the patient have a thrombotic tendency, renal failure, a karyotypic chromosome 13 abnormality, an access problem, neuropathy, or limited marrow reserve? In each of the aforementioned presentations, one novel agent over

continued on page 6



CANCER SURVIVORS HALL OF FAME

On Wednesday, November 12, Cancer Research & Treatment Fund held its 2008 Hall of Fame Dinner. Over 250 friends and guests gathered at the Hilton New York to honor the evening's distinguished guests.

Jane Brody, New York Times' "personal health" columnist was inducted into the Cancer Survivors Hall of Fame. CR&T was also pleased to recognize Raymond W. Kelly, Police Commissioner, City of New York, as this year's recipient of its Humanitarian Award. A special, first-time ever, Lifetime Achievement Award, was presented to Dr. Richard T. Silver. Dr. Silver is the Founder and Medical Director of CR&T.

The gathering was a festive event to celebrate these outstanding individuals, the accomplishments of CR&T, and the spirit and determination of cancer survivors to live actively and healthy and for inspiring those who continue to struggle with their own disease.

Kasia and Doug McCormick were Dinner Chairs, while Ali Velshi, CNN's chief business correspondent, acted as Master of Ceremonies. We thank all who made the night a wonderful success.



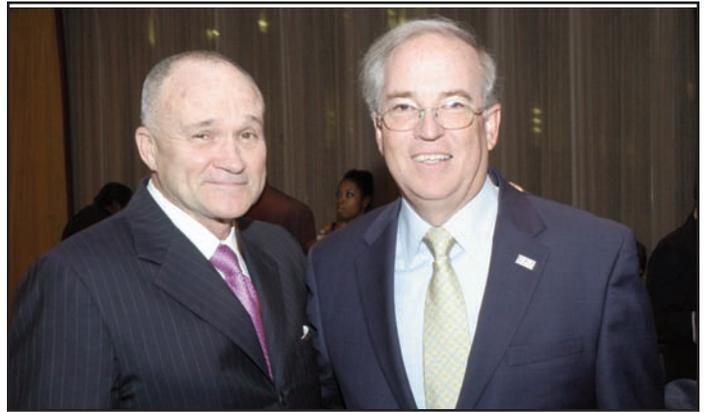
Richard Rose, CR&T Board President, Presenting Award to Jane Brody



Ray Kelly, receiving Humanitarian Award from Doug McCormick, CR&T Board Member and Dinner Co-Chair



Doug & Kasia McCormick, Dinner Chairs



Ray Kelly, Humanitarian Award Honoree and Richard Rose, CR&T Board President



Ali Velshi, Master of Ceremonies



Jane Brody, Hall of Fame Honoree and Ray Kelly, Humanitarian Award Honoree



Dr. Mark Pasmantier presenting Lifetime Achievement Award to Dr. Richard T. Silver



Adam Silver (far right) CR&T Board Member and friends



Amanda Johns Perez and Todd Shaw, CR&T Board Members and Kristen Shaw



Police Commissioner Ray Kelly & Kasia McCormick, Dinner Co-Chair



Dr. Silver (Center) being congratulated by friends and medical colleagues.

CANCER SURVIVORS HALL OF FAME NOVEMBER 12, 2008

Remarks by Honoree Jane Brody

In 1977 I wrote a book for the lay public called "You CAN Fight Cancer and Win." The first paragraph read as follows:

"This book is largely the product of the insights, courage, persistence, and painstaking efforts of thousands of physicians and scientists who for decades have been whittling away at the mysteries of cancer, making slow but steady gains toward conquering this killer. While their job is hardly completed, thanks to their progress so far in deciphering the causes of cancer, devising tests to detect hidden cancers, and working out curative therapies, each year countless thousands are spared from dying of this disease."

I remember, for example, writing about a young man named Michael Finamore, who in 1962 at age 12 was discovered to have acute lymphocytic leukemia, a disease that in the not-too-distant past had claimed the lives of 99 percent of its young victims. But thanks to a battery of then-experimental drugs that could destroy leukemic cells and radiation therapy to shrink a massive tumor in his chest, Michael didn't die. He went into remission and back to school. Two years later, his leukemia resurfaced. But by then, cancer researchers had another half-dozen drugs to help knock it out. And knock it out they did. Michael married at 26 and became a plumbing and heating contractor. He enjoyed water-skiing, scuba diving, snow skiing, tennis and baseball, and in his spare time, he did volunteer work for the American Cancer Society.

When Michael got cancer, half of all children diagnosed with cancer died of their disease. Today, more than 80 percent survive. And they survive because researchers devoted their lives to finding ways to treat their diseases and, at the same time, to minimize the long-term effects of that treatment.

I remember most vividly the science writers' conference I covered in the early 1970s at which four leading researchers presented their data demonstrating the ability to cure

Hodgkin's disease in each of its four stages. The results were so dramatic, I recommended that the story be published on page one of the NYT. Alas, my overly cautious editors feared raising people's hopes, and instead succeeded in limiting public access to the best available treatments for this killer of children and young adults.

This kind of timidity, I'm happy to say, no longer exists. The media are only too happy to be first with news of successes in treating cancer. And, I'm also happy to say, these successes are no longer limited to childhood cancers. With few exceptions, adult cancers are also yielding to the relentless efforts of cancer research, both thru improvements in early detection and the development of better treatments that are not only potentially curative but also leave far fewer footprints.

Today, two-thirds of cancer patients can expect to survive their disease for at least five years and most of those survive cancer-free indefinitely. And that statistic includes cancers against which little progress has been made to date, like cancers of the lung, pancreas and esophagus. So for many common cancers, like breast and colon, the survival rate exceeds two-thirds of patients at 5 yrs.

Interestingly, for two of those intractable cancers, lung and pancreas, the best known cause is totally preventable. You know what that is: smoking. As a journalist and public speaker, I have been staunch and persistent advocate of quit smoking and never smoking for the last 45 years.

And I have no intentions of giving up this battle. I predicted in a Page one story in the NY Times in the late-1970s that smoking would become a socially unacceptable behavior, and by golly, I am overjoyed that I have lived to see this become a reality!

Lung cancer death rates are at last on the decline. But the battle is far from over. We still need effective and affordable methods of early detection and, perhaps, better methods for helping people conquer their nicotine addiction and better methods for keeping young people of becoming hooked on this noxious weed.

And, of course, we need better treatments, not only for lung cancer but for a dozen other cancers related to smoking. Let's face facts, it will be decades before current and former smokers escape the cancer legacy of their addiction.

The same can be said of quite a number

of cancers that remain potent killers. Like ovarian cancer, the cancer that killed my mother at the tender age of 49. She died 4 weeks before I graduated from high school and one week before my brother's Bar Mitzvah.

After many years of undergoing annual transvaginal sonograms and blood tests that, it was hoped, would find an early ovarian cancer, I had my ovaries removed.

A rather drastic solution, you have to admit. Just think, if we knew which young men were at risk of developing testicular cancer, how many of them, do you think, would consider having their testicles removed?

Likewise, young women who are known to carry one of the BRCA mutations that greatly raises their risk of both breast and ovarian cancer are opting for bilateral mastectomies and oophorectomies. This is hardly an ideal solution. And it will be up to cancer research to come up with a better one.

As I see the future of cancer detection and treatment, it will be one based largely on the molecular characteristics of each person's disease. Researchers have already begun to distinguish between more and less aggressive cancers of the prostate, for example, based on molecular characteristics of individual cancers. This in turn would enable surgeons and oncologists to determine how best to treat each person's disease. As you know, most men with prostate cancer die WITH their disease, not because of it. And it makes no sense to subject those who will never develop symptoms to treatments that may compromise the quality of their lives.

Much work remains to be done in this area. Cancer is not one disease, not a hundred diseases, not a thousand diseases. It may turn out that each person's cancer is unique and will best be treated with therapies that cash in on that uniqueness.

At the same time, we must not neglect the aftermath of cancer treatment. Much research is still needed to reduce the long-term risks of cancer therapies, especially for children and young adults, who have many decades of life ahead of them in which to acquire second and even third cancers as a result of the treatment that saved their lives the first time.

More work is also needed in understanding the causes of cancer, both what might initiate it and what might promote it. I don't know about you, but I'm sick to death of the hysteria that periodically besets the public



Jane Brody

JANE BRODY

continued from page 5

with pronouncements that this or that substance we eat, breathe, touch, smell, etc. causes cancer in laboratory animals and thus may cause cancer in people. We need to identify the real bad actors and get rid of them, and not throw the baby out with the bathwater, as the public is now wont to do.

I once wrote a story based on the research of Dr. Bruce Ames in which I described the relative mutagenicity of various common substances. For example, I noted that the likelihood that eating peanut butter would cause cancer because of the possible presence of aflatoxin was no greater than the chances of getting cancer from eating 3 raw mushrooms. The most common reaction of my readers: "Now I can't eat mushrooms!"

So my hat goes out to all of you who support cancer research and foster its ability to continue to make progress so that my grandchildren and their children may grow up in a world in which one does not have to worry any more about cancer than about the common cold.

Thank you again for this lovely honor and for the opportunity to sound off.

NOVEL AGENTS IN MYELOMA

continued from page 2

the other would be selected.

The critical issues currently are what role will novel agents play in transplantation. Will they make transplantation more effective or will they turn myeloma into a chronic disease obviating the need for transplantation. Most importantly, have they improved the overall survival of myeloma patients? While some data are available and some are currently being culled, the answer appears to be a resounding yes.

Only several handfuls of institutions, countries, and studies have been mentioned, but to be certain there have been many other institutions throughout the world and many other pertinent studies that have contributed to our better understanding of these remarkable new agents. Indeed there is now a bewildering array of trials combining and using novel agents with themselves, steroids, and chemotherapy, and many other new agents are rapidly coming down the pike. It is an exciting time to be engaged in myeloma therapy.



Cancer Research and Treatment Fund Leadership

BOARD OF DIRECTORS

Joseph N. Aimi President Kenneth Bieber, Inc.	Jay J. Hochfelsen, JD President Compass Benefit Planning, LLC.
Henry J. Amoroso, Esq. President and CEO St. Vincent Catholic Medical Centers	Amanda Johns Perez Principal Amanda Johns Handcrafted Cards
Samuel First, DDS Principal Long Beach Plaza Dental	William R. Johnston, Emeritus Former President New York Stock Exchange
Philip Frese, Ph.D. President and CEO Catholic Charities of the Archdiocese of Newark	Michael C. Kempner Managing General Partner KS Capital Partners, L.P.
Terry Hermanson President Mr. Christmas Inc.	Douglas McCormick Venture Partner Rho Capital Partners

Richard J. Rose,
Board President
Senior Managing Director,
Retired
Shufro, Rose & Co., LLC.

Todd J. Shaw
First Vice President
Morgan Stanley

Adam Silver
Sr. Managing Member
Bennett Management

Richard T. Silver, M.D.
**Board Vice President
& Medical Director**

COUNSEL

Robert W. Slott, Esq.
Sunshine, Slott, Sunshine

VICE PRESIDENT OF DEVELOPMENT

Michael R. Wargo

Cancer Research and Treatment Fund, Inc.

is a non-profit group of physicians, nurses, and other medical professionals dedicated to research for the treatment of cancer and other blood diseases. Richard T. Silver, MD FACP founded CR&T in 1968.

Dr. Silver is Professor of Medicine and Director of the Leukemia and Myeloproliferative Center at Weill Medical College at Cornell University. He is Attending Physician at New York Presbyterian Hospital/Weill-Cornell Medical Center.

Cancer Research & Treatment Fund
500 East 77th Street, Suite 1001
New York, NY 10162

Telephone: (212) 288-6604
Fax: (212) 288-7704

Web Site: www.crt.org

Richard J. Rose, President

Richard T. Silver, MD FACP
Medical Director

Michael R. Wargo,
Vice President of Development