Hematologic Malignancies

ACUTE PROMYELOCYTIC LEUKEMIA

First-Line Arsenic Trioxide Improves Overall Survival

Adding arsenic trioxide to standard therapy for acute promyeloctytic leukemia improved overall and event-free survival in the phase III randomized North American Intergroup Protocol C9710 trial.

Estimated overall survival at 3 years was 86% for the experimental arm versus 79% for adults and 86% for children given standard treatment without arsenic trioxide (Trisenox), the lead investigator, Dr. Bayard L. Powell, reported in a plenary talk. The arsenic-based therapy was associated with acceptable toxicity, and benefits were observed in all risk groups.

"Arsenic trioxide is definitely established today in the first-line treatment of APL," Dr. Bob Lowenberg, professor of hematology and chair of the department of hematology at Erasmus University in Rotterdam, the Netherlands, responded in a subsequent discussion.

Arsenic trioxide is approved for second-line treatment of acute promyelocytic leukemia (APL). While APL patients with white blood counts greater than 10,000/mcL at diagnosis had a higher rate of death during initial therapy, “arsenic trioxide does substantially reduce the relapse rate for this high-risk group,” said Dr. Powell, professor and section head, hematology and oncology, Comprehensive Cancer Center, Wake Forest University, Winston-Salem, N.C.

After enrollment, 537 patients received initial induction therapy with oral tretinoin 45 mg/m² per day for 7 days plus cytarabine 200 mg/m² as a continuous infusion for 7 days, and daunorubicin 50 mg/m² for 4 days for those aged 3 years and older or 1.5 mg/m² as a continuous infusion for those less than 3 years of age.

The investigators then randomized 243 adults who had achieved complete or partial remission after induction therapy to two courses of arsenic trioxide 0.15 mg/kg per day. Patients received this course as a first consolidation therapy for 5 days each week for 5 weeks with a 2-week rest between cycles.

Subsequent consolidation therapy for all patients included two courses of oral tretinoin 45 mg/m² for 7 days plus 3 days of daunorubicin 60 mg/m² for patients 15 years and older (2 days for those younger than 15 years).

All patients still in remission after completing consolidation therapy were further randomized to 1 year of maintenance therapy with daily oral tretinoin repeated every other week alone or with 6-mercaptopurine 60 mg/m² daily plus methotrexate 20 mg/m² weekly.

In all, 243 adults were randomized to arsenic trioxide therapy. Randomized to standard therapy were 237 adults and 57 children less than 15 years of age. Based on white blood cell counts, 53 adults in the experimental arm were high risk, as were 58 adults and 14 children in the standard arm.

Remissions occurred in 90% of patients randomized to each arm; 75% died during induction, and 5% had insufficient data to determine response.

The Kaplan-Meier estimate for event-free survival at 3 years was better for patients randomized to arsenic trioxide than for adults randomized to standard therapy (81% vs. 66%) (P = .0007). The 3-year event-free survival for pediatric patients (62%) was not significantly different from that of adults who also received no arsenic trioxide.

Complete remission rates, death during induction, and relapse within 1 year were all similar between low- and intermediate-risk patients, but were inferior in high-risk patients.

Among the 243 patients randomized to arsenic trioxide, 16 died during induction, there were insufficient data for 7, and 2 did not achieve remission. Of the other 218 eligible for arsenic therapy, 202 received at least one course and 5 (2%) have relapsed.

Toxicity did not increase during consolidation therapy, nor were there lethal events. There were no grade 3-4 increases in the Q-T interval, which has been previously reported with arsenic trioxide.

In his discussion, Dr. Lowenberg suggested two potential implications of the C9710 trial. First, a dose reduction of anthracyclines used in traditional APL therapy might be possible without compromising outcomes, provided arsenic trioxide is introduced. Second, the addition of arsenic to full-dose optimal standard chemotherapy will allow for improved outcomes in high-risk patients.

Better ways are needed to exploit the therapeutic potential of arsenic, including method and time of application; integration into induction, consolidation, and/or maintenance therapy; whether a higher dose should be used; and how arsenic trioxide could serve patients such as the elderly in whom full-dose chemotherapy is contraindicated.


Commentary

Although acute promyelocytic leukemia accounts for only 10% of the cases of acute myeloid leukemia, it is often feared due to frequent complications, including life-threatening coagulopathy. Understanding of the critical role of the fusion protein PML-RARA in the pathophysiology of the disease and introduction of the differentiating agent all-trans retinoic acid (ATRA) into clinical practice almost 20 years ago revolutionized treatment. Over 70% of patients are now cured by the combination of cytotoxic therapy and ATRA. Arsenic trioxide is also a useful drug for APL patients in relapse. When it is used as a single agent in this setting, more than 80% of individuals achieve remission.

Dr. Bayard Powell presented the results of the latest North American Intergroup study on APL. This randomized phase III study asked whether the addition of two courses of postremission arsenic trioxide reduced the relapse risk for previously untreated patients. The final results confirmed the benefit of arsenic trioxide when given along with standard therapy. Not only event-free but also overall survival was significantly prolonged in the group that received arsenic trioxide. The therapy was well tolerated, and benefited patients in all risk categories. This study should change clinical practice. All patients with previously untreated APL should receive arsenic trioxide as one part of their treatment course. Improvements are still needed for high-risk patients with an initial WBC count higher than 10,000. Subsequent Intergroup studies will specifically target this patient population, and will also test whether lower-risk patients can omit maintenance therapy entirely.

— Steven E. Coutré, M.D.
Hematologic Malignancies | CHRONIC LYMPHOCYTIC LEUKEMIA

Five-Year Data Back FCR as Preferred First-Line Therapy

The combination of fludarabine, cyclophosphamide, and rituximab is the most effective front-line therapy in chronic lymphocytic leukemia, based on 5-year follow-up data from a single-arm study.

Dr. Constantine S. Tam reported on 300 patients who received fludarabine, cyclophosphamide, and rituximab (FCR) as initial therapy for chronic lymphocytic leukemia. Median follow-up was 62 months for responders. Preliminary data were reported previously (J. Clin. Oncol. 2005;23:4079-88).

Of the 300 patients, 72% achieved complete remission as confirmed by the absence of morphologic disease on bone marrow biopsy. Of these, 78% had no detectable disease on flow cytometry.

Partial response was reported in 12%, and nodular partial response in 10%. Only 4% were resistant to FCR. Time to progression for responders was 77 months.

When the analysis was limited to 190 patients with at least 5 years follow-up, actual 5-year-survival was 70%, said Dr. Tam, of the University of Texas M.D. Anderson Cancer Center in Houston.

In a multivariate analysis, independent risk factors for complete remission were age 70 years or greater (hazard ratio 2.1), and β2-microglobulin at least twice that of normal (HR 3.1).

A historical nonrandomized comparison of FCR with 190 patients who received fludarabine monotherapy and 140 patients who received fludarabine plus cyclophosphamide or mitoxantrone at M.D. Anderson indicates that FCR prolongs survival. At 5 years, patients receiving FCR have a 21% absolute improvement in survival as compared with fludarabine monotherapy.

“Compared with FC alone, FCR doubles the rate of complete remission to over 70% and doubles the time to progression to 6 and a half years,” he said. “This has led to a significant improvement in survival for our patients.”

The long-term data analysis gave some insight into late toxicities of FCR, which is intensely immunosuppressive in regard to CD4+ T-cell suppression. The annual risk of infection was 10% in the first year and decreased to 4% in the second year before leveling off at 1%. Opportunistic infections during remission were restricted primarily to the first year. Five infections were fatal.

The 5-year risk of late cytopenias was 25%, and the 5-year risks of Richter transformation and myelodysplasia were 3%. There were two deaths within 3 months of initiating therapy.

Discussant Dr. Kanti Roop Rai of Long Island Jewish Medical Center in New York called the results encouraging, but questioned whether patients with persistent cytopenias should be classified separately from partial responders with residual disease, as suggested by the investigators, when the overall survival curves do not significantly differ.

Dr. Rai called the use of rituximab at a dose of 500 mg/m² “arbitrary,” and suggested it is not worth pursuing without a controlled trial. There is convincing evidence of a synergy between chemotherapy agents and rituximab, “wherein 375 mg/m² rituximab seemed to be quite adequate and successful.”

Dr. Tam has published results of a smaller phase II trial showing favorable results with a rituximab dose of 375 mg/m² (Cancer 2006;106:2412-20). Unpublished results from M.D. Anderson show dose-escalation of rituximab up to 1500 mg/m² per cycle did not achieve superior outcomes in FCR when compared with historical experience with 500 mg/m².

Tam C.S. et al. Seventy percent of complete responders remain in continuous remission: Five-year follow-up of 300 patients treated with fludarabine, cyclophosphamide, and rituximab (FCR) as initial therapy of CLL. Abstract 7008.

Investigational Bcl-2 Blocker Appears Active in Advanced CLL

SPC2996, a novel investigational drug that blocks expression of Bcl-2, appears to be active in advanced chronic lymphocytic leukemia.

Dr. Hervé Tilly of the Centre Henri Bécquereau in Rouen, France, and his colleagues reported in a poster presentation partial responses, stable disease, down-regulation of Bcl-2 concentrations, and reduced lymphocyte counts in findings from an open-label, dose-escalating phase I/II study that administered SPC2996 to 25 patients with relapsed or refractory chronic lymphocytic leukemia (CLL) requiring therapy.

Santaris Pharma, which is developing SPC2996, sponsored the study. One of Dr. Tilly’s colleagues is vice president of clinical development at Santaris Pharma.

SPC2996 is a Bcl-2 mRNA antagonist that is based on a locked nucleic acid (LNA). LNAs are RNA analogs that can recognize and block endogenous gene expression at the chromosomal level. Bcl-2 is an antiapoptotic member of a family of proteins that regulate programmed cell death. Overexpression is thought to be linked with a poor prognosis in many types of cancer, including CLL.

SPC2996 was administered six times over a 2-week period. Patients were treated in five cohorts that received 0.2 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, or 4.0 mg/kg and followed for 6 months. Most patients were men. Overall, the mean age was 64 years, and mean disease duration 6.5 years.

Regression analysis showed a significant trend toward downregulation of Bcl-2 concentrations over the treatment period in the six patients given the highest dose. In addition, all patients in that group had a decrease in lymphocyte count that started within 24 hours of the first infusion. Five had maximum reductions of at least 50%, “indicating a clinically beneficial response,” wrote the authors, who are still studying dosing regimens.

“A dose response effect of SPC2996 on lymphocyte counts was also apparent in this study,” the researchers wrote. Doses of 2 mg/kg resulted in transient reductions of up to 50%. Doses of 1 mg/kg had little or no effect.

One patient in the 2-mg/kg group and two in the 4-mg/kg group had lymph node reductions of at least 50% in the sum of the products of the perpendicular diameters.

One patient in highest-dose group had a partial response that lasted 182 days. Another had a less durable partial response (28-42 days), but continued with stable disease for 4 months. Three other patients in this group also had stable disease. The median estimated time to progression reached 122 days at the highest dose.

Three cases of grade 3 thrombocytopenia were reported. One patient died after two 2-mg/kg infusions, with a diagnosis of tumor lysis syndrome. The data monitoring committee judged the diagnosis to be possibly related to the study medication.


Commentary

A highly regarded investigative team has developed a treatment regimen of fludarabine, cyclophosphamide, and rituximab (FCR) for chronic lymphocytic leukemia (CLL). Based on historic data, it appears that FCR is more effective than previous regimens in CLL. In the study by Tam et al., front-line FCR doubled the rate of complete remission and the time to progression. A critical issue to be delineated in future studies is whether FCR also prolongs survival when compared with other effective approaches. Randomized trials will be necessary to make this determination.

These data are provocative, but the regimen cannot be considered the gold standard at present. The toxicity profile makes it critical that we determine this is the most appropriate regimen to use first-line in CLL before we universally embrace FCR as initial therapy.
Dasatinib 100 mg Once Daily Is Optimal Dosing for CML

The 100-mg once-daily dose was associated with less thrombocytopenia and pleural effusion.

This phase III trial provides the first evidence that transient target inhibition with a tyrosine kinase inhibitor can preserve efficacy and improve tolerability. —Dr. Shah

It also produced significantly better progression-free survival when compared with the current standard dose of 70 mg twice a day (91% vs. 84%, P = .032). No overall survival data were reported.

Dasatinib, a short-acting oral tyrosine kinase inhibitor, mostly targets imatinib-resistant BCR-ABL protein mutations. It is approved at a dose of 70 mg twice daily for adults in all phases of chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib. Its use has been associated with increased pleural effusion, however.

This phase III trial provides the first evidence that transient target inhibition with a tyrosine kinase inhibitor can preserve the efficacy of more continuous inhibition and simultaneously improve tolerability, said the lead investigator, Dr. Neil P. Shah.

“Of course opens the door for consideration of intravenous kinase inhibitors and perhaps even less-frequent dosing as something that should be studied,” said Dr. Shah of the University of California, San Francisco.

The trial accrued patients at 139 centers from July 2005 to March 2006. Investigators first randomized 670 patients with late chronic-phase CML to total daily dasatinib doses of 100 mg or 140 mg. They then subdivided the population into four dasatinib arms: 100 mg once daily (165 patients), 50 mg twice daily (167 patients), 140 mg once daily (165 patients), and 70 mg twice daily (170 patients).

Among the 622 patients who received treatment, the median disease duration was 4 years or more before entering the study. Roughly one-third had previously received imatinib at a dose of more than 600 mg/day, and about three-quarters were resistant to imatinib.

Response rates, with a median treatment duration of 11.5 months, were similar across all arms, reported Dr. Shah, who is a consultant for and has received honoraria from Bristol-Myers Squibb Co., which markets dasatinib and sponsored the study.

The numbers of patients who progressed in each arm at a median of 11.5 months were 16 in the 100-mg once-daily arm; 22 in the 50-mg twice-daily arm; 23 in the 140-mg once-daily arm; and 30 in the 70-mg twice-daily arm.

The incidence of thrombocytopenia (22% vs. 38%, P = .044) and chronic heart failure (0% vs. 4%, P = .015) was significantly reduced when patients received 100 mg once a day compared with 70 mg twice a day.

The 100-mg once-daily dose was associated with a lower incidence of pleural effusion (10% vs. 18%) and neutropenia (33% vs. 43%) compared to the current standard, but the association was not statistically significant, Dr. Shah reported. Likewise, anemia (17% vs. 23%) and leukopenia (34% vs. 45%) were reduced but not significantly.

Treatment interruption (58% vs. 71%, P = .047), dose reduction (33% vs. 57%, P < .001), discontinuation (22% vs. 32%, P = .049) and discontinuation because of toxicity (6% vs. 15%, P = .012) were significantly lower in patients receiving 100 mg once daily rather than 70 mg twice daily, Dr. Shah said. Fewer patients had dose interruptions (66%) and reductions (45%) on 50 mg twice a day than with the standard dose, but the benefit was greater with 100 mg once a day.

The median daily dose was 99 mg in the 100-mg once daily cohort, 90 mg in the 50-mg twice daily cohort, 121 mg in the 140-mg once daily cohort, and 102 mg in the standard 70-mg twice-a-day cohort.

The rationale for the trial came from pharmacokinetic and pharmacodynamic data showing that, unlike most tyrosine kinase inhibitors, dasatinib has a relatively short biologic half-life of only 3.5 hours and does not appear to have a significant long-acting metabolite.

Surprisingly, phase I data demonstrated that dasatinib induces complete hematologic and major cytogenetic responses at total daily doses of 100 mg and 140 mg given once or twice daily, despite achieving only transient inhibition of the BCR-ABL kinase domain when administered once daily (N. Engl. J. Med. 2006;354:2531-41).

Shah N.P. et al. Dasatinib 50 mg or 70 mg BID, compared with 100 mg or 140 mg QD in patients with CML in chronic phase (CP) who are resistant or intolerant to imatinib: 1-year results of CA 180034. Abstract 7004.

The treatment options for patients with chronic myeloid leukemia continue to expand. Although imatinib remains the only tyrosine kinase inhibitor indicated for initial treatment of CML, results of a phase II trial using dasatinib as initial treatment highlight the possibilities for the future.

In that study from the M.D. Anderson Cancer Center in Houston (abstract 70 on the following page), rates of both cytogenetic and molecular responses with dasatinib were similar to those expected with imatinib, but the responses were more rapid than previously reported with imatinib.

Several other studies of dasatinib as initial therapy are ongoing. These include a Southwest Oncology Group trial that randomizes patients between two different starting doses of imatinib or dasatinib. Ultimately, the benefit of earlier responses, whether cytogenetic or molecular, will need to be confirmed by other end points, primarily progression-free survival.

Dasatinib is an approved treatment option for patients who are intolerant or resistant to imatinib. A second-generation kinase inhibitor, it is approved for dosing at 70 mg twice daily.

Note: Based on median treatment duration of 11.5 months.

Response Rates With Dasatinib for Chronic-Phase Chronic Myeloid Leukemia

<table>
<thead>
<tr>
<th>Dose</th>
<th>Complete Hematologic Response</th>
<th>Major Cytogenetic Response</th>
<th>Complete Cytogenetic Response</th>
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<td>100 mg</td>
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<td>62%</td>
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<tr>
<td>70 mg</td>
<td>89%</td>
<td>58%</td>
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Results of a randomized study have demonstrated that transient inhibition of BCR-ABL achieved with once-daily 100-mg dasatinib dosing was equally efficacious and associated with less toxicity than the approved dosing schedule. The study on this page confirms that patients receiving dasatinib for imatinib-resistant or -intolerant chronic-phase CML should be started at a dose of 100 mg once daily.

Finally, two additional second-generation kinase inhibitors, bosutinib and nilotinib, are active against imatinib-resistant CML, with results very similar to those reported for dasatinib. These oral drugs also seem to be well tolerated. Mutation analysis should be obtained prior to starting dasatinib or the two new second-generation tyrosine kinase inhibitors, since none of them have activity against the T315I mutation, which remains a concern.

That physicians soon may be faced with a wealth of choices in treating CML emphasizes the need for vigilance to ensure that our patients are achieving optimal responses, including not only complete cytogenetic remissions but also major molecular responses. —Steven E. Coutré, M.D.
First-Line Dasatinib Produces Rapid Cytogenetic Response

Complete cytogenetic responses were seen in 24 of 31 patients at 3 months and 20 of 21 at 12 months.

Bosutinib, Nilotinib Clinically Active in Imatinib-Resistant CML

The investigational second-generation kinase inhibitors bosutinib and nilotinib are clinically active in the treatment of chronic myelogenous leukemia that is resistant to or intolerant of imatinib, according to separate Italian studies.

Bosutinib (SKI-606), a synthetic quinolone derivative and oral dual inhibitor of the Src and Abl tyrosine kinases, was active across a wide range of mutations in a phase I/II trial that studied 110 patients with Philadelphia chromosome–positive chronic myelogenous leukemia (CML) or acute lymphoblastic leukemia (ALL).

All patients were either imatinib (Gleevec) resistant or intolerant.

Sixteen different imatinib-resistant mutations were found in 36 of 59 evaluable patients, including nine P-loop and eight T315I mutations, lead investigator Dr. Carlo Gambacorti-Passerini said. Complete hematologic response and major cytogenetic response rates did not differ substantially in patients with no mutations, P-loop mutations, or non-P-loop mutations, according to Dr. Gambacorti-Passerini of the Ospedale San Gerardo-Monza, Italy.

The study's primary end point of major molecular response at 12 months was similar to that of historical controls for 400 mg (24%) and 800 mg (47%) of imatinib per day.

The study's primary end point of major molecular response at 12 months was achieved in 56% of patients and a complete cytogenetic response was achieved in 40%.

There are several ongoing phase II trials of bosutinib (AMN107), a highly selective inhibitor of Bcr-Abl kinase activity that has been found, in vitro, to be active against 32 of the 33 most common Bcr-Abl mutations known to cause imatinib resistance. Dr. Gianantonio Rosti presented safety and efficacy data from a phase II open-label trial in which 320 patients with Philadelphia chromosome–positive chronic-phase CML received 400 mg of oral nilotinib twice daily for 6 months or more.

The study's primary end point of major cytogenetic response (MCyR) was achieved in 56% of patients, and a complete cytogenetic response was achieved in 40%.
MGCD0103 and Azacitidine Combination Active in Advanced MDS

The combination of investigational agent MGCD0103 and azacitidine was clinically active in one-third of adults with advanced myelodysplastic syndrome or acute myelogenous leukemia in a phase II/I trial.

Four of 37 patients (11%) achieved complete remission, 5 achieved complete remission without platelet or neutrophil recovery (14%), and 2 achieved partial remission (5%), according to data presented in a poster.

All four with complete remissions had acute myelogenous leukemia, suggesting MGCD0103 may represent a new therapy for them, said investigator Dr. Guillermo García-Manero in an interview.

The rationale for the study was preclinical work demonstrating antitumor synergy between agents that inhibit histone deacetylation and agents that reduce DNA methylation. aberrant DNA methylation and histone acetylation are common in leukemia.

MGCD0103 is a nonhydroxamate, orally available selective inhibitor of human histone deacetylase (HDAC) isoforms 1, 2, 3, and 11. Azacitidine (Vidaza) is a DNA hypomethylating inhibitor approved for myelodysplastic syndrome and chronic myelomonocytic leukemia. It is clinically active in patients with acute myelogenous leukemia.

Patients received azacitidine 75 mg/m² subcutaneously daily for 7 days of each 28-day treatment cycle and oral MGCD0103 three times weekly starting on day 5 of every cycle at an initial dose of 35 mg. MGCD0103 also was evaluated at 60, 90, 110, and 135 mg. Clinical activity at doses of 60, 90, and 110 mg was reported in 11 patients (30%) in the study, supported by MethylGene Inc. and Pharmion Corp., which have a licensing and collaborative agreement for MGCD0103.

HDAC activity was inhibited after treatment in most patients, said Dr. García-Manero of the M.D. Anderson Cancer Center in Houston. HDAC activity was increased at baseline in peripheral blooduffy coat cells and bone marrow of 26 patients, when compared with healthy volunteers. Induction of IL-6 also appeared to increase with dose.

Dose-limiting toxicities included nausea, vomiting, diarrhea, dehydration, and anorexia, and occurred in seven patients.

The maximum tolerated dose of MGCD0103 was initially determined to be 110 mg, but the incidence of dose-limiting toxicities was considered too high. Enrollment in Phase II is continuing at a dose of 90 mg.

No pharmacokinetic characteristics of either drug were altered by coadministration, the investigators reported.

García-Manero G. et al. Phase II/I study of a novel oral isotype-selective histone deacetylase (HDAC) inhibitor MGCD0103 in combination with azacitidine in patients (pts) with high-risk myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). Abstract 7062.
Thalidomide-Melphalan-Prednisone Is Safe After Age 75

The thalidomide-melphalan-prednisone regimen that is given to multiple myeloma patients newly diagnosed between the ages of 65 and 75 can be used in the very elderly as well, according to interim results of the placebo-controlled Intergroupe Francophone du Myelome 01-01 trial in patients 75 years of age and older. A recent interim analysis showed a trend toward better overall survival in patients who received thalidomide with melphalan and prednisone. Based on interim data, lead author Dr. Cyrille Hulin estimated their median overall survival to be 45 months vs. 28 months for a control group given a placebo instead of thalidomide.

Median progression-free survival was significantly longer with the three-drug combination: 24 months vs. 19 months (P = 0.004), Dr. Hulin reported. "Melphalan-prednisone-thalidomide is an effective combination with acceptable toxicity in patients with multiple myeloma who are older than 75 years of age, and these patients [achieve] a significant improvement in progression-free survival," said Dr. Hulin of the Intergroupe Francophone du Myelome.

The study is the first large, double-blind, randomized trial to examine this combination of agents in the older old—a population that accounts for a third of all those with multiple myeloma, according to a discussion by Dr. Sagar Lonial. "This really is a landmark study that's been done in a difficult patient population, and I think it really does potentially set the standard for a number of studies that we're going to be looking at in the future," said Dr. Lonial of the Winship Cancer Institute at Emory University in Atlanta.

The IFM 01-01 protocol called for all patients to receive 12 6-week cycles of melphalan 0.2 mg/kg daily and prednisone 2 mg/kg on days 1 through 4. In addition, they were evenly randomized to receive a placebo or 100 mg daily of thalidomide in two capsules for 72 weeks. No maintenance treatment was given, but everyone received clodronate. Those who had a recent thrombosis were excluded.

Randomization began in April 2002 and closed after enrollment of 232 patients. Dr. Jean-Luc Harousseau presented a planned interim analysis based on the first 200 patients, who were evenly randomized to the placebo and thalidomide arms. The median age was 79 years; one-third of the cohort was over age 80. On clinical assessment 60% presented with significant comorbidities.

After completing therapy, 61% of patients who were given thalidomide had a partial response, and 22% had a very good partial response. The comparable rates for the placebo group were 30% and 8%, respectively. Complete response was achieved in 7% with thalidomide and 1% for placebo, Dr. Hulin added. At 12 months, 61% of the thalidomide arm enjoyed a partial response—almost double the rate in the placebo arm.

Since the protocol started, 93 patients have died: 54 in the placebo arm and 39 in the thalidomide arm. There was, however, little difference in the causes of death, including myeloma and toxicity. Eighty-five patients withdrew from each arm. Toxicity was the primary cause of withdrawal in the thalidomide arm (53%), while disease progression was the primary cause in the placebo group (60%). Nonetheless, Dr. Hulin said that despite the high withdrawal rate, toxicity was acceptable in this population. Among side effects causing withdrawal, he cited, were peripheral neuropathy (11%), thrombosis (7%), or hematologic (7%), neurologic (7%), cardiac (3%), and other adverse events (10%): Causes of 13 toxicity-related withdrawals in the placebo arm included hematologic events (5), peripheral neuropathy (3), and non-peripheral neurological complications (2). There was a single case of thrombosis.

Although grade 3/4 neutropenia was higher in the thalidomide arm (21% vs. 9%), Dr. Hulin described it as manageable. “Four-fifths of patients in the [thalidomide arm] were able to tolerate treatment at least during the initial 6 months, and 65% were able to tolerate it for more than 1 year,” he said, adding that the level of peripheral neuropathy was acceptable and not surprising.

Dr. Hulin considered neurotoxicity might be reduced by shortening duration of thalidomide treatment. In addition, low-molecular-weight heparin or aspirin prophylaxis could reduce thrombosis, he said, concluding “melphalan-prednisone-thalidomide could be the reference treatment for all patients older than 65 years with newly diagnosed myeloma.”

Regarding the toxicity, Dr. Lonial noted that almost 30% of the cohort had peripheral neuropathy at baseline. “The objective testing that was performed in this excellent study is further corroboration that we really need to look at baseline neuropathy if we’re going to assess the neuropathic potential of our novel agents.”

Hulin C. et al. Comparison of melphalan-prednisone-thalidomide (MP-T) to melphalan-prednisone (MP) in patients 75 years of age or older with untreated multiple myeloma (MM). Preliminary results of the randomized, double-blind, placebo controlled IFM 01-01 trial. Abstract 8001.

**Commentary**

The treatment of elderly patients with multiple myeloma remains a challenge. Finding a regimen that is effective and that obviates the need for stem cell transplant is important. The results with melphalan, prednisone, and thalidomide are encouraging in this study of patients aged 75 and older.

Though toxicity was considered acceptable, it is critical that clinicians be aware of the side effect profile of this triple combination, and that they employ strategies to minimize morbidity. Neurotoxicity, observed in 18 of 45 patients who dropped out of the trial because of toxicity, might be reduced by shortening the duration of thalidomide.

— Steven T. Rosen, M.D.

Low-Dose Dexamethasone Plus Lenalidomide Improves Survival

The first results from a multicenter phase III trial by the Eastern Cooperative Oncology Group (ECOG 4A03) indicate low-dose dexamethasone combined with lenalidomide confers a survival benefit over the higher, standard dose of dexamethasone in newly diagnosed multiple myeloma patients.

The potential impact of these findings led the Data and Safety Monitoring Committee to recommend early release of the findings. “The high [96%] 1-year survival rate of low-dose dexamethasone and lenalidomide is striking,” said Dr. S. Vincent Rajkumar a professor of medicine at the Mayo Clinic, Rochester, Minn., where the regimen is now front-line therapy for transplant candidates.

ECOG 4A03 included 445 patients with untreated symptomatic multiple myeloma. All patients received 25 mg of lenalidomide (Revlimid) orally per day on days 1-21 of a 28-day cycle. In addition, 223 patients also received 40 mg of high-dose dexamethasone on days 1-4, 9-12, and 17-20. The remaining 222 patients received 40 mg of low-dose dexamethasone on days 1, 8, 15, and 22.

The first interim analysis included all patients. After 15 months of follow-up, 1-year overall survival was 96% in the low-dose dexamethasone arm, compared with 87% in the high-dose dexamethasone arm (P < .0001). Overall survival differences in favor of the low-dose arm were seen in patients under the age of 65—98% versus 91% (P = .01) and in those aged 65 and older—94%.
versus 83%, respectively (P = .004). Survival was already superior with the low dose at 4 months, and remained in excess of 90% even at 2 years.

The final efficacy data, including the other outcome measures, are expected to be announced at the American Society of Hematology meeting in December.

The low-dose arm was also less toxic. Major grade 3 or higher nonhematologic toxicities, included thrombocytopenia (24% in the high-dose vs. 9% in the low-dose dexamethasone arm), infection/pneumonia (15% vs. 5%), and hyperglycemia, 15% vs. 5%. In terms of major hematologic toxicities, only neutropenia was higher with the low-dose treatment (19% vs. 10%).

Dr. Rajkumar said that he believes the survival benefit is a consequence of improved safety and "possibly improved efficacy," and should be consistent over time. "We don’t expect the survival curves to change. I think this is definite," he added in an interview.

In addition, he said the findings have implications for other regimens. He advises not only switching to lower doses of dexamethasone in combination with lenalidomide, but also considering the termination of the routine use of high-dose dexamethasone in general.

Discussant Dr. Paul Richardson of Harvard University, Boston, applauded ECOG for performing this research in "what will be a landmark study." Dr. Richardson, clinical director of the Jerome Lipper Multiple Myeloma Center at the Dana-Farber Cancer Institute in Boston, said, "The estimated 1-year survival in patients in whom lenalidomide was added would argue this is potentially a new standard for upfront therapy."


Doxorubicin Adds to Bortezomib Benefits in Refractory Disease

The addition of pegylated liposomal doxorubicin to bortezomib increases overall survival and response rates among patients with relapsed or refractory multiple myeloma, according to new data from the multinational phase III DOXIL-MM4-3001 trial.

At a median follow-up of 14 months, 82% of patients in the combination arm and 75% of those treated with bortezomib alone were alive (P = .05). Because the overall survival curves of the two study arms began to diverge at 1 year, the lead author, Dr. Jean-Luc Harousseau, suggested that longer follow-up may bring more significant survival advantages in the combination arm.

Initial results of the DOXIL-MM4-3001 study, presented at the American Society of Hematology meeting in December 2006, showed better response rates and time to progression with the combination of pegylated liposomal doxorubicin (Doxil, Caelyx) and bortezomib (Velcade), but the overall survival advantage was not yet apparent. Doxorubicin is a product of Ortho Biotech Products L.P., a subdivision of Johnson & Johnson, the study's sponsor.

Updating the results, Dr. Harousseau said the primary end point of time to progression had stayed constant, with a 45% risk reduction with pegylated liposomal doxorubicin and bortezomib (PLD-B). Median time to progression was 9.3 months in the PLD-B arm and 6.5 months in the bortezomib-alone arm.

"The combination of PLD plus bortezomib significantly improved not only the time to progression as shown at ASH, but also the overall survival and the response rates," said Dr. Harousseau, professor of hematology at University Hospital in Nantes, France.

Based on the earlier results, the U.S. Food and Drug Administration approved the combination in May 2007 for the treatment of multiple myeloma in patients who had not previously received bortezomib but had at least one prior therapy.

The trial enrolled 646 patients (mean age 62 years), with a median time from diagnosis of 3 years. About 90% of the patients were in relapse; the rest were primary refractory.

Subjects were randomized in a 1:1 ratio to receive either bortezomib at 1.3 mg/m² on days 1, 4, 8, and 11 of every 21-day cycle for up to 8 cycles, or the same dose and schedule of bortezomib but with the addition of the anthracycline PLD at 30 mg/m² given on days 4 of each cycle. Treatment continued for up to a total of 8 cycles unless a complete response, disease progression, or unacceptable treatment-related toxicity occurred.

Dr. Harousseau described the patients as heavily pretreated with one or more lines of therapy, including anthracyclines, thalidomide, or lenalidomide. More than half had undergone at least one autologous transplantation.

Virtually all subgroups, including relapsed and primary refractory patients, benefited from the multidrug regimen, according to Dr. Harousseau. Whether patients had prior stem cell transplantation, anthracycline, or thalidomide treatment did not affect response. "The combination was superior to bortezomib alone in younger patients and those over age 65, as well as patients with intermediate and high levels of β2-microglobulin, while there was no difference in those with low levels of β2-microglobulin," he said.

The overall response rate was 52% for PLD-B, compared with 44% among patients randomized to bortezomib alone. Complete response was similar in both arms, but the investigators produced a significant advantage for the combination therapy group by combining complete response with "very good partial response": 30% vs. 20%.

Both groups received a median of 6 cycles of therapy, compared with 5 cycles at the interim analysis. The addition of PLD did not compromise the ability to administer bortezomib, since the median dose of the proteasome inhibitor in the combination arm was 1.21 mg/m² vs. 1.23 mg/m² in the single-treatment arm.

"The incidence of serious adverse events was slightly increased over what was shown at ASH," Dr. Harousseau said. As expected, the incidences of thrombocytopenia and neutropenia were higher in the combination arm. Grade 3/4 thrombocytopenia occurred in 24% of the single-treatment group and 32% of the combination group, while grade 3/4 neutropenia was seen in 16% of both groups. Peripheral neuropathy occurred with similar frequency in the two groups, at a rate of 42% and 45%, respectively, and grade 3/4 events occurred in about 10% of all patients.

PLD-related events, such as stomatitis and hand-foot syndrome, were rarely observed. "The combination was superior to bortezomib alone in younger patients and those over age 65, as well as patients with intermediate and high levels of β2-microglobulin, while there was no difference in those with low levels of β2-microglobulin," he said. "For the first time, we see that the addition of a traditional agent—an anthracycline—to a novel agent makes a difference" in multiple myeloma, said Dr. Comenzo of Memorial Sloan-Kettering Cancer Center in New York.

Harousseau J.L. et al. Effect of the combination of pegylated liposomal doxorubicin and bortezomib on time to progression (TTP) and overall survival of patients with relapsed/refractory multiple myeloma compared with bortezomib alone. Abstract 8002.

Commentary

This study by French investigators showed that a combination of two active drugs—bortezomib plus liposomal doxorubicin—appeared more effective than bortezomib alone, with a toxicity profile that was acceptable. Overall survival was improved, but the difference was only 3 months. While the initial results are encouraging, especially when considering that these were heavily pretreated patients, we cannot definitively say combination therapy is more effective than the sequential use of these agents. A future challenge for investigators is to study a spectrum of potential combinations and determine which has the greatest benefit for multiple myeloma at each stage of the disease.

— Steven T. Rosen, M.D.