

Highlights From the 46th Annual Meeting of the American Society of Hematology

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Commentaries by: Athanasios Fassas, MD, Bart Barlogie, MD, James Feusner, MD, Neil E. Kay, MD, and John R. Wingard, MD

Multiple Myeloma

Athanasios Fassas, MD

Associate Professor of Medicine
Myeloma Institute for Research and Therapy,
University of Arkansas for Medical Sciences,
Little Rock

Bart Barlogie, MD

Director
Myeloma Institute for Research and Therapy,
University of Arkansas for Medical Sciences,
Little Rock

In Abstract 639 presented at the 2004 annual meeting of the American Society of Hematology (ASH), Stromberg et al¹ presented evidence suggesting that inhibition of insulin-like growth factor-1 receptor tyrosine kinase (IGF-1RTK) in multiple myeloma (MM) cells may be an attractive therapeutic target. IGF-1, produced by the bone marrow stromal cells, is an important mediator of survival, proliferation and migration, and cytotoxic drug resistance in MM cells. Recently, members of the cyclolignan family were found to selectively inhibit the phosphorylation of the IGF-1R α -chain without downregulating the RTK activity of the insulin receptor (and thus avoiding the diabetogenic effect of nonselective compounds). Two IGF-1RTK inhibitors, picropodophyllin (PPP) and deoxypodophyllotoxin, inhibited growth in 9 MM cell lines, providing increased apoptosis and cell cycle arrest at G2/M phase (including 2 drug-resistant subclones). The 2 compounds do not interfere with any specific phosphorylation site of the receptor but rather act via general downregulation of the TK activity. Administration of PPP to mice injected with 5T33MM cells led to significantly lower plasmacytosis, serum paraprotein levels, and marrow microvessel density, and to significantly higher survival compared to control mice (Abstract 640).²

In Abstract 1492, Raje et al³ presented evidence of strong synergism between lenalidomide (Revlimid, Celgene), an immunomodulatory analogue of thalidomide (Thalomid, Celgene) with known in vitro and in vivo single-agent activity against MM, and the mammalian target of rapamycin (mTOR) inhibitor rapamycin, leading to apoptosis of MM cell lines. The combination was able to overcome resistance of MM cell lines to melphalan (Alkeran, Celgene), dexamethasone and doxorubicin and the growth advantage conferred to MM cells by interleukin (IL)-6, IGF-1 or adherence to marrow stromal cells.

In Abstract 536, Cavo et al⁴ updated the results of the “Bologna 96” clinical trial, which prospectively compared a single (Tx-1; 115 patients) versus double (Tx-2; 113 patients) autologous transplantation as first-line treatment in MM patients under the age of 60. Remission induction treatment was with vincristine, doxorubicin, and dexamethasone (VAD) for 4 cycles, followed by high-dose cyclophosphamide and stem cell collection. A conditioning regimen consisting of melphalan 200 mg/m² for Tx-1 and melphalan 120 mg/m² plus busulfan 12 mg/kg for Tx-2 was also administered. With a median follow-up of 45 and 54 months for the Tx-1 and Tx-2 arms, respectively, Tx-2 prolonged event-free survival (EFS) by 12 months ($P=.001$) in comparison with Tx-1. The 6-year projected overall survival (OS) probability was 44% for Tx-1 and 63% for Tx-2 ($P=.3$). Double transplant particularly benefited patients who failed to achieve complete response (CR) or near CR after the first transplant. Compared to Tx-1, Tx-2 significantly extended OS ($P=.04$) and EFS ($P<.0001$) among patients who failed CR or near CR at the completion of the entire assigned treatment program. This report confirms the findings of Intergroup Francophone du Myelome (IFM) 94 trial.

The benefit (if any) and the duration of maintenance treatment following autologous transplantation in MM are not yet defined. In Abstract 535, Attal et al⁵ presented preliminary data from IFM 9902, a prospective trial of MM patients under the age of 65 who, in the absence of

progressive disease 2 months after double transplant, were randomized to no maintenance treatment, pamidronate (Aredia, Novartis) maintenance or pamidronate plus thalidomide maintenance. With a median follow-up from diagnosis of 26 months (in 580 randomized patients) thalidomide improved EFS ($P < .01$). The OS was similar in the 3 groups. These data should be weighed against the information reported in Abstract 1483 by Barlogie et al,⁶ who found inferior postrelapse survival in patients receiving thalidomide from diagnosis (through the transplant phase and as maintenance treatment) compared to patients who were randomized to no upfront use of thalidomide in a prospective, randomized trial, thus suggesting the emergence of a more aggressive disease clone in patients already exposed to thalidomide. More data are needed to optimally integrate the use of thalidomide (and other emerging therapeutic agents) in MM management.

As active new agents are increasingly used in an effort to halt the progression of monoclonal gammopathy of undetermined significance (MGUS) to MM, more reliable predictors of this transition are needed. In this setting, Rajkumar et al⁷ describe their findings of an abnormal serum free light chain (FLC) ratio as an independent risk factor for progression of MGUS to MM (Abstract 3647). Serum samples for measurement of serum free κ and λ light chains were available in 1,148 out of 1,384 patients diagnosed with MGUS at the Mayo Clinic over a period of 35 years (1960–1994). At a median follow-up of 15 years, progression to MM and other related disorders occurred in 87 (7.6%) patients. An abnormal FLC ratio was detected in 379 (33%) patients. Patients with an abnormal FLC ratio had a significantly higher risk of progression (hazard ratio: 3.5; $P < .001$) compared to patients with normal ratio. The hazard ratio decreased only slightly after adjusting for the size of the serum paraprotein; rates of progression were 17% and 35% at 10 and 20 years, respectively for patients with an abnormal FLC ratio. For patients with a normal FLC ratio, the rates of progression were 5% and 13% at 10 and 20 years, respectively.

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Acute Promyelocytic Leukemia

James Feusner, MD

Chief, Oncology

Children's Hospital Oakland

Adjunct Professor, Pediatrics

University of California, San Francisco

Of the more than 90 abstracts on acute promyelocytic leukemia (APL) presented or published at the 2004 American Society of Hematology annual meeting, 2 topics were of particular interest: the role of cytosine arabinoside (AraC) in treatment of APL, and the expanding use of arsenic trioxide (ATO).

Ades et al¹ reported on their recently closed prospective, randomized trial of AraC in patients with newly diagnosed APL. All patients with a presenting white blood cell (WBC) count of less than 10,000/ μ L were randomized to receive or not receive AraC. All patients received daunomycin (60 mg/kg/day, days 1–3) and all-trans retinoic acid (ATRA; 45 mg/m²/d) as induction therapy, and the same agents for 2 cycles of consolidation. All patients remaining in remission were then placed on maintenance therapy consisting of daily 6-mercaptopurine, weekly methotrexate, and pulses of ATRA (15 days every 3 months) for 2 years.

The study was closed prematurely 38 months after initiation due to findings of significantly inferior relapse-free survival (RFS) in the patients not receiving AraC. Specifically, the CR for the 2 groups (80 receiving AraC vs 87 not receiving AraC) was not significantly different (98% vs 94%), but the 2-year RFS and EFS rates were different: 3.8% vs 11.9%, $P = .021$; and 93.6% vs 83.4%, $P = .019$. In addition, there was a trend to inferior 2-year survival in the non-AraC group: 89.9% vs 97.4% ($P = .085$). This high-quality data strongly suggest that AraC does in fact have a role in APL treatment, at least when daunomycin is used as the anthracycline.

The activity of ATO in APL has been known in China for decades, but only since the mid-1990s in the West. The role of ATO was first investigated in the US in relapsed APL, and now there are an increasing number of reports of its use in newly diagnosed patients. Two reports

at ASH highlighted the potential role of ATO in newly diagnosed APL patients.^{2,3}

A study from the University of Texas M. D. Anderson Cancer Center by Estey et al² utilized ATRA 45 mg/m²/d, starting d 1, plus ATO 0.15 mg/kg/d, starting d 10 as the backbone of therapy for patients with newly diagnosed APL. Gemtuzumab ozogamycin (Mylotarg, Wyeth) 9 mg/m² was given once in induction for high-risk patients (diagnostic WBC count >10,000/ μ L). Once in CR, patients were continued on the ATO/ATRA combination for another 6 months. The CR rate was 88% for the patients overall, with a rate of 85% among high-risk patients. Seventeen patients were managed with ATRA/ATO alone for a median of 7 months (range, 3–24 months). To date, only 2 of these 17 have become positive by polymerase chain reaction for PML-RAR α , the molecular marker for this disease. Although the number of patients is small and the follow-up still relatively short, this preliminary data is exciting and needs to be confirmed.

The second report of ATO highlighted here is from India, by George et al.³ Newly diagnosed APL patients were treated primarily with ATO alone: 10 mg/day in adults and 0.15 mg/kg/day in children. Patients were treated for up to 60 days for remission of induction, followed by 28 days rest and then maintenance with 10 days ATO every month for 6 months. Patients who developed rising WBC counts (exact values not specified) were given hydroxyurea (n=43), and 3 patients received an anthracycline (details not provided). The overall CR rate (intent to treat) was 81%, and this rate increased to 95% when the 9 patients who died from intracranial hemorrhage less than 2 weeks into treatment were excluded. At a median follow-up of 23 months (range, 3–79 months), 45 patients remain alive in molecular remission. Only 4 patients have relapsed, and 3 of these achieved a second remission with ATO used in combination with ATRA. These data are very impressive, although there are some deficiencies and oddities in this report. For example, the exact definition of APL diagnosis was not provided, and details on hydroxyurea and anthracycline use were lacking. The incidence of the differentiation syndrome is unclear, and there was a very high incidence of fatal intracerebral hemorrhage (17%). However, the longer-term follow-up and definitive report on this treatment approach should be followed closely. This report may have tremendous impact on how APL is treated in countries with limited healthcare resources.

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Chronic Lymphocytic Leukemia

Neil E. Kay, MD
Professor of Medicine
Staff Physician
Mayo Clinic

It is not often that truly significant advances in the overall management of human malignancies can be discerned without the perspective of time. However, within the limited space here I will highlight some work from recent publications and ASH abstracts that indicate that we are living within such a moment in the care of B-cell chronic lymphocytic leukemia (CLL) patients. This advancement is occurring for several aspects of management, including more specific sensitive monitoring of CLL clones,¹ development and incorporation of novel prognostic parameters, for counsel of individual patients,² and more effective combination therapies. I will briefly review some of the advances in combination therapies and/or use of novel agents for CLL presented at the ASH meeting in December 2004. These approaches provide unique and more effective treatments for both previously untreated and relapsed/refractory CLL patients.

What do we have to offer as novel therapies beyond the chemoimmunotherapy (CIT) approaches, which utilize either fludarabine (Fludara, Berlex) or pentostatin (Nipent, SuperGen) with rituximab (Rituxan, Genentech/IDEC) for CLL patients? It is important to recognize the contribution from the Eastern Cooperative Oncology Group reported by Flinn et al.³ A phase III randomized study of fludarabine (F) versus fludarabine and cyclophosphamide (FC) was conducted in patients with previously untreated CLL. Seventeen percent of patients receiving FC had grade 4 or higher nonhematologic toxicities, while in the F alone arm, 13% had high-grade toxicities. Infections were observed in 17% of FC patients versus 11% of F-alone patients. In the FC arm (n=125), CR was seen in 22.4% and partial response (PR) in 48.0%, for an overall response (OR) rate of 70.0%. In contrast, only 5.8% of patients on the F-alone arm experienced a CR and 43.8% a PR, for an OR rate of 49.6%. The investigators estimate that the median progression-free survival time was 41.0 months for the FC arm, and

17.7 months for the F regimen. This important study shows that the F-alone regimen had a CR rate of 5% and that the FC combination is significantly better for previously untreated CLL patients.

Wierda et al⁴ further explored the use of CIT in relapsed/refractory CLL patients in a phase II trial. A "CFAR" regimen, which consisted of cyclophosphamide (C) 250 mg/m² d 3–5; F 25 mg/m² d 3–5; alemtuzumab (A [Campath, Berlex]) 30 mg, d 1, 3, 5; and rituximab (R) 375–500 mg/m² d 2, was administered every 28 days for 6 cycles. This group of CLL patients was very difficult to treat, as evidenced by the number of prior treatments (median, 4; range, 1–8), and 13 and 10 patients were refractory to alkylator or fludarabine therapy, respectively. In addition, 11 patients had previously received FCR and 2 had undergone allogeneic or autologous stem cell transplant. Nevertheless, the CR, PR, and OR rates (by National Cancer Institute Working Group criteria) for 21 patients were 14%, 38%, and 52% respectively. Importantly, patients in CR were found to be negative for residual disease in the bone marrow using a 2-color flow cytometry method. However, grade 3/4 neutropenia was found in 23% and 39% and grade 3/4 thrombocytopenia occurred in 23% and 16% of 70 evaluable courses, respectively. Cytomegalovirus (CMV) reactivation was also noted in 5 of 21 patients. While the CFAR regimen is clearly active in a heavily pretreated cohort of CLL patients and should be considered an option, the toxicity of marrow suppression and prevalence of CMV reactivation remains an issue.

In a related CIT approach, Lammana et al⁵ reported on the use of pentostatin, cyclophosphamide and rituximab (PCR) in relapsed/refractory CLL. The PCR regimen consisted of pentostatin 4 mg/m² and cyclophosphamide 600 mg/m² upfront, with rituximab 375 mg/m² added starting with cycle 2. This therapy was given every 3 weeks for a total of 6 cycles and was administered to heavily pretreated CLL patients with a median number of prior regimens being 2 (range, 1–7). Thirty-two patients with CLL were treated on this regimen and 28 were evaluable for response. Among this group of patients, 79% exhibited clinical responses, including 29% who achieved a CR. Thus, pentostatin combination approaches appear very promising for relapsed/refractory CLL.

A long-awaited study was reported by Rai et al.⁶ This trial employed the use of antisense to the antiapoptotic Bcl-2 protein designated as oblimersen (Genasense, Genta) in combination with F and C for relapsed or refractory B-CLL. In this randomized, multinational phase III trial, the 3-drug combination was compared to FC alone. In this protocol, all patients received fludarabine 25 mg/m²/d plus cyclophosphamide 250 mg/m²/d for 3 days. Patients were randomized to oblimersen 3 mg/kg/d

× 7 days by intravenous infusion, beginning 4 days before FC and on each day of FC treatment. Subsequent cycles were repeated every 28 days for a maximum of 6 cycles or to the time of CR, intolerable toxicity, or progression. Seventy-one patients received oblimersen plus FC and 62 received FC alone. The patients were equivalent with respect to Rai stage, prior therapies, age, and gender distribution. The prior therapies were very widespread in type, with both groups having a median of more than 3 prior regimens. Patients receiving oblimersen plus FC had a shorter time to response and superior response levels, with a 16% OR rate (11% CR and 5% nodular [n] PR) compared to an 8% OR (3% CR and 5% nPR) for patients receiving FC alone ($P=.039$). The remission duration for patients receiving oblimersen plus FC was 16.5+ months, compared to 14.⁹ months for the FC cohort. OS for the former group was not yet reached at the time of the report, compared to 26.2 months for the FC cohort. However, in relapsed CLL, marrow suppression was prominent for both groups. Grade 3/4 neutropenia was observed in approximately 60% of patients in both cohorts and grade 3/4 thrombocytopenia was observed in 55% of patients on the oblimersen-containing arm and 32% of patients receiving FC alone. Nevertheless, this novel combination approach is encouraging and adds a unique strategic opportunity to exploit in our attempt to better treat CLL.

In summary, an array of novel combinations is now available for this still incurable disease. It is encouraging that we are now able to choose from several therapeutic options for the relapsed/refractory CLL patient. However, this enthusiasm is tempered by the occurrence of marrow and immune suppression and the consequences of these for our patients.

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Can T Regulatory Cells Be Used to Optimize Adoptive Immunotherapy?

John R. Wingard, MD
Professor and Program Director
University of Florida Health Sciences Center

Regulatory T cells are under current investigation for their potential to explain a variety of immunologic clinical phenomena, with an eye to exploitation for treatment of a variety of immunopathologic conditions. Although collectively known as “Tregs,” the cells that functionally exert immunoregulatory effects are heterogeneous. Tregs are known to regulate allograft rejection and tolerance, control graft-versus-host disease (GVHD), and mediate a variety of other immunologic responses, and deficiencies seem to account for various autoimmune phenomena. Several groups have explored the role of Tregs in GVHD and their antitumor effects after hematopoietic cell transplantation (HCT). In preclinical models, the number of Tregs in donor grafts was associated with less GVHD and infusion of donor Tregs led to amelioration of GVHD.

Lan et al,¹ from Stanford University, have shown in an animal model of HCT that one type of Tregs (natural killer [NK]-T) can be given a selective advantage by the use of total lymphoid irradiation (TLI) rather than total body irradiation (TBI) as a conditioning regimen. The increased percentage of regulatory NK-T cells was sustained and these cells elaborated interleukin (IL)-4 and IL-10. The results of a phase I/II clinical trial were presented at the 2004 ASH annual meeting.² The goal of the trial was to determine if the human experience mirrors the findings in mice with lower rates of GVHD and to determine if antitumor effects are sustained and protection against infectious complications is preserved.

Participants were conditioned with 800 cGy TLI given in 10 fractions plus 5 doses of rabbit antithymocyte globulin at a dose of 1.5 mg/kg/day. Thirty-seven patients with high-risk hematologic malignancies were transplanted using granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood mononuclear cells from HLA-matched donors. Engraftment occurred in all patients by 2 months. Twenty-seven of the 37 patients were alive at a median of 262 days. Only 1 patient developed acute GVHD (grade 3), and 6 patients developed chronic GVHD (of 35 patients followed for at least 100 days). Of 18 patients transplanted in partial remission, 11 converted to complete remission, suggesting retention of the

graft-versus-tumor effect. CD4-positive T cells collected 1–6 months after HCT showed an increase in secretion of IL-4 following in vitro stimulation and significantly reduced proliferative responses to allogeneic targets in mixed lymphocyte reaction assays, as compared to normal controls. CD8-positive T cells demonstrated robust cytolytic activity in the cell-mediated lympholysis assay. These data suggest that T regulatory cells were favored as in the animal model. There was no apparent increase in infections. The authors noted that the regimen was generally well tolerated and could be largely performed in the outpatient setting, and concluded that this regimen offered promise in achieving an immunotherapeutic benefit with a lesser risk of GVHD.

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Hemostasis and Thrombosis

Thomas L. Ortel, MD, PhD
Associate Professor of Medicine
Division of Hematology
Duke University Medical Center

The diagnosis and management of hemostatic and thrombotic disorders featured prominently at the 2004 ASH annual meeting. Four educational sessions, 14 simultaneous sessions, and 15 poster sessions covered a broad array of topics relevant to the hematologist specializing in hemostatic and thrombotic disorders.

Two presentations relevant to thrombotic disorders were included in the plenary session. First, Westrick et al¹ used a genome-wide N-ethyl-N-nitrosourea (ENU) mutagenesis screen in the mouse to identify new genetic modifiers that impact on thrombotic events, which may lead to identifying new prothrombotic mechanisms in humans. Second, Green et al² reported on the results from the Medical Research Council PT1 trial comparing hydroxyurea to anagrelide (Agrylin, Shire) in patients with essential thrombocythemia at high risk for vascular

events. This prospective, international, randomized controlled trial found that the composite primary outcome of arterial thrombosis, venous thrombosis, or major hemorrhage was significantly more common in patients treated with anagrelide and aspirin compared to hydroxyurea and aspirin ($P=.03$).

Prevention and treatment of inhibitor development in patients with hemophilia remains an important clinical problem. Santagostino et al³ reported that starting prophylaxis early in patients with severe hemophilia A, within the first 20 exposure days, decreased the risk of inhibitor development independently of age at first factor VIII exposure. Strategies exploring the possibilities of oral tolerance regimens, using fragments of the factor VIII molecule,⁴ and whether recombinant hybrid human/porcine factor VIII molecules might be less immunogenic⁵ were studied in murine models of hemophilia.

Kuter et al⁶ reported on the use of a novel thrombopoietic agent that binds and activates the thrombopoietin receptor in a randomized, double-blind placebo-controlled phase II trial in patients with immune thrombocytopenic purpura. They found that the agent was well-tolerated and increased platelet counts to a target range of 50–450 × 10⁹ platelets/L in 7 of 8 patients receiving the 1 µg/kg dose of study drug. Over half of the responding patients had had a prior splenectomy. In contrast to the problems encountered in patients with low platelet counts, Khorana et al⁷ reported that cancer patients with platelet counts ≥350 × 10⁹ platelets/L prior to initiation of chemotherapy had a 3-fold greater risk for developing venous thromboembolism.

Several oral presentations discussed important issues concerning the management of antithrombotic therapy. First, Dr. Buller, representing the MATISSE Investigators, reported safety and efficacy data for the initial outpatient treatment of patients with deep venous thrombosis or pulmonary embolism with fondaparinux.⁸ He also presented a subset analysis documenting safety and efficacy of fondaparinux (Arixtra, GlaxoSmithKline) in obese patients.⁹ Second, Kearon et al¹⁰ reported that subcutaneous, fixed-dose, weight-based administration of unfractionated heparin (UFH) was as effective and safe as low-molecular weight heparin (LMWH). They randomized patients with acute venous thromboembolism to receive either UFH (333 U/kg load, followed by 250 U/kg subcutaneous every 12 hours, with no active partial thromboplastin time monitoring) or LMWH, converted to warfarin with a target international normalized ratio of 2–3. After 3 months, the incidence of recurrent thromboembolism or major bleeding was similar for patients receiving UFH or LMWH, suggesting that using UFH by

this approach may be an alternative for initial outpatient therapy of venous thromboembolism. Lastly, several groups reported on the safety and efficacy of bridging strategies with LMWH in patients requiring temporary cessation of long-term oral anticoagulant therapy for surgery or invasive procedures, including patients with prosthetic heart valves,^{11,12} and Wang et al reported on the safety of coadministration of prophylactic LMWH and epidural analgesia in patients after major orthopedic surgery.¹³

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