

Multiple myeloma: present and future

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Multiple myeloma is a clonal B-cell tumor of slowly proliferating plasma cells within the bone marrow. Among hematologic malignancies, it constitutes 10% of the cancers and ranks as the second most frequently occurring hematologic cancer in the United States, after non-Hodgkin lymphoma. Interleukin-6 is an important cytokine in myeloma cell growth and proliferation. Close cell-to-cell contact between myeloma cells and the bone marrow stromal cells triggers a large amount of interleukin-6 production, which supports the growth of these cells, as well as protecting them from apoptosis induced by dexamethasone and other chemotherapeutic agents. Therapies modulating the tumor and its microenvironment are being actively pursued with the goal of converting multiple myeloma to a chronic disease with the patients maintaining a normal lifestyle. *Curr Opin Oncol* 2002, 14:31–35 © 2002 Lippincott

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Abbreviations

HDT high-dose therapy
VEGF vascular endothelial growth factor

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Multiple myeloma is a clonal B-cell tumor of slowly proliferating plasma cells within the bone marrow [1]. Among hematologic malignancies, it constitutes 10% of the cancers and ranks as the second most frequently occurring hematologic cancer in the United States, after non-Hodgkin lymphoma. A recent study explored whether dietary factors contribute to the risk of multiple myeloma and the twofold higher incidence among black people compared with white people in the United States. Data from a food frequency questionnaire were analyzed for 346 white and 193 black subjects with multiple myeloma, and 1086 white and 903 black control subjects who participated in a population-based case-control study of multiple myeloma in three areas of the United States. This study concluded that the greater use of vitamin C supplements by whites and the higher frequency of obesity among blacks may partially explain the higher incidence of multiple myeloma among blacks compared with whites in the United States. In addition, the increasing prevalence of obesity may have contributed to the upward trend in the incidence of multiple myeloma during recent decades [2••]. The median age of onset of multiple myeloma is 68 years. The exact etiologic agent in the causation of myeloma is unknown, but several agents have been strongly associated with the development of this disease. Ionizing radiation is the strongest described risk factor for development of multiple myeloma [3]. Atomic bomb survivors have almost five times the risk of a control group [4]. Nickel, agricultural chemicals, petroleum products and other aromatic hydrocarbons, benzene, and silicon have been considered potential risk factors. Even though monoclonal gammopathy of undetermined significance is considered a premalignant condition, very few patients go on to develop myeloma, and additional genetic changes seem to be required for this progression to occur [5]. The role of human herpesvirus-8 in the causation of myeloma remains intriguing, but human herpesvirus-8 has not been convincingly depicted as a causative agent, nor do patients with myeloma have antibodies against the virus [6,7].

Tumor biology

Cytogenetic and molecular genetic alterations

Cytogenetic alterations have major prognostic and therapeutic implications in patients with acute leukemia. Because of the low proliferative activity of the mature B-cell clone in multiple myeloma, standard cytogenetics yields abnormal karyotypes in only 30% to 50% of the cases studied. On detailed analysis using fluorescent in

situ hybridization probes, 80% of 50 patients studied were found to have molecular deletions, with 13q14 representing the most frequently involved site [8]. Complex karyotypes involving more than three chromosomes occur in about 80% of the patients when tested with more sensitive techniques. Furthermore, the cells with “normal” karyotype that are often found usually derive from the normal hematopoietic cells and not from the malignant clone [9]. Partial or complete deletion of chromosome 13q- arm has been shown to confer a poorer prognosis and a poor response to therapy [10]. Data on 1000 consecutive patients treated with high-dose therapy at a single institution showed that chromosome 13 abnormalities were present in 16% of treated patients. The presence of chromosome 13 abnormalities reduced the 5-year event-free survival rate from 20% to 0% and the overall survival rate from 44% to 16% (both $P < 0.0001$) [11••]. Although cytogenetic and molecular deletion of chromosome 13 is associated with poor prognosis, a multiple myeloma tumor suppressor gene has not been identified [12].

Cytokines, adhesion molecules, and angiogenesis

Interleukin-6 is an important cytokine in myeloma cell growth and proliferation [13]. Close cell-to-cell contact between myeloma cells and the bone marrow stromal cells triggers a large amount of interleukin-6 production, which supports the growth of these cells, as well as protecting them from apoptosis induced by dexamethasone or other chemotherapeutic agents [14]. Interleukin-6, however, is not an absolute requirement for the proliferation of myeloma cells, and anti-interleukin-6 antibody has not been shown to provide much clinical benefit [15]. A recent study shows that vascular endothelial growth factor (VEGF), in addition to its known stimulation of bone marrow angiogenesis, also has direct effects on multiple myeloma cells. The results of this study suggest that VEGF stimulates proliferation and migration of multiple myeloma cells by both autocrine and paracrine mechanisms. Within the bone marrow, VEGF is produced by both multiple myeloma cells and bone marrow stromal cells. Interleukin-6 secreted by bone marrow stromal cells enhances the production and secretion of VEGF by multiple myeloma cells; conversely, VEGF secreted by multiple myeloma cells enhances interleukin-6 production by bone marrow stromal cells. Moreover, binding of multiple myeloma cells to bone marrow stromal cells enhances both interleukin-6 and VEGF secretion, suggesting an autocrine VEGF loop [16••]. Therefore, treatment strategies targeting the different cytokines involved in the growth and development of the myeloma cell are currently being investigated.

Therapy

Therapy for multiple myeloma could be artificially divided into categories of active care and supportive care. Active care could be further divided into an induction

phase and a maintenance phase. With this algorithm in mind, we will briefly discuss new and upcoming aspects of each category.

Active care

Autologous and stem cell bone marrow transplant

The low rate of morbidity and the improved results in selected patients, as well as the psychological effects of taking an aggressive treatment approach, are resulting in the increased use of single bone marrow transplantation in the management of multiple myeloma. In a report of 77 patients with multiple myeloma who fulfilled the criteria for transplant (age younger than 66 years, stage II or III disease, good performance status, and disease responsive to initial chemotherapy) but who were treated with conventional chemotherapy, median survival was 5 years, which is similar to the result in patients treated with autologous stem cell transplantation [17]. A randomized trial by the French Myeloma Group compared high-dose chemotherapy and autologous bone marrow transplantation with conventional chemotherapy in 200 previously untreated myeloma patients younger than 65 years of age [18]. Data were analyzed on an intention-to-treat basis, in which 25% of the patients who were randomized to transplantation did not receive a transplant. The response rate (81% versus 57%) and complete responses (22% versus 5%) were superior in the transplant group. The 5-year event-free survival rate (28% versus 10%) and overall survival rate (52% versus 12%) were superior in the transplant group. In the multivariate analysis of all 200 patients, event-free survival was significantly related to the level of β_2 -microglobulin in serum ($P < 0.001$) and the treatment assignment ($P = 0.01$). Overall survival was related only to the level of β_2 -microglobulin ($P < 0.001$), suggesting that patient selection plays an important role in response and survival. Another issue in the use of autologous bone marrow transplantation is the timing of the transplant, that is, early versus late. In a multicenter, sequential, randomized trial designed to assess the optimal timing of high-dose therapy (HDT), 185 patients were randomly assigned to receive HDT and peripheral blood stem cells (early HDT group, $n = 91$) or a conventional-dose chemotherapy regimen (late HDT group, $n = 94$). In the late HDT group, HDT and transplantation were performed as rescue treatment in cases of primary resistance to conventional-dose chemotherapy, or at relapse in responders. Peripheral blood stem cells were collected before randomization, after mobilization by chemotherapy. In the two groups, HDT was preceded by three or four treatments with vincristine, doxorubicin, and methylprednisolone. Data were analyzed on an intent-to-treat basis. Within a median follow-up period of 58 months, estimated median overall survival was 64.6 months in the early HDT group and 64 months in the late group. Early HDT may be preferred because it is associated with a shorter period of chemotherapy [19].

Tandem transplant became an attractive therapeutic tool because of the low rates of morbidity and mortality associated with the procedure. Although tandem transplant carries a slightly higher risk when compared with single autotransplant, it appears to offer a survival advantage, especially in the group of patients who receive their second transplant in a timely fashion and did not express chromosome 13 abnormalities [11••]. This could be a function of changing the tumor biology or of treatment selectivity, which allows patients with the best performance status and prognostic criteria to receive the second transplant. The French group has updated the data of the IFM94 of single versus double transplant in an abstract format, where double transplant was not found to improve the median event free of overall survival rate [34]. Longer follow-up and further research in this area is underway. Until these data are available, the use of this procedure should be within the confinements of well-designed studies.

Allogeneic bone marrow transplantation

The major advantage with allogeneic bone marrow transplantation is that the graft contains no tumor cells that can lead to a relapse in addition to the theoretical benefit of graft-versus-myeloma effect. Unfortunately, over 90% of patients with multiple myeloma are ineligible because of their age, lack of an HLA-matched sibling donor, or inadequate renal, pulmonary, or cardiac function. Furthermore, there is currently a mortality rate of at least 25%.

In a report of 266 patients from the European Blood and Bone Marrow Transplantation registry, 51% obtained a complete response. The overall treatment mortality rate was approximately 40%. The actuarial survival rate was 30% at 4 years and 20% at 10 years [20]. This treatment modality should be used within the boundaries of research studies.

Thalidomide and its immune modulators

Although thalidomide was initially used to treat multiple myelomas because of its known antiangiogenic effects, the mechanism of its anti-multiple myeloma activity is unclear. Thalidomide and its second-generation immune modulators induce apoptosis or G1 growth arrest in multiple myeloma cell lines and in patient multiple myeloma cells that are resistant to melphalan, doxorubicin, and dexamethasone [21••]. Moreover, by modulating the profile of adhesion molecules, thalidomide may influence the growth and survival of tumor cells [22]. The adhesion of malignant plasma cells to bone marrow stromal cells triggers the secretion of cytokines, augmenting the growth and survival of myeloma cells and inducing drug resistance in them [21,23]. In the largest study to date, single-agent thalidomide was administered orally to 169 patients, at a starting dose of 200 mg/d that was escalated in 200 mg increments every 2 weeks to a maximum dose of 800 mg/d, as tolerated. In 36% of those

patients, there were partial to complete responses (25% to 100% reduction in serum or urine monoclonal protein levels). At a median follow-up of 22 months, 48% of patients are projected to be alive at 2 years, with 26% of those patients disease-free [24••]. When the same thalidomide dose schedule was administered in combination with dexamethasone to 47 patients with relapsed or refractory myeloma, the overall response rate was 52% (based on greater than 50% reduction in serum M protein), with a projected median remission duration of more than 10 months [25]. This group of drugs has been a major addition to the therapy of myeloma, and ongoing clinical research should characterize the dose, timing, and duration of therapy and its role in combination with other biologics as well as chemotherapy.

Arsenic trioxide

Arsenic trioxide (As_2O_3) has recently been used successfully in the treatment of acute promyelocytic leukemia. However, the mechanism by which arsenic trioxide exerts its antileukemic effect remains uncertain. Roboz *et al.* [26] have shown that treatment of proliferating layers of human umbilical vein endothelial cells with a variety of concentrations of arsenic trioxide results in a reproducible dose- and time-dependent sequence of events marked by change to an activated morphologic type, up-regulation of endothelial cell adhesion markers, and apoptosis. Also, treatment with arsenic trioxide caused inhibition of VEGF production in the leukemic cell line HEL. Finally, incubation of human umbilical vein endothelial cells with arsenic trioxide prevented capillary tubule and branch formation in an in vitro endothelial cell-differentiation assay. Thus, arsenic trioxide interrupts a reciprocal stimulatory loop between leukemic cells and endothelial cells by causing apoptosis of both cell types and by inhibiting leukemic cell VEGF production. Moreover, preclinical evidence generated by Deaglio *et al.* [27••] suggests an immunologic mechanism behind the therapeutic effects of arsenic trioxide on myeloma cells. Exposure of RPMI 8226, Karpas 707, and U266 human myeloma-like lines to low doses of arsenic trioxide was followed by a marked increase in lymphokine-activated killer-mediated killing and up-modulation of CD38 and CD54, two molecules involved in cell-cell interactions. The expression of CD31 (CD38 ligand) and CD11a (CD54 ligand) was also up-regulated by lymphokine-activated killer cells, suggesting that increased adhesion was responsible for the improved killing. These findings indicate that arsenic trioxide through its modulation of the VEGF and the immune systems may be useful in the management of plasma cell dyscrasia. Another mechanism of action could be related to the intracellular glutathione content that has a decisive effect on As_2O_3 induced apoptosis. Highly sensitive NB4 cells had the lowest glutathione and the sensitivity of other cell lines was inversely proportional to their glutathione content. The t (14; 18) B-cell lymphoma cell line

had low glutathione levels and sensitivity to As_2O_3 at levels slightly higher than in APL cells. Experimental modulation of glutathione content decreased the sensitivity to As_2O_3 . Ascorbic acid and buthionine sulfoxide decreased glutathione largely, and rendered malignant cells more sensitive to As_2O_3 . As_2O_3 induced apoptosis was not enhanced by ascorbic acid in normal cells, suggesting that the combination of ascorbic acid and As_2O_3 may be selectively toxic to some malignant cells. Ascorbic acid enhanced the anti-lymphoma effect of As_2O_3 in vivo without additional toxicity. Thus, As_2O_3 alone or administered with ascorbic acid may provide a novel therapy for lymphoproliferative disorders [33]. Indeed, preliminary clinical data suggest a role in the management of the disease; however, this is more likely to be in combination with other immunomodulators or chemotherapy.

Supportive care

Bisphosphonates

Bisphosphonates are potent inhibitors of osteoclastic activity and are used in the treatment of multiple myeloma in combination with chemotherapy. In 62 newly diagnosed patients with multiple myeloma, the effect of pamidronate on markers of bone resorption cross-linked *N*-telopeptide of type I collagen, markers of bone formation such as serum alkaline phosphatase and osteocalcin, interleukin-6, β_2 -microglobulin, C-reactive protein, paraprotein, and disease-related pain as well as skeletal events has been evaluated. The patients were randomly assigned to two groups: group I consisted of 32 patients receiving chemotherapy and pamidronate and group II of 30 patients receiving chemotherapy only. The addition of pamidronate to chemotherapy resulted in a significant reduction of *N*-telopeptide, interleukin-6, and paraprotein from the 3rd month and of β_2 -microglobulin, C-reactive protein, and pain from the 6th month of treatment. No changes of *N*-telopeptide, interleukin-6, β_2 -microglobulin, C-reactive protein, or skeletal events were observed in patients of group II, whereas paraprotein was significantly reduced after 6 months of treatment. The differences in *N*-telopeptide, interleukin-6, paraprotein, and β_2 -microglobulin were statistically significant between the two groups. Multivariate analysis revealed a significant correlation between changes of *N*-telopeptide, changes of interleukin-6 in both groups, and reduction of pain and paraprotein in group I [28•]. These results suggest that pamidronate may have a synergistic action with chemotherapy in decreasing osteoclastic activity, in reducing markers of myeloma activity and myeloma-related pain, and in improving the quality of life in patients with multiple myeloma.

Zoledronic acid is a new highly potent nitrogen-containing bisphosphonate being developed for skeletal events related to malignancies. A recently published phase III trial comparing zoledronic acid 4 mg with

pamidronate 90 mg in the treatment of hypercalcemia of malignancy demonstrated that zoledronic acid is superior to pamidronate in the initial treatment of hypercalcemia [29••].

In a randomized, phase III, double-blind trial, 350 patients were enrolled with Durie-Salmon stage III multiple myeloma and at least one osteolytic lesion confirmed by radiographic evidence of bone metastases. The primary efficacy parameter was the proportion of patients experiencing at least one skeletal event (radiation therapy, surgical intervention, pathologic fractures to the skeletal system or spinal cord compression) at month 13. This phase III trial confirms the efficacy of zoledronic acid for the treatment of bony complications in multiple myeloma patients with a safety profile similar to pamidronate [30••]. Of interest is the statistically significant decrease in the bone resorption factors in the zoledronic acid arm as compared with the pamidronate arm. This could possibly translate into clinical benefit with a longer follow-up period [29••].

Kyphoplasty

Improving therapy and supportive care for myeloma and the probable increase in overall survival makes effective skeletal care of ever-increasing importance. Even though bisphosphonates have resulted in a significant decrease of skeletal morbidity, skeletal damage already sustained at the time of diagnosis, as well as the pain resulting from these events, limits mobility and thus increases morbidity and probably mortality. Kyphoplasty is a new technique that involves the introduction of inflatable bone tamps into the vertebral body [31••]. Once inflated, the bone tamps restore the vertebral body back toward its original height, while creating a cavity that can be filled with highly viscous bone cement. We described the results of 55 consecutive kyphoplasty procedures over 27 sessions in 18 patients who had vertebral compression fractures due to multiple myeloma. There were no major complications related directly to the use of this technique. On average, 34% of height lost at the time of fracture was restored. Asymptomatic cement leakage occurred at 2 of 55 levels (4%). Significant improvement in SF36 scores occurred for Bodily Pain, Physical Function, Vitality, and Social Functioning. The kyphoplasty inflatable bone tamp was effective in the treatment of vertebral compression fractures due to multiple myeloma. Kyphoplasty is associated with early clinical improvement of pain and function as well as some restoration of vertebral body height in these patients [32••].

Conclusion

The advances in the understanding of the disease biology and the progress made in surgical techniques have resulted in improvements in the quality of life and the survival time of myeloma patients. Studying the use of biologic modifiers in combination with each other or with

chemotherapy should result in converting myeloma into a chronic, manageable disease similar to hypertension and diabetes.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

- 1 Bartl R, Frisch B, Fateh-Moghadam, et al.: Histologic classification and staging of MM: a retrospective and prospective study of 674 cases. *Am J Clin Pathol* 1987, 87:342.
- 2 Brown LM, Gridley G, Pottern LM, et al.: Diet and nutrition as risk factors for multiple myeloma among blacks and whites in the United States. *Cancer Causes Control* 2001, 12:117–125.
- An interesting concept that identifies a possible explanation for the differences in incidence in races as well as the prevalence in old age.
- 3 Riedel DA, Pottern LM: The epidemiology of MM. *Hematol Oncol Clin North Am* 1992, 6:225.
- 4 Ichimaru M, Ichimaru T, Mikami M, et al.: MM among atomic bomb survivors in Hiroshima and Nagasaki, 1950–76: relationship to radiation dose absorbed by marrow. *J Natl Cancer Inst* 1982, 69:323.
- 5 Avet-Loiseau H, Facon T, Daviet A, et al.: 14q32 Translocations and monosomy 13 observed in monoclonal gammopathy undetermined significance delineate a multi-step process for the oncogenesis of MM. *Intergroupe Francophone du myelome. Cancer Res* 1999, 59:4546.
- 6 Berenson JR, Bergsagel PL, Munshi N: Initiation and maintenance of MM. *Semin Hematol* 1999, 36:9.
- 7 Ablashi D, Chatlynne L, Thomas D, et al.: Lack of serologic association of human herpes virus-8 (KHSV) in patients with monoclonal gammopathy of undetermined significance with and without progression to multiple myeloma. *Blood* 2000, 96:2304.
- 8 Shaughnessy J, Barlogie B: Chromosome 13 deletion in myeloma. *Curr Top Microbiol Immunol* 1999, 246:199.
- 9 Tricot G, Sawyer J, Jagannath S, et al.: The unique role of cytogenetics in the prognosis of patients of myeloma receiving high-dose therapy and autotransplants. *J Clin Oncol* 1997, 15:2659.
- 10 Tricot G, Sawyer J, Jagannath S, et al.: Poor prognosis in multiple myeloma is associated only with partial or complete deletion of chromosome 13 or abnormalities involving 11q and not with other karyotype abnormalities. *Blood* 1995, 86:4250.
- 11 Desikan R, Barlogie B, Sawyer J, et al.: Results of high-dose therapy for 1,000 patients with multiple myeloma: durable complete remissions and superior survival in the absence of chromosome 13 abnormalities. *Blood*. 2000, 95:4008–4010.
- Well-controlled large study that makes important observations.
- 12 Shaughnessy J, Tian E, Sawyer J, et al.: High incidence of chromosome 13 deletion in multiple myeloma detected by multiprobe interphase FISH. *Blood* 2000, 15:1505–1511
- 13 Anderson KC, Lust JA: Role of cytokines in multiple myeloma. *Semin Hematol* 1999, 36:14.
- 14 Grigorieva I, Thomas X, Epstein J: The bone marrow stromal environment is a major factor in myeloma cell resistance to dexamethasone. *Exp Hematol* 1998, 26:597.
- 15 Bataille R, Barlogie B, Lu ZY, et al.: Biologic effects of anti-IL-6 murine monoclonal antibody in advanced multiple myeloma. *Blood* 1995, 86:685–691.
- 16 Podar K, Tai Y, Davies FE, et al.: Vascular endothelial growth factor triggers signaling cascades mediating multiple myeloma cell growth and migration. *Blood* 2001, 98:428–435.
- A very well-conducted study and a comprehensive discussion of tumor and micro-environment interaction and interdependability.
- 17 Blade J, San Miguel JF, Fontanillas M, et al.: Survival of multiple myeloma patients who are potential candidates for early high-dose therapy intensification/autotransplantation and who were conventionally treated. *J Clin Oncol* 1996, 14:2167–2173.
- 18 Attal M, Harousseau JL, Stoppa AM, et al.: A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *Intergroupe Francais du Myelome. N Engl J Med* 1996, 335:91–97.
- 19 Fermand JP, Ravaud P, Chevret S, et al.: High-dose therapy and autologous peripheral blood stem cell transplant in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood* 1998, 92:3131–3136.
- 20 Gharot G, Tura S, Svansson H, et al.: Allogeneic bone marrow transplantation in multiple myeloma: an update of the EBMT registry. Boston: Harvard Medical School. Sixth International Workshop on Multiple Myeloma. Syllabus, Boston, MA, June 14 to 18, 1997.
- 21 Hideshima T, Chauhan D, Shima Y, et al.: Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood* 2000, 96:2943–2950.
- A clear series of elegant in vitro studies that shed some light on the mechanism of action of thalidomide.
- 22 Geitz H, Handt S, Zwingenberger K: Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. *Immunopharmacol* 1996, 31:213–221.
- 23 Damiano JS, Cress AE, Hazelhurst LA, et al.: Cell adhesion mediated drug resistance (CAM-DR): role of integrins and resistance to apoptosis in human myeloma cell lines. *Blood* 1999, 93:1658–1667.
- 24 Barlogie B, Spencer T, Tricot G, et al.: Long term follow up of 169 patients receiving a phase II trial of single agent thalidomide for advanced and refractory multiple myeloma (MULTIPLE MYELOMA). *Blood* 2000, 96:514a.
- An update on the largest group of patients treated with single-agent thalidomide.
- 25 Weber DM, Rankin K, Gavino M, et al.: Thalidomide with dexamethasone for resistant multiple myeloma. *Blood* 2000, 96:167a.
- 26 Roboz GJ, Dias S, Lam G, et al.: Arsenic trioxide induces dose- and time-dependent apoptosis of endothelium and may exert an antileukemic effect via inhibition of angiogenesis. *Blood* 2000, 96:1525–1530.
- 27 Deaglio S, Canella D, Baj G, et al.: Evidence of an immunologic mechanism behind the therapeutical effects of arsenic trioxide (As₂O₃) on myeloma cells. *Leuk Res* 2001, 25:227–235.
- Elegant group of in vitro experiments that explores the mechanism of action of arsenic trioxide.
- 28 Terpos E, Palermos J, Tsionos K, et al.: Effect of pamidronate administration on markers of bone turnover and disease activity in multiple myeloma. *Eur J Haematol* 2000, 65:331–336.
- An interesting observation, but a small number of patients.
- 29 Major P, Lortholary A, Hon J, et al.: Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, control clinical trials. *J Clin Oncol* 2001, 19:558–567.
- The first bisphosphonate that shows activity in bony disease from different malignancies.
- 30 Rosen LS, Gordon D, Kaminski M, et al.: Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase iii, double-blind, comparative trial. *Cancer J* (in press).
- A large, well-conducted trial comparing the effects of Aredia to Zometa in myeloma and breast cancer.
- 31 Lieberman IH, Dudeney S, Reinhardt MK, et al.: Initial outcome and efficacy of "kyphoplasty" in the treatment of painful osteoporotic vertebral compression fractures. *Spine* 2001, 26:1631–1637.
- The only comprehensive review of kyphoplasty as treatment for patients with osteoporosis and myeloma vertebral compression fractures.
- 32 Dudeney S, Hussein M, Karam MA, et al.: Kyphoplasty in the treatment of vertebral compression fractures due to multiple myeloma. *VIIIth International Myeloma Workshop, Banff, Canada, May 4–8, 2001; Abstract P156.*
- A new procedure that will not only help in pain management but also will decrease morbidity and mortality associated with spinal complications of myeloma.
- 33 Dai J, Weinberg RS, Waxman S, et al.: Malignant cells can be sensitized to undergo growth inhibition and apoptosis by arsenic trioxide through modulation of the glutathione red of system. *Blood* 1999, 93:268–277.
- 34 Attal M, Harousseau JL, Facon TT, et al.: Single versus double transplantation in myeloma: a prospective randomized trial of the intergroupe. *Francophone Du Myeloma (IFM). Blood* 2000, 96.