Bench-to-bedside translation of targeted therapies in multiple myeloma

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Multiple myeloma (MM) is characterized by excess monoclonal plasma cells in the bone marrow (BM), in most cases associated with monoclonal protein in blood or urine. Nearly 50 years ago, the use of combined melphalan and prednisone was shown to extend median survival of patients with MM to 2-3 years. In an approach pioneered by Prof. Tim McElwain in the 1970s, high-dose melphalan followed by BM transplantation in the 1980s and peripheral blood stem cell rescue in the 1990s further increased median survival to 3-4 years. Since 1998, MM has represented a new paradigm in drug development due to the remarkable therapeutic efficacy of targeting tumor cells in their microenvironment[1,2]—an approach perhaps best exemplified by the use of the proteasome inhibitor bortezomib and immunomodulatory drugs (IMiDs) thalidomide and lenalidomide to target the MM cell in the BM microenvironment. This approach has rapidly translated from bench to bedside, producing six new Food and Drug Administration (FDA)-approved treatments in the past 7 years and a doubling of patient survival from 3-4 to 7-8 years as a direct result.[3] My colleagues and I have made contributions in the areas of identifying novel targets in the tumor and microenvironment, confirming the activity of inhibitors directed at these targets, and then leading clinical trials assessing the efficacy and safety of these agents. These collaborative efforts have included basic and clinical investigators, the pharmaceutical industry, the National Cancer Institute, FDA regulators, and patient advocacy groups, with the common focus and sole goal of improving MM treatments.[4] Indeed, the use of novel targeted inhibitors in relapsed refractory MM, relapsed MM, newly diagnosed MM and, most recently, consolidation and maintenance therapies has totally transformed MM therapy and patient outcome.

I have been carrying out bench-to-bedside research in MM now for 38 years, initially inspired by my mentor Dr. Richard L. Humphrey, who taught me the two most important lessons that have shaped my research and clinical practice ever since. When I was a medical student at Johns Hopkins, he instilled in me the opportunity in MM to "make science count for patients" by developing laboratory and animal models of disease and then rapidly translating promising leads from the bench to the bedside in clinical trials. Moreover, he showed me the importance of treating patients as family. He has served as my inspiration and role model ever since.

Monoclonal antibodies and immune-based therapies

After an introduction to MM in both the laboratory and the clinic at Johns Hopkins during my medical school and internal medicine training, I moved to the Dana-Farber Cancer Institute for training in medical oncology, hematology, and tumor immunology. There, Drs. George Canellos and Robert Mayer showed me the importance of clinical investigation. Under the tutelage of Drs. Lee Nadler and Stuart Schlossman, I was part of a team that developed monoclonal antibodies (MoAbs) directed at B-cell malignancies, including MM.[5,6] It was an extraordinary time, since these MoAbs allowed for

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identification of the lineage and stage of differentiation of B-cell malignancies, as well as permitting comparisons of the neoplastic B-cell to its normal cellular counterpart. A panel of B-cell MoAbs was very useful for complementing histopathologic diagnosis and identifying non-T-acute lymphoblastic leukemia, chronic lymphocytic leukemia and lymphomas, and MM as tumors corresponding to pre-B cells, isotype diversity B differentiative stages, and plasma cells, respectively.[5]

From the outset, these MoAbs were also used in innovative treatment strategies in MM, and our efforts to develop immune-based MoAb and immunotoxin therapies, tumor vaccines, and mechanisms to abrogate host immunosuppression continue to the present. For example, given that high-dose therapy and autologous BM transplantation achieved remarkable extent and frequency of response, we early on examined whether cocktails of MoAbs (CD 10, CD20, PCA-1) could purge MM cells from autografts ex vivo prior to autologous BM transplantation.[7] Although effective at purging 2–3 logs of MM cells, this strategy had little impact on overall outcome, likely due to residual systemic tumor burden. T-cell (CD6)-directed MoAbs were used to purge T cells from allogeneic BM grafts to abrogate graft-versus-host disease.[8] However, the transplant-related mortality of allotransplantation in MM remains unacceptably high to the present, and we continue to carry out studies to identify targets of allogeneic graft-versus-myeloma effect (GVM)[9] and develop clinical protocols of nonmyeloablative allografting in order to exploit GVM while avoiding attendant toxicity.

Over many years, we have continued to carry out preclinical and clinical studies of MoAbs targeting MM cells, tumor-host interactions, and cytokines, as well as evaluating MoAb-based immunotoxin therapies.[1,10,11] For example, we found CS-1 to be highly and uniformly expressed at the gene and protein levels in patient MM cells, and then showed that targeting this antigen with elotuzumab was effective in preclinical models of MM in the BM milieu both in vitro and in vivo.[12] These promising data in turn motivated a clinical trial of elotuzumab, which showed that the agent achieved stable disease in relapsed refractory MM but did not induce responses sufficient to warrant new drug development. However, our preclinical studies showed that lenalidomide enhanced antibody-dependent cellular cytotoxicity triggered by elotuzumab,[12] providing the rationale for a combination clinical trial with very promising results. This bedside-to-bench-and-back iterative process illustrates our translational focus. An example of an immunotoxin clinical trial is that of CD138 linked to maytansinoid toxin DM, which is currently ongoing based upon our promising data both in vitro and in xenograft models of human MM in mice.[13]

Our more recent focus in immune therapies has been on the development of vaccines. Vasair and colleagues have shown in murine MM[14] and Rosenblatt and colleagues in human MM[15] that vaccination with fusions of dendritic cells (DC) with tumor cells allows for generation of T- and B-cell tumor-specific responses in vitro and in vivo in preclinical models. Recent clinical trials of MM-DC vaccinations to treat minimal residual disease after transplantation show that these vaccinations are triggering host antitumor T and humoral responses associated with high rates of complete response. An alternative strategy is the use of cocktails of peptides for vaccination. Specifically, we have shown that CS-1, XBP-1, and CD138 are functionally significant targets in MM cells, and we have gone on to derive peptides from these antigens that can be presented to trigger cytotoxic T-lymphocyte responses in HLA-A2-positive patients.[16] Ongoing clinical trials are evaluating vaccination with cocktails of these peptides in patients most likely to respond, with the goal of triggering clinically significant immune responses.

We have also characterized the underlying immunodeficiency in MM patients in order to design strategies to overcome it.[17] Our studies have demonstrated decreased help, increased suppression, pro-MM growth cytokines, and dysregulated immune-homeostasis. And, for example, the demonstration of increased TH-17 cytokines promoting MM cell growth has set the stage for a related clinical trial of anti-IL-17 MoAb in MM.[17] In our studies of host accessory cells, we have shown that plasmacytoid DCs (pDCs) in MM patients do not induce immune effector cells as do normal pDCs, but instead promote tumor growth, survival, and drug resistance.[18] In preclinical studies, maturation of pDCs with CpG oligonucleotides both restores immune stimulatory function of pDCs and abrogates their tumor, promoting activity, setting the stage for a related clinical trial.

The tumor in its microenvironment

Therapies targeting MM

From the 1990s to the present, we have developed in vitro and in vivo models to define the role of MM-BM interactions in pathogenesis, identify novel targets, and validate novel targeted therapies. As a result, we have been able to take multiple single and combination agents targeting the tumor and microenvironment from bench to bedside in clinical trials. We have also used oncogenomics to characterize pathogenesis, identify novel targets, predict response, and inform the designs of single-agent and combination treatment clinical trials.

Specifically, we have developed models of MM in the BM microenvironment that have been useful in defining the roles of tumor cell-BM accessory cell contact as well as cytokines in the BM milieu, in conferring growth, survival, and drug resistance in MM.[1,19,20] These models have allowed for the identification of agents that can overcome cell adhesion-mediated drug resistance to conventional therapies. The proteasome inhibitor bortezomib, for example, triggers MM cell cytotoxicity in the BM, whereas the anti-tumor activity of dexamethasone is attenuated.[21] At both the gene transcript and proteasome activity levels, the ubiquitin proteasome cascade is upregulated by MM-BM binding, perhaps contributing to its enhanced activity in this context.[22] Bortezomib directly targets chymotryptic proteasome activity, inhibits growth and survival, induces apoptosis, upregulates heat shock proteins, inhibits DNA damage repair, and induces endoplasmic reticulum stress in MM cells; downregulates adhesion molecules on the tumor and in BM, thereby abrogating adhesion; and targets the microenvironment to trigger anti-angiogenesis, as well as triggering apoptosis of osteoclasts while promoting osteoblast differentiation.[21,23-27] This drug was rapidly translated from the bench to the bedside and received accelerated FDA approval in 2003 for treatment of relapsed refractory MM, followed by approval for relapsed MM and as initial therapy based upon its superiority in randomized phase III clinical trials.[28-30] Most recently, very promising data on the use of bortezomib as consolidation and maintenance therapy are emerging.

However, not all MMs respond to bortezomib, and some tumors ultimately develop resistance. From the outset, we have therefore tried to identify gene signatures of response versus resistance to bortezomib in MM[33] as well as to develop functional assays to better predict whose cancer is most likely to respond. For example, we developed a predictive model in which tumors like MM with high proteasome load and low proteasome capacity have high proteasome stress and are therefore susceptible to proteasome inhibition, whereas solid tumors with high proteasome capacity and low proteasome load are relatively resistant to proteasome inhibitors.[32] It is remarkable that bortezomib has opened a whole new area of preclinical and clinical experimentation in cancer targeting the ubiquitin proteasome cascade; the strategies include targeting deubiquitinating enzymes upstream of the proteasome, selective and broad targeting of proteasome activity, and targeting the immunoproteasome. For example, our preclinical studies show that inhibitors of deubiquitinating enzymes upstream of the proteasome, such as USP-7 inhibitor P5091, inhibit human MM cell growth and prolong host survival in a murine xenograft model. Carfilzomib, a next-generation, more potent intravenous inhibitor of chymotryptic activity, has overcome bortezomib resistance in preclinical and early clinical trials. Oral proteasome inhibitors targeting chymotryptic activity that have translated from the bench to bedside in phase I clinical trials include Onx 0912, which triggers cytotoxicity against MM cell lines and patient cells, and MLN2238/9708, which demonstrates more potent preclinical activity against MM cells in vivo than bortezomib.[33-38] NPI-0052 targets chymotryptic, tryptic-like, and caspase-like activities, and similarly shows clinical promise.[37] Finally, inhibitors of the immunoproteasome, such as the PR-924 inhibitor of the LMP-7 immunoproteasome subunit, also block MM growth in vitro and in vivo.[39]

Since the empiric observation that thalidomide had anti-MM activity in 1998, we have studied the IMiDs thalidomide, lenalidomide, and pomalidomide in our models of MM in the BM microenvironment. These agents directly trigger caspase 8-mediated apoptosis; decrease binding of tumor cells to BM; inhibit constitutive and MM cell binding-induced secretion of cytokines from BM; inhibit angiogenesis; and stimulate autologous NK, T, and NK-T cell immunity to MM cells.[40-43] Like bortezomib, lenalidomide was rapidly translated from the bench to the bedside. Our preclinical studies demonstrated increased responses when lenalidomide (triggers caspase 8-mediated apoptosis) was combined with dexamethasone (induces caspase 9-mediated apoptosis); our phase I and II clinical trials established the maximum-tolerated dose and confirmed the enhanced clinical efficacy of combined lenalidomide and dexamethasone, informing the design of phase III clinical trials leading to its FDA and European Medicines Agency approvals to treat relapsed MM.[28,29,43-47] Trials of lenalidomide as initial therapy in both the transplant candidate and elderly populations, as well as in consolidation and maintenance therapy, have yielded very promising results.[48,49] For example, maintenance lenalidomide has been shown to add years of progression-free survival (PFS) in both newly diagnosed transplant and nontransplant candidates. We and others recently have shown that the second-generation IMiD pomalidomide produces remarkable and durable responses, with a favorable side effect profile, even in the setting of MM resistant to lenalidomide and bortezomib.[50,51]

Targeting the tumor in the microenvironment

Bortezomib and lenalidomide are examples of targeting the tumor and also impacting the microenvironment, since both have a positive impact on bone disease in MM.[27,52] We have also had a long-term interest in targeting the MM BM microenvironment with the goal of

triggering MM responses. For example, MM cells secrete DKK-1, which downregulates osteoblast function via an effect on Wnt signaling. In our preclinical murine xenograft models of human MM, the neutralizing anti-DKK-1 BHQ880 MoAb not only triggers new bone formation, but also inhibits MM cell growth;[53] a clinical trial of BHQ880 MoAb is ongoing. We have also shown that B-cell activating factor (BAFF) is elevated in the BM plasma of patients with MM and mediates osteoclastogenesis, as well as tumor cell survival and drug resistance; anti-BAFF MoAb can neutralize these effects,[54] and a clinical trial of this MoAb is ongoing. Most recently, we have shown that targeting BTK in our preclinical models not only blocks osteoclast formation and growth, thereby maintaining bone integrity, but also inhibits MM cell growth. These studies illustrate the principle that targeting cytokines or accessory cells in the tumor microenvironment can also impact MM cell growth, further validating the utility of our in vitro and in vivo model systems.

Preclinical studies to identify combination targeted therapies

We have used functional oncogenomics to inform the design of novel combination therapies. For example, bortezomib was shown to inhibit DNA damage repair in vitro,[27] providing the rationale for its combination with DNA damaging agents to enhance or overcome drug resistance. Indeed, a large randomized phase III trial of bortezomib versus bortezomib with pegylated doxorubicin showed prolonged PFS and overall survival and increased extent and frequency of response with the combination,[55] leading to FDA approval of bortezomib with pegylated doxorubicin to treat relapsed MM.

In a second example, we found heat shock protein 27 (Hsp 27) to be increased at transcript and protein levels in patient MM cells in the setting of bortezomib refractoriness. Our bedside-back-to-bench studies showed that overexpression of Hsp 27 conferred bortezomib resistance, whereas knockdown of Hsp 27 in bortezomib-resistant MM cells restored sensitivity.[56] Hideshima and colleagues then showed that p38MAPK inhibitor decreased downstream Hsp 27 and thereby overcame bortezomib resistance in MM cell lines and patient cells,[57] providing the rationale for a clinical trial of bortezomib and p38MAPK inhibitor.

In another example, based upon hallmark cyclin D abnormalities in MM, Raje and colleagues have studied cyclin D kinase inhibitors alone and in combination in MM.[58,59] In addition, Ghobrial and colleagues have translated promising preclinical data on an mTOR inhibitor and bortezomib into clinical trials.[60] We also have shown that bortezomib triggers activation of Akt, and that bortezomib with the Akt inhibitor perifosine can overcome resistance to bortezomib in preclinical models.[61] Our phase I and II trials of this combination therapy showed durable responses even in the setting of bortezomib resistance, and a phase III trial of bortezomib versus bortezomib with perifosine in relapsed MM is ongoing.

Finally, we believe that protein homeostasis represents one of the most attractive novel therapeutic targets in MM. Specifically, we have shown that inhibition of the proteasome upregulates aggresomal degradation of protein, and, conversely, that blockade of aggresomal degradation induces compensatory upregulation of proteasomal activity.[62] Most important, blockade of aggresomal and proteasomal degradation of proteins by histone deacetylase (HDAC) inhibitors (vorinostat, panobinostat, tubacin) and proteasome inhibitors (bortezomib, carfilzomib), respectively, triggers synergistic MM cell cytotoxicity in preclinical studies.[62-64] We are leading international phase I/II trials combining the HDAC inhibitors vorinostat or panobinostat with bortezomib, which have thus far shown that responses are achieved in the majority of patients with relapsed bortezomib-refractory MM, as well as phase III trials for FDA registration of these combinations. A very promising finding is that an HDAC6-selective inhibitor causes acetylation of tubulin and more potently and selectively blocks aggresomal protein degradation, providing synergistic MM cytotoxicity when combined with bortezomib. This combination has rapidly translated from our laboratory to the bedside in clinical trials aimed at determining whether clinical efficacy can be achieved without the side effect profile of fatigue, diarrhea, thrombocytopenia, and cardiac abnormalities associated with the more broad type HDAC1 or 2 inhibitors.

To date, the most exciting combination emerging from our preclinical studies is that of lenalidomide and bortezomib, with the respective caspase 8-mediated apoptosis and caspase 9-mediated apoptosis inducing synergistic cytotoxicity in models of MM cells in the BM milieu.[65] Richardson and colleagues led efforts to translate these findings to clinical trials in advanced MM, which showed that lenalidomide, bortezomib, and dexamethasone achieved a response rate of 58% in relapsed MM that was often refractory to either agent.[66] Most important, our center has shown that lenalidomide, bortezomib, and dexamethasone combination therapy achieves a response rate of 100% in newly diagnosed MM, with 74% of patients having at least very good partial response and 52% having complete or near complete response.[45] Given these unprecedented results, a clinical trial is now evalu-

ating whether high-dose chemotherapy and stem cell transplantation adds value in the context of this high extent and frequency of response to combined novel therapies.

The integration of novel combination therapy, predicated upon scientific rationale, has transformed and continues to transform the treatment of MM. Going forward and based upon these exciting results, we are now carrying out high throughput drug screening to identify novel agents active against MM cells bound to BM stromal cells reflective of their microenvironment.

Oncogenomic studies

From the 1990s to the present, we have used oncogenomics to characterize MM pathogenesis, identify novel targets, predict response, and inform the design of single-agent and combination therapy clinical trials. Our earliest studies profiled transcriptional changes occurring with transition from normal plasma cells to monoclonal gammopathy of undetermined significance to MM, as well as identifying gene and protein changes distinguishing patient MM cells from normal plasma cells in a syngeneic twin.[67] We have repeatedly used transcript profiling to identify signatures of response, initially with bortezomib and subsequently with multiple other single-agent and combination therapies,[31] and most recently showed that microRNA profiling can also identify prognostic subgroups. Our DNA-based array comparative genomic hybridization studies have identified copy number alterations (CNAs) and suggested novel MM oncogenes or suppressor genes; once validated using knock in and knock down experiments in our models of MM cells in the BM milieu, these may serve as potential therapeutic targets.[68]

Single nucleotide polymorphism (SNP) arrays have also identified CNAs and allowed for the development of novel prognostic models.[69] For example, recent SNP analyses of clinically annotated samples identified CNAs that may predict clinical outcome, including increased 1q and 5q as sites for putative MM oncogenes and decreased 12p as a site of putative MM suppressor genes.[69] Most important, as one of the founding centers of the Multiple Myeloma Research Consortium, we have participated in MM genome sequencing studies that have revealed mutated genes involved in protein homeostasis, NF-κB signaling, IRF4 and Blimp-1, and histone methylating enzymes, all consistent with MM biology.[70] These studies also identified unexpected mutations, such as those in BRAF observed in melanoma, and these discoveries may have clinical application in the near future. Finally, we have now shown that there is continued evolution of genetic changes with progressive MM, strongly supporting the view that personalized medicine in MM must include profiling patient tumor cells not only at diagnosis, but also at time of relapse.

Future directions and conclusions

Our ongoing efforts include identification and development of immune strategies (vaccines and adoptive immunotherapy), novel agents targeting the MM cell in the BM microenvironment, and rational multi-agent combination therapies and use of genomics to improve patient classification and allow for personalized medicine in MM. With continued rapid progress, MM will become a chronic illness with sustained complete responses in a significant proportion of patients.

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Therapeutic optimization of aromatase inhibitor–associated arthralgia: etiology, onset, resolution, and symptom management in early breast cancer

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Third-generation aromatase inhibitors (AIs) used in the treatment of hormone-responsive breast cancer are associated with arthralgia, which is the most common reason for treatment discontinuation. This review characterizes the observed arthralgia and describes its variable definitions in key clinical trials; its typical onset and duration; symptom management strategies; and symptom resolution. The symptomatic manifestations of AI-associated arthralgia are highly variable, with typical onset occurring 2-6 months after treatment initiation. Aromatase inhibitor-associated arthralgia is most often bilateral and symmetrical, involving hands and wrists. Other common locations include knees, hips, lower back, shoulders, and feet. To improve standardization of care as well as patient quality of life, we propose a diagnostic algorithm for the management of patients who receive AIs and who develop arthralgia or worsening symptoms from preexisting joint pain. We conclude that although arthralgia is often associated with AI therapy, prompt diagnosis and management of musculoskeletal symptoms may ensure continued AI treatment and improve quality of life.

The use of third-generation aromatase inhibitors (AIs) such as anastrozole, letrozole, and exemestane for the treatment of postmenopausal women with hormone-sensitive breast cancer has increased steadily since 2000, and AIs have been incorporated into many clinical practice guidelines as an effective therapeutic option.[1,2] In the adjuvant setting, AIs reduce the risk of recurrence by 20%-29% relative to tamoxifen.[3,4] Increased use of AIs has led to broader awareness of their side-effect profiles, leading clinicians to consider proactive management of some symptoms with the intent to improve adherence to therapy.

Anastrozole and letrozole reversibly block the cytochrome P450 enzyme aromatase, while exemestane irreversibly blocks aromatase, but a review of the major adjuvant studies has shown that the three AIs have similar safety profiles and disease-free survival rates.[5] One of the commonly reported adverse events (AEs) is arthralgia, which occurs in 18%-36% of patients[5-7] and is particularly important for postmenopausal women who have an increased incidence of joint complaints. Indeed, the reported arthralgia incidence in the general population of postmenopausal women is as high as 74%.[8] In a recent survey of 416 breast cancer specialists, 92% graded AI-induced arthralgia as important or very important.[9]

Subsequent data analyses of AI adjuvant studies show that about 2%-20% of patients reporting arthralgia discontinue treatment.[7,10,11] In addition, retrospective analyses of survey data and medical records from either clinical practice or prescription refill databases have shown that adherence to AI regimens significantly decreased after 1 year of treatment (to 82%-88%) and continued to decrease through year 3 (to 62%-79%).[12-14] The reasons for treatment nonadherence were varied, but they included AEs, especially those events that decrease quality of life, such as arthralgia.[5,15] Reduced medication compliance may then lead to de-

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creased efficacy and increased rates of breast cancer recurrence.[7] Although arthralgia-related symptoms may be severe and lead to discontinuation of AI therapy, data from the ATAC (Arimidex, Tamoxifen Alone or in Combination) study suggest that symptoms may improve within 6 months with continuous AI therapy.[8] It is therefore clinically relevant to differentiate between any comorbid arthralgia and the arthralgia/musculoskeletal symptoms (MSS) that are associated with AI therapy.

Despite the uncertainty surrounding the establishment of an accurate incidence of AI-related arthralgia/MSS (partly due to the wide variability of symptoms and terms used to define arthralgia in clinical studies), several studies have attempted to evaluate and identify potential risk factors for developing arthralgia/MSS during AI therapy. A cross-sectional survey of patients who were treated in the community setting identified prior taxane chemotherapies as a risk factor,[16] and a retrospective analysis of ATAC identified prior chemotherapy, prior hormone therapy, positive hormone-receptor status, anastrozole treatment, and obesity as risk factors.[17] In addition, AI-induced arthralgia seems to be related inversely to the length of time since cessation of menstrual function, with incidence significantly lower in patients whose last menstrual period was more than 10 years ago.[18,19] Prompt diagnosis and management of MSS could ensure continued AI treatment and improve quality of life.[15]

This review characterizes arthralgia-related symptoms, discusses the temporal relationship between symptom onset and duration and the possible etiologies of arthralgia-related symptoms in these patients, and presents diagnostic criteria for arthralgia as well as management strategies to ameliorate these symptoms.

Methods

Evidence was collected from a literature review of the PubMed database through December 2011. Search terms were aromatase inhibitors and breast cancer with arthralgia or musculoskeletal; the permutations included anastrozole, letrozole, or exemestane. Additional information was garnered from oncology conference Web sites.

Arthralgia definition and diagnosis

Arthralgia is commonly defined as pain in one or more joints, and is distinguished from arthritis by the absence of joint inflammation related to structural damage, infection, autoimmunity, or metabolic conditions.

Clinical history and physical examination provide the best assessment tools; laboratory and radiographic analyses can provide additional information.[20] The medical history should include a brief assessment for any comorbidities or medication usage that may contribute to the presence of MSS. A focused physical examination should note any extra-articular features such as nodules, tophi, rashes, or joint effusion, as well as the number of affected joints and any pattern of joint symptoms. The joint pain's location (eg, inside or surrounding the joint), time of onset (eg, morning or at rest), and duration (eg, intermittent or constant), as well as any associated symptoms, are important for determining the cause of arthralgia.[21] A baseline clinical assessment of MSS and the proactive treatment of preexisting joint symptoms are important before AI therapy is initiated.

Typically, AI-associated arthralgia is reported as stiffness, achiness, or pain that is symmetrical, is most noticeable in the morning, and may improve with activity.[22] It is most often bilateral, involving hands and wrists. Other common locations include knees, hips, lower back, shoulders, and feet. However, joint pain has also been reported in the feet, pelvis, arms, and back.[22] There may also be soft tissue thickening and/or fluid in the tendon sheaths.[20,22] Clinical evidence of joint changes has been reported in several small studies.[23-26]

Two studies evaluating musculoskeletal pain during AI therapy found fluid in the sheath surrounding the digital flexor tendons, as well as tendon sheath thickening and enhancement (tenosynovial changes); however, in one of these studies, the majority of patients had tenosynovial changes before initiating AI therapy.[24,25] A retrospective study in patients with AI-induced arthralgia identified a trend toward reduced incidence of arthralgia among patients receiving chronic diuretics, further suggesting the value of reducing fluid in the joints.[27] Another study found no association between tenosynovial changes and reports of new MSS;[23] still another study found no correlation between tenosynovitis and AI use, although MSS were more common among patients receiving AIs.[28] Therefore, although there is some evidence of joint changes in patients receiving AIs, it remains unclear whether those changes are associated with AI therapy.

The most recent National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) for assessing arthralgia severity integrates both pain severity and its effect on physical functioning.[29] According to these criteria, arthralgia ranges from grade 1 (mild pain with no limitations on activities of daily living) to grade 3 (severe pain that limits self-care and activities of daily living).

Onset and duration of MSS

The temporal relationship between MSS onset and the initiation of AI therapy is important in identifying possible etiologies. The most thorough assessment of time to first joint symptoms in patients with BC receiving AI therapy

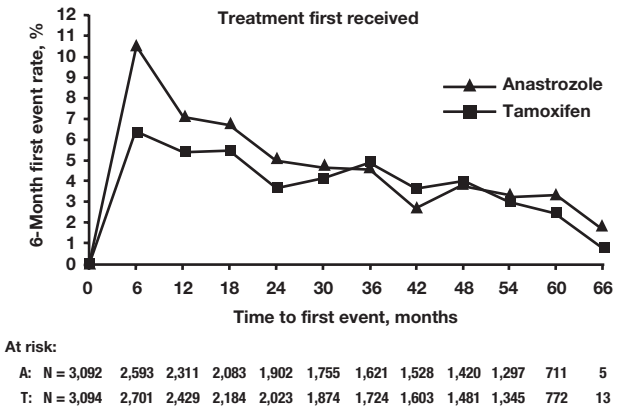

FIGURE 1 Time to onset of first joint symptom event in the ATAC trial. The 6-month first event rate = D/S, where D is the decrement in the Kaplan-Meier event-free estimate over the previous 6 months and S is the Kaplan-Meier estimate 6 months before the time point. Reprinted with permission from Mackey J, Gelmon K. Adjuvant aromatase inhibitors in breast cancer therapy: significance of musculoskeletal complications. *Curr Opin Oncol*. 2007;19:S9-S18,[31] originally appeared in poster by Buzdar AU, presented at 2006 ASCO meeting.

was conducted in the ATAC study (Figure 1).[10,30,31] This subanalysis showed that the event rate for joint symptoms peaked within 6 months after initiation of AI therapy and decreased thereafter. The majority of events (anastrozole, 68%; tamoxifen, 59%) were reported within 24 months of AI therapy initiation.[10] Among patients reporting joint symptoms, 46% had exacerbation of an existing condition.[10] In addition, patients who received prior chemotherapy had a higher incidence of joint symptoms and a shorter median time to onset (TTO).[31] A recent analysis of the Breast International Group (BIG) 1-98 study showed that the incidence of arthralgia/myalgias in patients who received letrozole was higher in years 1 and 2 than in years 3-5 (26% vs. 14%, respectively).[32] A recent 1-year, prospective, joint-symptom evaluation in a clinical practice involving 58 postmenopausal women who initiated AI therapy showed that MSS were increased from baseline at both 3 and 6 months after treatment began.[33] Rheumatologic evaluation of the hands showed worsening function, stiffness, and pain at 3 months; however, only function continued to worsen at the 6-month evaluation, when a significant decrease in pinch grip strength was noted ($P = .05$). The 1-year results were not available.

Several AI studies have reported a median TTO of arthralgia, which yields more precise timing of onset. In a study involving 97 postmenopausal women who were randomized to either exemestane or letrozole for 1 year, 44 women met the criteria for rheumatologic evaluation.[34] Among those evaluated, the median TTO was 1.6 months (range, 0.4-10 months). In another study involving 24 patients who were referred for rheumatologic evaluation, the median TTO was 2.5 months.[5] The timing of arthralgia in these two AI studies was similar to what was observed in 102 premenopausal women receiving leuprolide, a drug that reduces hormone production to menopausal levels; the timing suggested that estrogen deprivation may be involved in the development of arthralgia.[35] In fact, the prevalence of arthralgia peaks in women during menopause (age 50-59 years).[15,35] In this study, the AEs of estrogen deprivation (such as vaginal dryness) began 2 weeks after leuprolide initiation and corresponded to the decline of estradiol to menopausal levels. The development of arthralgias and myalgias began during weeks 3-7 of therapy, with 25% of patients experiencing symptoms.[35] Symptoms resolved at 2-12 weeks after discontinuing leuprolide treatment. In a separate study, conjugated estrogen therapy in postmenopausal women reduced the risk of developing MSS by up to 38%, compared with placebo.[35]

These studies suggest that a high percentage of postmenopausal women with breast cancer may be predisposed to develop joint symptoms, or may have a preexisting joint condition. Therefore, in general, arthralgia that is related to estrogen suppression may worsen or develop within the first few months of AI treatment initiation, and subside within a few months after treatment has been discontinued.

Potential etiologies for MSS with AI use

Despite increased awareness of the clinical importance of AI-associated MSS, the mechanisms underlying symptom development remain poorly understood. Given symptom variability, multiple etiologies likely can lead to the development of MSS in individual patients on AI therapy.[5] Several potential mechanisms have been discussed in recent reviews, including estrogen deprivation, inflammatory or autoimmune response, the direct off-target effect of AIs or their metabolites, and vitamin D deficiency.[5,36,37] Identification of the mechanisms leading to MSS may facilitate the development of directed approaches for symptom management.

A recent case-control, genomewide association study of patients in the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA.27 phase III study of anastrozole and exemestane identified four single-nucleotide polymorphisms that were related to the incidence of grade 3 or 4 musculoskeletal symptoms.[38] Genetic polymorphisms in CYP19A1 (the final enzyme in estrogen synthesis) is also associated with patient-reported arthralgia.[39] Further investigation of these genetic variations may lead to a better understanding of the mechanism, more effective symptom management, and earlier identification of patients at risk of developing arthralgia.

Estrogen deprivation is thought to be a crucial contributing factor for AI-associated MSS because estrogen is involved in various signaling pathways that are implicated in MSS etiology.[5,8,15,35,37] Current evidence suggests that estrogen is involved in bone and collagen maintenance, peripheral and central nervous system pain perception, and inflammation.[5,8,15,35,37] Accordingly, patients with osteoporosis have an increased risk for MSS during AI therapy.[40] Estrogen deprivation also seems to lower the pain threshold, and the increased pain perception may expose an underlying joint pathology.[15] Low estrogen levels may alter the natural melatonin cycle, leading to morning joint stiffness.[41] However, a definitive relationship between decreased estrogen levels and the development arthralgia has not been established.

Several recent studies have reported conflicting results with regard to the involvement of inflammation in the development of MSS.[34,42,43] Currently, there is no consistent evidence based on inflammatory biomarkers, but a link may exist. Localized inflammation in the joint may activate nociceptive fibers that innervate the joint capsule and ligaments.[35,37] Joint inflammation may also lead to an expansion of the nociceptive fields, thereby sensitizing nociceptive receptors to pain signals that might otherwise be ignored, or to pain signals originating from other parts of the body.[35,37] Therefore, if inflammation surrounding the joints is promoted by AI-induced estrogen deprivation, then a peripheral nociceptive mechanism may explain the development of joint pain. One case-control study of 30 participants that was part of a larger, prospective, randomized clinical trial found no statistically significant changes in 36 inflammatory cytokines and lipid mediators that were assayed after AI treatment, compared with pretreatment levels.[44] However, further research is necessary to clearly define the role of inflammation in the development of AI-associated arthralgia.

Although it is possible that AIs or their metabolites may affect the development of arthralgia through a direct off-target mechanism, this is less likely than other proposed mechanisms, based on the observation that musculoskeletal AEs are common to steroidal and nonsteroidal AIs as well as to gonadotropin-releasing hormone antagonists.[5,45] Further studies investigating AI metabolism are necessary to elucidate whether this is a viable hypothesis.

Another potential mechanism is exacerbation of an existing vitamin D deficiency. Vitamin D deficiency can lead to musculoskeletal pain and joint stiffness/discomfort, and a recent study reported that 88% of women with early breast cancer had vitamin D deficiency.[46] Nevertheless, the data supporting this hypothesis are inconsistent. An intervention study showed a significant inverse correlation between arthralgia symptoms and vitamin D levels, and lowered pain scores were reported in a randomized study with high-dose vitamin D supplementation (50,000 IU weekly), compared with placebo.[47-49] Another prospective study suggested that a vitamin D target concentration of 40 ng/mL may prevent the development of AI-induced arthralgia.[50] In contrast, a study in postmenopausal women receiving anastrozole or placebo reported no effect of baseline vitamin D levels on arthralgia incidence.[51] Interestingly, one prospective study noted that vitamin D levels increased significantly from baseline during 6 months of AI treatment ($P = .004$), although this study also found no association between AI-associated symptoms and vitamin D concentration.[52] In summary, several of these potential mechanisms may play a role, but further study is needed.

Limitations to determining etiology

Analysis of MSS etiology during AI therapy in postmenopausal women with breast cancer is complicated by a variety of factors, including prior or concomitant anticancer therapy and/or comorbidities. For example, MSS may occur as a result of chemotherapy.[53] In a neoadjuvant docetaxel study involving 45 patients with operable breast cancer, 6.7% developed grade 3 myalgia/arthralgia during chemotherapy.[54] Among 18 patients who received chemotherapy for a variety of tumor types and then developed arthralgia, their joint symptoms arose about 6 months after the first chemotherapy session and lasted for a mean of 3 months with treatment.[55] Therefore, MSS may overlap between treatments, or may arise during subsequent treatment but be related to the prior treatment. Arthralgias are also known to occur after treatment with certain antihypertensives, statins, and vaccines.[20,53]

To add to the complexity, there are 41 preferred terms for MSS in the CTCAE (version 4.0).[29] In Common Toxicity Criteria (version 2.0), there are just seven preferred terms for MSS (arthralgia, arthritis, muscle weakness, myalgia, myositis, osteonecrosis, and other).[56] Indeed, arthralgia arising during AI therapy is difficult to distinguish from bone diseases, inflammatory and degenerative arthropathies, and secondary pain from other causes.[20] Clearly, a uniform assessment of arthralgia/MSS in AI-treated patients is lacking.[35] To facilitate the identification of AI-induced arthralgia, we propose a diagnostic algorithm (Figure 2) rather than a more comprehensive rheumatologic evaluation, which may not be applicable.

Optimal management

Management of MSS is usually palliative, with patients primarily receiving nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors (coxibs), and opioids (for severe symptoms).[15] Interventions to reduce ar-

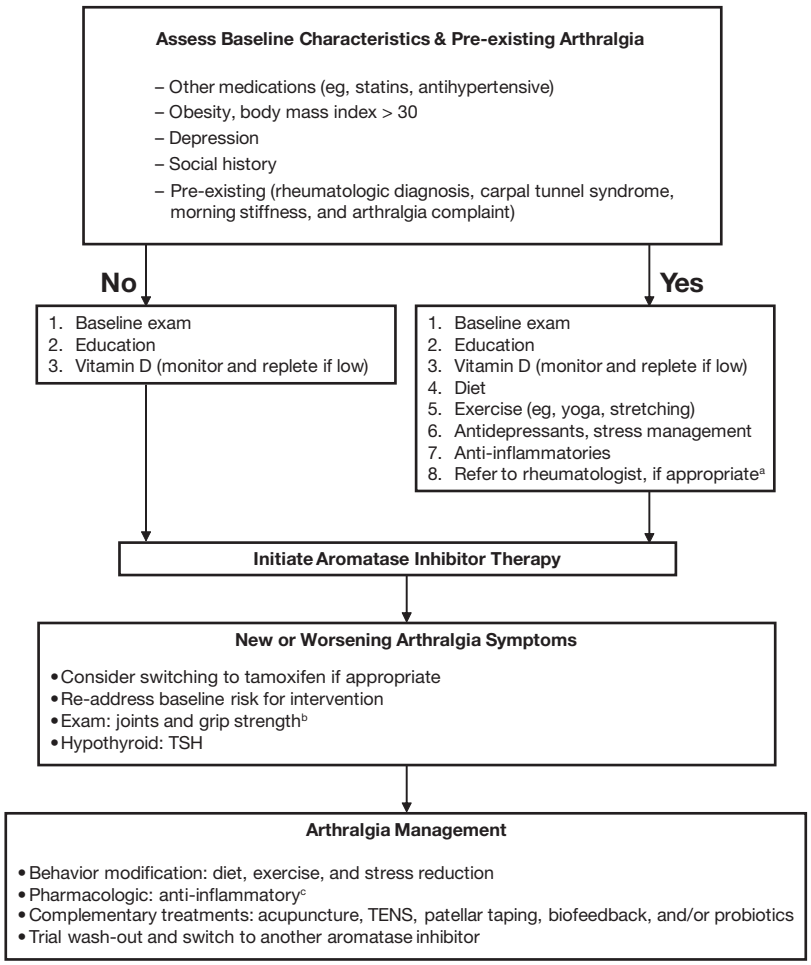

FIGURE 2 Algorithm for diagnosis and management of AI-associated arthralgia. TSH indicates thyroid-stimulating hormone; TENS indicates transcutaneous electrical nerve stimulation. [a]Criteria for referral include ≥ 3 swollen joints, metatarso-/metacarpophalangeal involvement, and morning stiffness that lasts ≥ 30 minutes. [b]Joint examination is for absence of effusion and pain (mild tenderness permissible), with no associated joint changes (if positive, refer to rheumatologist); grip strength should be normal. [c]Treatment is with a nonsteroidal anti-inflammatory agent, ibuprofen, naproxen, or diclofenac, or a cyclo-oxygenase-2–specific inhibitor such as celecoxib, if not contraindicated.

thralgia symptoms during AI treatment have not been formally studied; they have been extrapolated from the current management of arthritis and other related entities. Treatment of MSS symptoms should be individualized based on symptoms, differential diagnoses, and concomitant therapies. Furthermore, arthralgia symptoms could be an early sign of rheumatoid arthritis, requiring referral to a rheumatologist (Figure 2).[53]

Published recommendations from experts in the field and an arthralgia working group for the management of arthralgia symptoms in patients receiving AI therapy suggest a sequential use of lifestyle changes and pharmacologic interventions, depending on symptom severity (Figure 2).[6,15] The recommendations also stress patient counseling and education as important components of arthralgia management. Advising patients that arthralgia is common with AI treatment—and that symptoms can be managed—may increase the likelihood that patients will report these events. This, in turn, promotes appropriate symptom management and discourages AI therapy discontinuation or nonadherence.

Lifestyle changes—including dietary changes, weight loss, and exercise—are suggested for patients with either preexisting or new-onset symptoms.[15] Weight loss may decrease the risk for joint symptoms, as obese women (BMI > 30 kg/m^2) in the ATAC study were more likely to report joint symptoms than were overweight or normal-weight women (BMI ≥ 30).[17] In a prospective study of tenosynovial changes in patients who were treated with an AI or tamoxifen, a regression analysis suggested that grip strength decreased more for patients with high or low body mass index (BMI).[57] Yoga, exercise (especially weight-bearing exercise) with regular stretching, and physical therapy with joint-mobility exercises have been suggested for the management of mild arthralgia pain.[5,53,58] Such measures may also support breast cancer treatment goals, for example, in patients without hot flashes who were effectively treated for breast cancer, dietary changes that were maintained over 4 years were also shown to reduce the risk of breast cancer.[59] Exercise may also contribute to improved survival after adjuvant breast cancer treatment.[60] Other nonpharmacologic approaches to MSS management include heat (eg, hot packs), footwear with lateral-wedge insoles (for knee-associated symptoms), massage therapy, and acupressure (Figure 2).[5,6,53]

Pharmacologic treatment options for AI-associated arthralgia that reportedly provide symptom relief include conventional NSAIDs (eg, ibuprofen),[11,16] analgesics (eg, acetaminophen),[16] coxibs (eg, celecoxib), tramadol, glucosamine plus chondroitin sulfate,[16] opioids,[16] probiotics

(eg, VSL#3), bisphosphonates, vitamin D supplements, antidepressants, sleep aids, nerve-pain medication, and topical capsaicin plus methylsalicylate.[5,15,20,53] Recently, testosterone undecanoate was reported to reduce joint symptom morbidity.[61] According to one recommendation, conventional NSAIDs and coxibs should be started at a high dose to provide rapid symptom relief, followed by titration down to the minimum effective dose.[15] Duloxetine (a selective serotonin norepinephrine reuptake inhibitor that has been used to treat chronic pain) has recently been tested in a randomized phase II study for 29 patients with AI-induced MSS.[62] Results were promising; 72% of patients receiving duloxetine had at least 30% reduction in average pain.[62] By allowing normal joint function to resume quickly, these drugs may encourage patients to continue AI treatment.

Switching to another AI may reduce arthralgia symptom severity. Although all three AIs reduce estrogen levels through inhibition of the aromatase enzyme, they differ in terms of their pharmacokinetics and their effects on lipid parameters, aldosterone levels, and cortisol levels.[63] The dissimilarities among AIs may lead to variations in tolerability, and switching agents may allow patients to continue AI therapy. Several studies have evaluated this strategy.[64-66] Among 182 patients randomized to receive 12 weeks of letrozole followed by 12 weeks of anastrozole and vice versa, joint pain was reported by 131 patients.[64] However, 56% of those who reported joint symptoms with upfront letrozole did not report these symptoms after they switched to anastrozole; similar results were observed with the opposite sequence. Patients who discontinued anastrozole because of grade 2 or 3 arthralgia or myalgia and switched to letrozole after a 1-month period without AI therapy experienced a significant improvement in pain and disability scores after 6 months.[65] Another similarly designed study involved patients who discontinued anastrozole because of musculoskeletal pain; among those who switched to letrozole, about 30% fewer patients reported pain after 6 months.[66] Therefore, switching to another AI may allow patients to continue treatment and maximize benefits.[43]

Resolving MSS

Spontaneous resolution of arthralgia-related AEs associated with AI therapy occurs slowly during treatment, but resolution is common after cessation of AI therapy.[8,15] In one study, 53% (56 of 106 patients) with joint pain and/or stiffness reported use of oral medications for symptom relief (including NSAIDs, acetaminophen, and opiates), as well as oral supplements (eg, glucosamine, chondroitin sulfate, omega fish oils); 46% used a nonpharmacologic intervention (eg, exercise).[16] Among patients who used oral medications, 78% reported moderate to complete relief of joint symptoms. Among 34 patients reporting arthralgia and/or bone pain in a clinical setting, 50% stated that NSAIDs were effective for pain relief.[11] Testosterone and dehydroepiandrosterone-sulfate have each been reported to reduce the severity of pain and stiffness (as measured by visual analog score or questionnaire) in patients receiving AI therapy.[61,67]

Although there are few published clinical studies for nonpharmacologic interventions, three small studies in postmenopausal women with early breast cancer who reported MSS during AI therapy showed that acupuncture reduced pain severity, reduced joint symptoms, improved joint function, and was well tolerated.[68-70] However, supporting data from larger studies are necessary to establish benefits from acupuncture.

Temporary discontinuation of an AI with or without initiation of tamoxifen may be useful to establish MSS causality and health care providers may then decide whether to switch to another AI or to tamoxifen. Completion of adjuvant endocrine therapy is important for the cancer patient to receive maximum treatment benefit. To that end, physicians may improve adherence to therapy through patient education about arthralgia and effective symptom management.[15]

Conclusion

Adjuvant AI therapy is associated with arthralgia/MSS in approximately one-third of patients with hormone-sensitive early breast cancer. Although the reported symptoms are primarily mild to moderate, the development of more severe arthralgia does occur in approximately 2%-12% of patients treated with an AI.

Because of variability in the definition of arthralgia, the limitations in the data establishing causality, and the high baseline incidence of MSS in postmenopausal women, an accurate estimate of the incidence and etiology of AI-associated arthralgia is difficult to establish. Nonetheless, the risk-benefit ratio favors adjuvant AI therapy.[32,71-73] Therefore, steps to manage MSS should be taken in order for patients to complete AI therapy and receive its full clinical benefit. These steps include a baseline examination and patient education before initiating AI therapy, as well as lifestyle changes and pharmacologic treatment, if necessary, when arthralgia develops or worsens during AI therapy. Because the majority of patients who develop new or worsening arthralgia during AI therapy report ameliorated symptoms with palliative treatment—and algorithms to aid in optimal arthralgia management are available—arthralgia should not be a deterrent to using AIs in this patient population.

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Extramedullary BCR-ABL positive T-lymphoblastic leukemia in a patient with chronic myelogenous leukemia

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The introduction of imatinib has significantly improved outcomes in patients with chronic myelogenous leukemia (CML). Before the Food and Drug Administration (FDA) approved imatinib for leukemia in 2001, progression from chronic phase to CML blast crisis was almost inevitable in the absence of allogeneic stem cell transplantation. However, in the recent update of the IRIS trial, 93% of patients who received imatinib defied the natural history of the disease progression from a relatively protracted, benign chronic phase to the accelerated phase, and then the terminal blast phase.[1] CML is an early stem cell disease, so its blast transformation may be myeloid, lymphoid, or of undifferentiated nature. Fifty percent of blast transformation has myeloid blast phenotype and 25% has lymphoid phenotype, of which most are of B-cell lineage. T-cell blast crisis is rare and associated with poor prognosis. To date, there are a few case reports on precursor T-cell blast crisis, but none are as interesting as the current case about the demonstration of predominantly extramedullary nodal T-cell blastic transformation while the bone marrow remained in chronic phase CML.

Case report

A previously healthy 59-year-old black man presented with a 1-month history of fatigue, weight loss, drenching night sweats, and enlarging axillary and cervical adenopathy. On admission, the results of a complete blood count test showed that he had profound leukocytosis, with a total white blood cell count (WBC) of 255,000 cells per microliter, which was comprised predominantly of neutrophils in different stages of maturation and blasts accounting for less than 2% of the total WBC. Initial laboratory findings showed a hemoglobin count of 9.4 g/dL, normocytic anemia with a mean corpuscular volume of 92 fL, leukocytosis with 54% neutrophils, 18% basophils, 6% lymphocytes, 2% monocytes, 3% metamyelocytes, 15% myelocytes, and 2% blasts (Figure 1). The patient was treated with hydroxyurea and supportive care measures, and achieved a nice reduction in his white blood cell count.

A physical examination, also at admission, revealed multiple 2-3 cm (diameter), palpable, fixed, nontender bilateral cervical, axillary, and inguinal adenopathy and hepatomegaly, and a markedly enlarged spleen. A computed tomography scan showed extensive lymphadenopathy in the patient's neck, mediastinum, and hilum axillary, with bulky retrocrural and inguinal lymphadenopathy and moderate hepatosplenomegaly. The patient underwent a left inguinal lymph node excisional biopsy (Figure 2) and the results of a flow cytometry analysis showed extramedullary T-lymphoblastic transformation with 86% positive for CD34, CD13, CD2, CD5, CD7, and terminal deoxynucleotidyl transferase (TdT), and negative for myeloperoxidase. He had an abnormal male 52,XY karyotype with the identification of the Philadelphia (Ph) chromosome translocation at t(9;22) in one out of four metaphases and numerous other chromosomal changes, +5,+7,+8,-9,+10,+13+19. No clonal T-cell or immunoglobulin heavy gene rearrangement was detected. A bone marrow biopsy revealed 100% cellularity with occasional micromegakaryocytes. Fewer than 5% of blasts detected in the flow cytometry analysis were positive for

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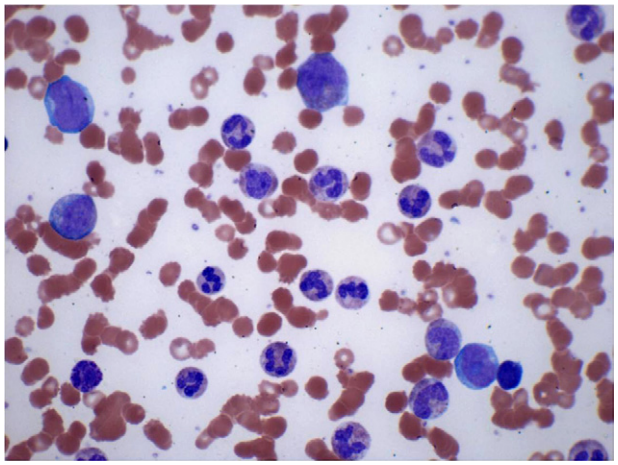

FIGURE 1 Peripheral blood smear upon diagnosis demonstrating an increase in myeloid cells at different stages of maturation.

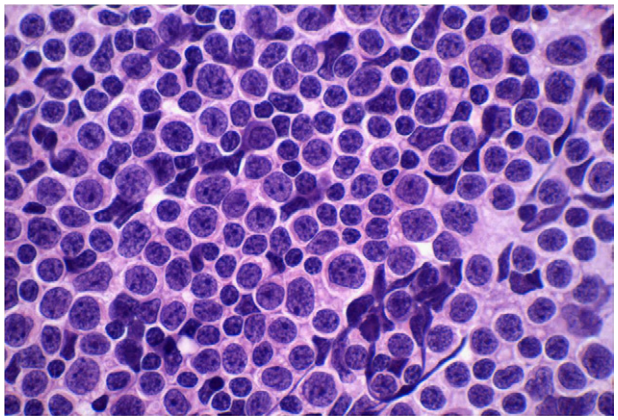

FIGURE 2 Inguinal node excisional biopsy with diffuse effacement by leukemic cells.

CD2, CD5, CD13, CD34, and TdT (Figure 3). A quantitative reverse transcription polymerase chain reaction of the patient's peripheral blood identified a major breakpoint cluster region in intron b3 forming the fusion gene b3a2, which encodes for the 210 kDa BCR-ABL protein known as p210, accounting for 130% units (130,000 cells out of 100,000 total cells) consistent with chronic myelogenous leukemia.

The rest of the relevant laboratory results were as follows: iron level, 20 mg/dL; iron saturation, 14%; and elevated ferritin, 579 ng/mL. Except for an elevated level of lactate dehydrogenase (553 u/L), the rest of his chemistry panel was unremarkable: calcium (8.5 mg/dL), phosphorus (3 mg/dL), potassium (5.1 mEq/L), uric acid (8.9 mg/dL), and creatinine (1.4 mg/dL). An echocardiogram showed a well-preserved left ventricular function of 75%. The results of a baseline CSF analysis before therapy initiation were unremarkable.

The patient was started on the ECOG-2993 protocol (an acute lymphoblastic leukemia [ALL] induction chemotherapy) and standard dose imatinib. During the first induction phase treatment (weeks 1-4), he received daunorubicin 60 mg/m^2 on days 1, 8, 15, and 22; vincristine 1.4 mg/m^2 on days 1, 8, 15, and 22; prednisone 60 mg/m^2 on days 1-28; PEG-asparaginase 2,500 u/m^2 on day 17, and intrathecal (IT) methotrexate 12 mg on day 23, during week 1 to week 4. He achieved complete hematologic remission and substantial decrease in his adenopathy within 1 month after therapy initiation. Repeated CSF analysis was negative for CNS involvement. During the second induction phase (weeks 5- 8), he was treated with cyclophosphamide 650 mg/m^2 on days 1, 15, and 29; cytarabine 75 mg/m^2 on days 1-4, 8-11, 15-18, and 22-25; and methotrexate IT 12 mg on days 1, 8, 15, and 22. After completion of the second induction phase, his bone marrow biopsy was remarkably hypocellular, consistent with postchemotherapy effect (Figure 4), and a flow cytometry analysis showed no evidence of residual disease. During the third month (weeks 9-12), conventional karyotype and FISH (fluorescence in-situ hybridization) cytogenetics identified no BCR-ABL rearrangement in 75 interphase cells that were examined, consistent with achievement of a complete cytogenetic response. A plan for nonmyeloablative allogeneic stem cell transplant with a haploidentical donor is in process.

Discussion

Numerous studies have demonstrated that the dysregulation of normal apoptotic process by BCR-ABL underlies the major mechanism providing a milieu for accumulation of genetic mutations.[2] As a result, clonal evolution becomes a common phenomenon rather than an exception during continued unperturbed BCR-ABL independence. Two other BCR-ABL proteins, p190 and p230, generated by variant fusion genes are occasionally detected in classic CML. Expression of p210 BCR-ABL, an oncoprotein with constitutive tyrosine kinase activity, is necessary for malignant transformation and has been strongly linked to the leukemogenesis in murine CML models. Gross cytogenetic abnormalities are commonly seen in the blast crisis, including duplication of the Ph chromosome, trisomy 8, and isochrome 17.[3] Alterations in p53 genes and loss of p16 genes have also been reported in the lymphoid blast crisis. As many as 83% of patients with lymphoid blast crisis also develop gene amplification, which results in protein overexpression and/or point mutations in the ABL tyrosine-kinase domain. However, it is not known if these additional chromosomal changes alter the management of blast crisis, and there is intensive study underway in this area. The sudden onset of the blast

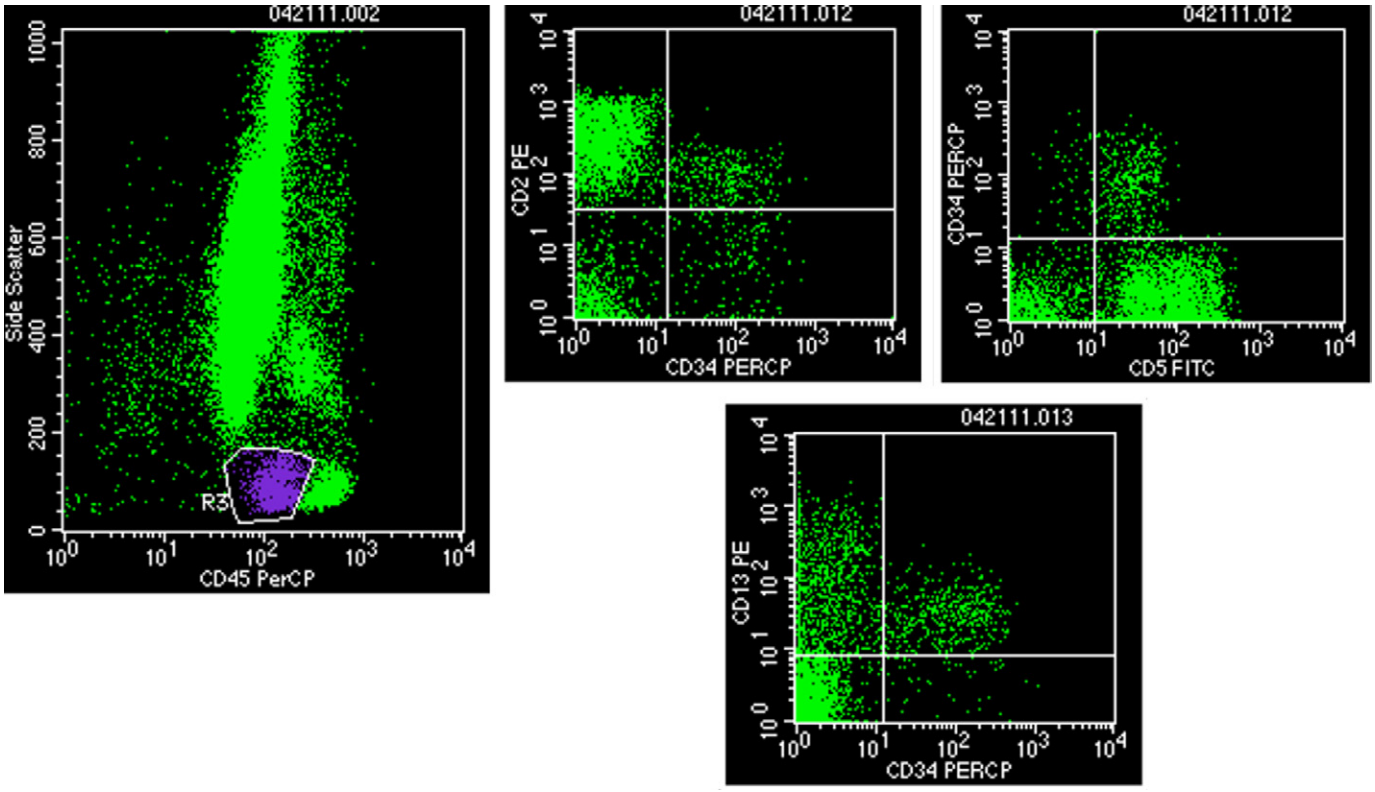

FIGURE 3 Flow cytometry revealing 97% of mature myeloid cells with 2% CD34, CD2, CD5, CD13 positive T-cell myeloblasts.

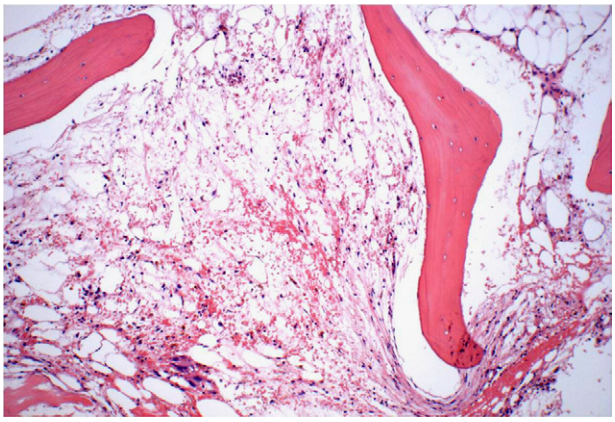

FIGURE 4 Bone marrow biopsy showing decreased cellularity at 5% consistent with postchemotherapy effect.

phase has been cited as a reason for advocating early allogeneic transplant, despite the inherent high mortality rate in the first year after transplant. Most lymphoid blast crises are associated with a favorable prognosis, and the achievement of second remission through intensive chemotherapy is possible and critical for better outcomes after stem cell transplantation. Front-line therapy with a high-dose combination ALL chemotherapy regimen produced a high response rate of 70%, but the duration of the response was disappointing. Addition of imatinib to the above regimen, however, could result in a significant improvement in both hematologic and cytogenetic response rate and better durable disease control.[4]

Furthermore, the second-generation, multitargeted kinase inhibitor, dasatinib, has a 325-fold greater potency attributed to its binding to BCR-ABL in its active and inactive conformations.

In the START-L trial, 42 patients with lymphoid blast crisis who either progressed through imatinib or who were intolerant of imatinib were started on standard-dose dasatinib and maintained until disease progression. In this cohort, 79% of patients had received previous chemotherapy. At the 8-month follow-up, 31% of the patients achieved a major hematologic response and 50%, a major cytogenetic response (MCyR).[5] In a phase II study of another second-generation, multikinase TKI, nilotinib, 13% of patients achieved complete hematologic response (CHR) with a median duration of 3.6 months and a 52% major cytogenetic response. However, nilotinib has not been approved by the FDA approved for the treatment of patients with blast crisis for CML. Although a significant portion of these patients achieve an MCyR, concomitant

CHR tends to be short-lived because of cytopenias.[6] Fava et al reported that failure to achieve complete hematologic response at the time of MCyR is associated with an inferior outcome with a 2-year survival rate that declined precipitously from 77% to 37%.[7]

In summary, chemotherapy in combination with imatinib or dasatinib and followed by immediate allogeneic stem cell transplant is the current standard care for patients with de novo BCR-ABL positive blast phase CML. In the German CML IV study, transplantation for blast phase was associated with a poor survival of 16%.[8] Despite ongoing advances in molecular DNA assessment and more accurate human leukocyte antigen (HLA) typing, limited availability in HLA-matched donors, and risks associated with allogeneic transplantation often restrict the use of stem cell transplantation upfront. As the ultimate salvage therapy for blast crisis continues to evolve, we believe that with the advent of the second-generation ABL tyrosine-kinase inhibitors and nonmyeloablative approach, reduced intensity allogeneic stem cell transplant and novel tyrosine-kinase agents may provide better therapy for the treatment of blast crisis in CML.

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Decitabine-induced acute lung injury

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Acute fibrinous and organizing pneumonia (AFOP) is a distinct histologic pattern of acute lung injury.[1] It can occur with a spectrum of clinical associations, including drug-induced acute lung injury. AFOP is not a known complication of decitabine. However, early recognition and diagnosis are important to prevent disease progression and associated morbidity and mortality.

Case presentation

A 62-year-old man presented with chills, nonproductive cough, and malaise; he had been running a fever for 4 days before presentation. He had a history of myelofibrosis with increased blasts and had received 2 cycles of decitabine, the second a week before he was admitted to hospital. The patient had a temperature of 102.3°F, a pulse rate of 116/minute, blood pressure of 130/70 mm Hg, respirations of 18/minute, and oxygen saturation of 96% on room air when he was admitted.

An examination of the patient was unremarkable, except that, he had right basilar crackles in the right lung. The patient was pancytopenic, with a leukocyte count of 2,000 K/uL, a hemoglobin value of 8 g/dL, and a platelet count of 110,000 K/uL; results of other laboratory studies were normal. A chest radiograph showed a right lower- lobe infiltrate, so the patient was started on the broad-spectrum antibiotics, moxifloxacin, vancomycin, and piperacillin-tazobactam (Figure 1). A CT scan showed consolidation in the right lower lobe. The patient remained febrile despite the antibiotic therapy.

The patient underwent bronchoscopy with bronchoalveolar lavage and transbronchial biopsy. All of the cultures and stains were negative. Pathology results showed areas of organizing connective tissue in alveolar septae and acutely inflamed fibrin in alveolar spaces. A diagnosis of AFOP was made, with decitabine as a likely etiology. The antibiotic therapy was stopped, and treatment with the immunosuppressant prednisone was started. The patient's condition improved, and a follow-up CT scan at 4 weeks showed resolution of the infiltrate.

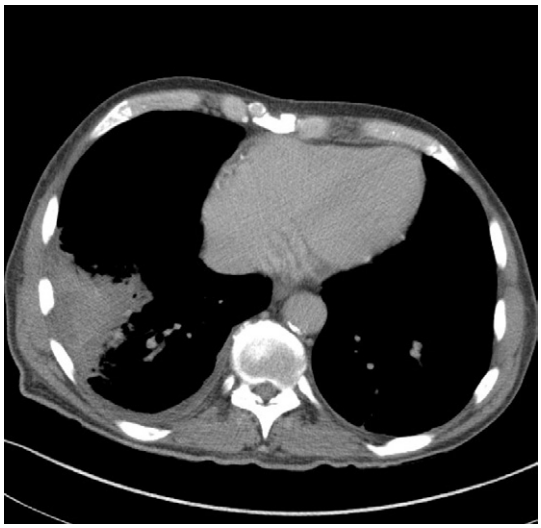

FIGURE 1 A CT scan of the chest showing right lower-lobe infiltrate.

Discussion

Decitabine is a hypomethylating agent used for the treatment of myelodysplastic syndromes and acute myeloid leukemia. Known adverse reactions to decitabine are myelosuppression, infections, vomiting, diarrhea, peripheral edema, arthralgia, and hyperbilirubinemia.[2]

There is one previous documented case of decitabine-induced acute lung injury,[3] which shares striking similarities with the current case: the 2 cycles of decitabine therapy, fever spikes, focal infiltrates, and a similar histologic pattern of AFOP. In both of these cases, the patients improved with steroid treatment.

AFOP is a histologic pattern of acute lung injury that does not meet the criteria for diffuse alveolar damage, organizing pneumonia (OP), or eosinophilic pneumonia. It is characterized by predominantly intra-alveolar fibrin and OP and

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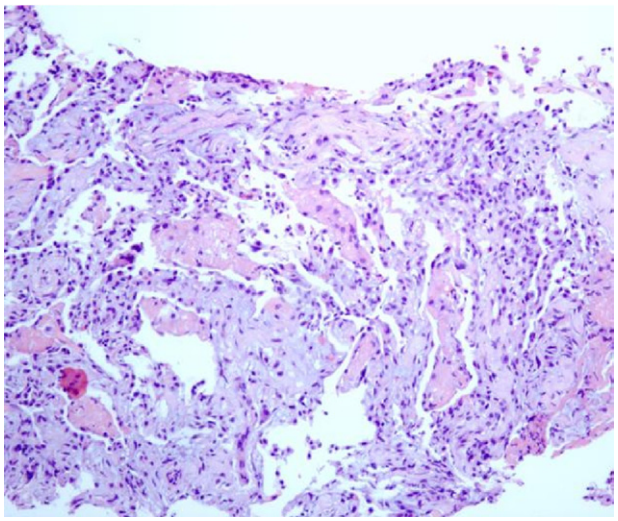

FIGURE 2 Pathology specimen, showing fibrin deposition within the alveolar spaces with thickened alveolar septae (organizing pneumonia).

was first described in 2002 (Figure 2).[1] Typical symptoms described in that study were "spiking" fever, cough, and malaise, all of which our patient experienced. Dyspnea and hemoptysis were also described. The known associations with AFOP are collagen vascular disease, lymphoma, *Acinetobacter* sp., *Haemophilus influenzae*, and use of the antiarrhythmic agent, amiodarone. AFOP has also been associated with acute lymphoblastic leukemia,[4] systemic lupus erythematosus,[5] *Pneumocystis jiroveci*,[6] and drugs such as abacavir and busulfan.

AFOP is associated with a 50% mortality rate,[1] signifying a poor prognosis. In previous studies of patients with AFOP, the treatment modality used did not correlate with patient outcome, except for a high mortality rate in patients who needed mechanical ventilation, and there is no consensus on optimal treatment.[1] If decitabine-induced ATOP is suspected, then the agent should be discontinued, the patient should receive supportive care, and corticosteroid therapy should be initiated.

Conclusion

The current report is the second documented case of decitabine-induced AFOP, even though AFOP is not a known adverse effect of the agent. However, the presentation described here suggests that AFOP could be a potentially serious side effect of decitabine and that physicians should be vigilant about this possibility.

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Creating partnerships for survival

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The projected increase in the number of cancer survivors will present unprecedented challenges for community-based practices, and the Institute of Medicine[1] and the American College of Surgeons' Commission on Cancer[2] have made recommendations to meet the needs of this growing patient population. However, most community-based practices do not have the resources to implement the recommendations and will have to work closely with resources outside of the practice to develop financially viable and sustainable programs.

Survivorship care should incorporate prevention, early diagnosis, pretreatment evaluation, treatment, evaluating distress, ensuring good nutrition, counseling, rehabilitation, spiritual care, and advanced care planning. It should be rooted in the concept of shared decision-making during all phases of the cancer trajectory up to and beyond the completion of treatment, with the goal of improving the patient's quality of life (QOL). The definition of survivorship has evolved over time. In its definition of survivorship, the National Coalition for Cancer Survivorship (NCCS)[3] emphasizes that a patient becomes a survivor at diagnosis and remains a survivor through treatment and afterward until the end of life. It also stresses that survivorship planning and management should include family members, friends, and caregivers. Few programs focus on survivorship throughout the patient's cancer journey in the way the NCCS recommendations do.

A diagnosis of cancer can unleash substantial physical and psychosocial distress in a patient, which could have a bearing on quality of life and disease outcome. As such, it is important that patients' physical, spiritual, and psychosocial needs are addressed in addition to their receiving the appropriate anticancer treatment. Patients and caregivers can experience a range of emotions, from anger and depression to fatigue and a sense of extreme loss. There is a growing expectation among survivors that their needs, both during and following their course of treatment, will be met.

At our practice, we are developing a comprehensive model for survivorship that incorporates assessment of a patient's QOL and identifies patient concerns and needs. Unlike most academic organizations, we do not have services such as psychological counselling, rehabilitative care, or complementary medicine options (acupuncture, massage, healing touch, and so on) within the practice, so we have to refer patients to groups such as the American Cancer Society, community wellness programs, disease-specific organizations, wig or prosthetic suppliers, or support groups, for that assistance. Our model is led by advanced practice registered nurses (APRNs), who create a survivorship care plan that is tailored to the patient's physical, emotional, functional, and social concerns. The APRN facilitates care at all phases of the cancer trajectory, from explaining the treatment decisions and symptom management, to ensuring a seamless transition between the phases of care, as well as advocating for the patient to ensure that their care is patient centered. We believe that over time, the empirical data will demonstrate the effectiveness of identifying real-time patient concerns, improvements in QOL, and the extent to which the APRN's interventions make a difference in patient outcomes.

Key to our program, known as Stride for Stride: A Partnership for a New Normal, is that team members work closely with the oncologist to ensure that survivorship care is part of the overall treatment plan focusing on what Mullan[4] called the "seasons" of survivorship: acute (diagnosis and initial treatment), extended (watchful waiting), transition, and permanent.[5] The survivorship plan should ideally begin shortly after the oncologist has determined a treatment plan. This is often a difficult and confusing time for the newly diagnosed patient and introducing survivorship care

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A survivor speaks

My nurse navigator taught me to be a cancer survivor.

I was very fortunate to have access to a nurse navigator support system, from my diagnosis for lung cancer, through surgery, chemotherapy, and maintenance drug therapy. My nurse navigator taught me to be a cancer survivor.

My diagnostic visit was traumatic. The doctor said, "It's cancer and surgery is necessary." But survivorship begins at diagnosis, and Michele, my nurse navigator, was there to help me and my husband through the emotional trauma. She put us on the path to dealing with cancer. We left with surgery scheduled, medication prescribed, and I was told I could call her any time! There was somebody there for me, and it helped me feel more confident about my care. Physicians do not have the time to sit with a patient and deal with the emotional aspects of this horrible disease. It is the nurse navigator who pulls it all together.

My second survivorship visit was right after I had completed chemo, and I was falling apart. I was physically exhausted, wanted my hair back . . . life was a bitch. Michele helped me refocus emotionally—helping me understand that cancer is a journey of the body, mind, and spirit. At that meeting, we also touched on maintenance therapy with erlotinib. At my third visit, a month after chemo and just before I was due to start maintenance therapy, Michele explained how the therapy worked and what side effects to expect. Part of me wanted to be done and I worried about quality of life issues. Again, she guided me through that.

We developed a great relationship through these visits, which improved my quality of life and outcome. When I began my therapy, Michele held my hand through the initial 30-day period. I had a major reaction to erlotinib and an allergic reaction to the antibiotic for side effects, but with her guidance and support, I stayed out of hospital.

I work for a small mental health clinic and understand the importance of mental health in recovery from illness. How one is cared for during one's journey with cancer affects the outcome of the disease. I regained my mental and physical health through treatment, exercise, weight loss, and a very caring supportive team of physicians, my nurse navigator, and other providers. And for that, I am very grateful.

— Sharon Rothgeb

early can help the patient cope with the physical, logistical, and psychological rigors of therapy. Our program includes a series of at least three, one-on-one patient-APRN visits, at diagnosis, treatment completion, and 3-6 months after treatment completion. These are billable visits that allow financial viability. The focal point of these visits is a QOL assay that allows real-time measurement of distress and issues of concern. At that point, based on the assessment findings, the patient can be referred to the relevant experts and/or programs for support, assistance, and follow-up. The premise is that the earlier the patient's concerns and distress are identified and addressed, the better.

To implement a similar program a practice, one should consider the following:

- Define the starting point for initiating survivorship care. We have found that patients are not reluctant to have the extra office visit, but rather appreciate time to review their concerns before they start therapy.
- Identify reliable, easy-to-use screening tools that can be administered to gauge a patient's distress level, concerns, and QOL.
- Clarify how to administer the tool, establish the score, and interpret the results before you administer it. Multiple QOL tools exist, and no one tool is ideal.
- Assemble a group of physicians, APRNs, social workers, dieticians, and therapists to be part of the team.
- Meet with the patient to discuss concerns relating to the diagnosis and treatment as well as psychosocial, spiritual, and financial matters, before treatment begins.
- Establish who comprises the patient's support system—family members, friends, care givers, and so on—and evaluate their potential influence and impact on the patient's well-being.
- Draw up a list of experts, specialists, programs, and community resources to which patients might be referred once they been assessed.
- Integrate care between the patient, the oncologist, and the primary care provider.

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Moving up in the world: screening for lung cancer

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In one of our previous articles, we discussed a study of screening for prostate cancer.[1] Now we're going to move up a bit, at least anatomically, and discuss a study of screening for lung cancer.[2] We have previously defined ourselves as curmudgeons and skeptics; to those self-descriptions we now add a new term, "chutzpahniks." For those of you who may be unfamiliar with that Yiddish term, it means people who have chutzpah, which was defined by Leo Rosten[3] as: "that quality enshrined in a man who, having killed his mother and father, throws himself on the mercy of the court because he is an orphan." Our chutzpah stems from the fact that we are criticizing the results of a study that was published in the *New England Journal of Medicine* and highly praised in an editorial in that journal.[4] If we had less chutzpah, we wouldn't contemplate such a critique, but then again, if we had less chutzpah, we—a clinical psychologist and a nuclear physicist—wouldn't be writing articles in a cancer journal. So, on to the study.

Participants were people between the ages of 55 and 74 years who were currently or had previously been heavy smokers (at least 30 pack years), and were randomly assigned to be screened with either low-dose CT (26,722 participants) or chest radiography (26,732). They were screened at baseline and then 1 and 2 years later; those in whom lung cancer was diagnosed were not offered subsequent screening. What brought joy to the hearts of the researchers and the editorialist was the fact that there were 309 deaths from lung cancer per 100,000 person-years in the radiography group and only 247 deaths per 100,000 person-years in the CT group, representing a reduction of 20.0%. All-cause mortality was also reduced by 6.7% in the CT group. From a methodological point of view, it would be hard to fault this study. It involved over 53,000 patients enrolled in 33 sites, with adherence rates of 95% in the low-dose CT group and 93% in the radiography group over the three rounds.

Given these impressive figures, what leads to our curmudgeonly, skeptical, and chutzpahdikeh feelings? Actually, a number of things. The first is the sample size. As we've mentioned in a previous article,[5] sample size is much like the magnification in a microscope; the smaller the phenomenon you're looking at, the larger the sample size has to be. We have also said that you should be suspicious of relative statistics—the odds ratio and relative risk[6] (we just love it when we can quote ourselves). Both factors come into play here. Our feeling is that if you need over 50,000 patients, followed for 3 years, to demonstrate something, that something must be very small. That's masked by presenting the results as a relative reduction in mortality. To the authors' credit, they also give us the actual numbers, so we can see how large—or small—the effect actually is. Using their figures, the absolute reduction in deaths was (309 – 247) per 100,000 patient years, or 1 additional year of life for 62 people for every 100,000 screened. We leave it to you to determine if that's a lot or a little. *Ceteris paribus* (that's Latin for "All other things being equal," and used here merely to be a bit pretentious), we should switch immediately from radiography to low-dose CT scans. But, all things being equal, all things are never equal. At least two questions need to be raised.

The first is economic; how much more will it cost to replace all the X-rays with CT scans, and all those X-ray machines with CT scanners? There is a concept from economics called "opportunity costs;" that is, what opportunities are we foregoing by spending money on a given program? Money for health care is finite, as we are constantly reminded, so every extra dollar that is spent for CT scans rather than X-rays means that one

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less dollar is available to spend on other screening programs, prevention interventions, surgery, rehabilitation, or whatever.

The second question is risk. CT scans have a huge radiation dose relative to radiographs. In one review article, a dose for chest CT was 300-400 times greater than for CXR.[7] So-called "low-dose" CT is perhaps 20% of that; still a large amount of radiation. To put that in perspective, our favorite statistic in this regard, direct from BBC World, is that if you are fool enough to add a whole body CT scan to your annual physical, at a cost, we're told, of about $1,000, you will receive the same amount of radiation you would get standing a mile and a half from ground zero at Hiroshima when the bomb went off. More seriously, there is some evidence that diagnostic imaging may induce delayed cancer.[8]

But, there is still a larger issue; that of false positives. When we wrote about mass screening,[9] we pointed out many problems that it can cause, especially when the prevalence of the disorder is low, the course of the disease is variable (aggressive in some people and lethargic in others), and the treatment far from perfect. The major difficulty is that, with a low prevalence, there will be many false positive results. This then leads to follow-up evaluations, with their associated costs and possible risks.

This is a particular problem in this study. There were a total of 75,126 low-dose CT scans given over the three screening rounds. Of these, 18,146 (24.2%) were positive. So far, so good; not a bad detection rate. But, of this number, there were only 649 confirmed cases of lung cancer. This represents less than 1% of all scans done. More tellingly, it means that the false positive rate was a whopping 96.4%. For the other group, there were 73,470 radiographs performed, of which 5,043 (6.9%) were positive, and 279 were confirmed to have lung cancer—fewer than 0.4% of the tests, and a false positive rate of 95.5%. That's about the same false positive rate as mammography, by the way.

And the result of these extremely high false positive rates? An additional 14,130 imaging examinations, 494 percutaneous cytological exams or biopsies, 896 bronchoscopies, and 952 surgical procedures, including mediastinoscopy or mediastinotomy, thoracoscopy, and thoracotomy. We'll leave it to the health economists to figure out the cost of all these. We have no way of figuring out the psychological costs due to the anxiety generated by a false positive diagnosis of possible lung cancer.

There's one last point that we haven't mentioned, because it's not mentioned in the paper – what was the false negative rate? That is, even with all those scans and X-rays, were any cases missed? Unfortunately, all the paper says is "Detailed calculations of sensitivity, specificity, positive predictive value, and negative predictive value are not reported here" (p. 400).[2] Reporting on diagnostic tests without giving those figures is tantamount to ripping out the last chapter of a murder mystery before passing it on. We want to know who done it or, in this case, who got cancer that wasn't detected. The results may not be known for some years, but it's a vital piece of information before we can pass judgment on these two diagnostic approaches. In the meantime, we'll stick with the Scottish legal phrase of "Not proven."

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How I treat . . . ASH

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We've attended numerous conferences during our medical careers, but none has compared with our experience as first-time attendees at the annual meeting of the American Society of Hematology meeting in San Diego. The meeting was huge, drawing more than 20,000 scientists, clinicians, students, researchers, and members of industry, from all over the world, and choc-full of choices when it came to deciding what to attend. It could have been a logistical nightmare, but it was meticulously organized, and from the registration process to the post-conference shipping of our DVDs, it could not have gone more smoothly. We learnt a few other things about preparing for and navigating the conference, and we thought we'd share those lessons as they could be applied to other conferences as well.

Two words sum up lesson 1: early bird. And we mean really early. We registered 4 months ahead of ASH and were already too late to get into any of the recommended hotels. We had to settle for a hotel about 10 miles from the convention center. Registration for the conference and accommodation can be done easily online and once that is behind you, it means you have online access to conference information and can start preparing ahead of time. Also be mindful to register early for the satellite symposia and industry-sponsored CME-certified meetings (lesson 2), which at ASH were held a day ahead of the official opening. Those sessions are not included in the basic registration and you don't want to be wasting time at the conference standing in line to register and risk missing part of the presentation.

Talking of preparing ahead, ASH had launched a mobile app that included the schedule, conference information, and updates. It was extremely useful and user-friendly—there was no need to lug around books or the bulky paper schedule and it allowed one to prepare and schedule sessions well ahead of the conference (lessons 3 and 4: get the app and plan ahead). Careful planning is key for a conference this size. We suggest that you review the reading materials that you receive after (early) registration and draw up a schedule before you arrive at the conference.

Here are a few additional tips for the novice conference attendee. Dress business-casual—be comfortable but don't wear jeans, T-shirts, or sneakers. Save money by bringing your own refreshments; our only criticism of the conference is that meals and refreshment costs were so inflated. And at the risk of sounding like parents, enjoy your evenings but don't stay up late—sessions begin early, usually around 7am.

None of this is intended to diminish the range and substance of the superb line-up of presentations and at the meeting. As clinicians, we opted to focus on the educational sessions, although we also managed to attend parts of some of the other sessions. (It helped tremendously that many sessions were featured at an alternative time to minimize clashes with other presentations.) The educational sessions offered reviews and expert guidance in the management of specific diseases and updates in advances and developments in the field. The speakers were clearly leaders in their fields, and we recognized many of the names from our readings. Our top choices from the educational sessions include a presentation and question-and-answer session by Theodore E. Warkentin, MD, on the diagnosis and management of heparin-induced thrombocytopenia, and a comparison of commonly used chemotherapy regimes by Ranjana Advani, MD, who discussed the role of radiation therapy for patients with Hodgkin lymphoma.

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