March 2009 www.clinicaladvances.com Volume 7, Issue 3, Supplement 8

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# Hematologic Malignancies in the Aging Population: Biology, Molecular Prognostic Markers, and Novel Treatment Strategies

A Review of a Symposium Held at the 50th Annual American Society of Hematology Meeting
December 6–9, 2008
San Francisco, California

Supported through an educational grant from Cephalon Oncology.

Clinical Advances in HEMATOLOGY & ONCOLOGY™
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# Prognostic Factors in Elderly Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia and the Implications for Treatment

Harry P. Erba, MD, PhD

## Treatment of Patients with Myelodysplastic Syndrome (MDS)

The incidence of MDS is approximately 3 per 100,000 per year in the United States[1] and increases with advancing age.[1,2] In the International Prognostic Scoring System (IPSS), the standard for predicting prognosis in MDS,[3] patients are grouped into 4 categories, from low- to high-risk, based on 3 major risk factors: marrow blast percentage, number of cytopenias, and marrow blast karyotype (Table 1). IPSS categories correlate with survival, with median survivals of 5.7 years, 3.5 years, 1.2 years, and 0.4 years for patients with low-, intermediate-1–, intermediate-2–, and high-risk disease, respectively.[3]

Typical treatments for MDS have included low-dose cytarabine (Ara-C), intensive chemotherapy (anthracycline and ara-C combination [7+3]), and best supportive care. A recent randomized study compared these approaches to azacitidine in 358 MDS patients with advanced disease.[4] Azacitadine showed an overall survival benefit in this population, with a median survival of 24.4 months versus 15 months for the conventional care regimens ($P$=.0001). Subanalyses further showed that azacytidine was favored over the conventional care regimens regardless of patient age, gender, IPSS score, cytogenetics, MDS subtype, or lactate dehydrogenase levels.

## Acute Myeloid Leukemia (AML)

The azacitadine data provide hope that the prognosis of older patients with MDS and AML may improve with new, better-tolerated agents. Like MDS, the incidence of AML also increases with age[5,6] (Figure 1). In a review of the Swedish Acute Leukemia Registry, the median age of AML patients was 72 years.[5] Similar data are available from the U.S. Surveillance Epidemiology and End Results (SEER) registries.[6]

Older patients with AML have poorer outcomes for a variety of patient-specific and leukemia-specific reasons. In terms of patient-specific factors, advancing age, poor performance status, comorbid illnesses, and organ dysfunction all impact the ability of older patients to tolerate intensive chemotherapy. Leukemia-specific risk factors for older patients include unfavorable risk class karyotype, antecedent hematologic disorder, and multidrug resistance (MDR) gene expression. An analysis of nearly 1,000 chronic myelogenous leukemia (CML) patients treated on 5 different Southwest Oncology Group (SWOG) protocols showed that occurrence of treatment resistance is more common with older patients, while complete remission (CR) and overall survival rates decline in this population.[7] Older AML patients are also more likely to have comorbid illness and unfavorable blast karyotype,[7,8] both of which are associated with dimished response to therapy and decreased overall survival times.[8-10]

### *Intensive Chemotherapy in Older Patients*

There is conflicting evidence as to the benefit of intensive chemotherapy in older patients. Perhaps as a result, the proportion of patients who receive any form of chemotherapy

**Table 1.** International Prognostic Scoring System for Myelodysplastic Syndromes

| Prognostic Variable | Score Variable | | | | |
|---|---|---|---|---|---|
| | 0 | 0.5 | 1.0 | 1.5 | 2.0 |
| Bone marrow blasts | <5% | 5–10% | — | 11–20% | 21–30% |
| Karyotype* | Good | Intermediate | Poor | | |
| Cytopenias† | 0 or 1 lineage | 2 or 3 lineages | | | |

*Karyotype: good=normal, -Y, del (5)(q), del (20)(q); intermediate= all other single and double cytogenetic changes not good or poor risk; poor=complex or chromosome 7 abnormalities.

†Cytopenias: hemoglobin <10 gm%, absolute neutrophil count < 1,500/mL, platelets <100,000/mL.

Data adapted from Greenberg et al. *Blood.* 1997:89:2079.

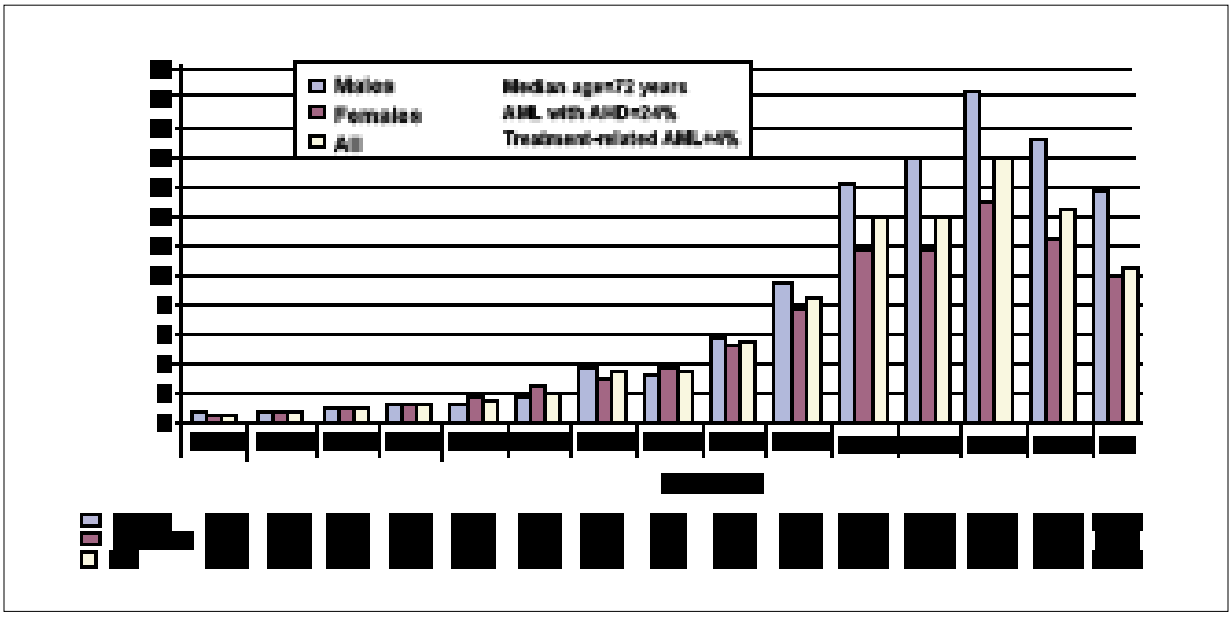


**Figure 1.** Swedish acute leukemia registry: non-APL AML, 2005, new cases per 100,000.

Data from Juliusson et al. *Blood* 2008: Nov 13 [Epub ahead of print].

AML=acute myeloid leukemia; AHD=antecedent hematologic disorders; APL=acute promyelocytic leukemia.

declines with advancing age. In an analysis of 2,657 AML patients 65 years of age or older, only 30% received any form of intravenous (IV) therapy.[11] The median survival of this group of patients was only 2 months, but was longer in patients who received chemotherapy at the recommendation of their physician (7 months vs 1 month for untreated patients), suggesting not only that therapy is effective but also that physicians can successfully choose patients who will be able to tolerate chemotherapy.

In an attempt to evaluate the optimal treatment regimen for poorer-risk patients, a prospective study included 217 patients deemed unfit for intensive chemotherapy who were randomized to receive low dose Ara-C (20 mg, twice daily for 10 days) or hydroxyurea with or without all-trans-retinoic acid (ATRA).[12] Low dose Ara-C resulted in a higher CR rate (18% vs 1%; *P*=.00006) and better overall survival (odds ratio, 0.60; *P*=.0009) in patients with favorable and intermediate-risk blast karyotypes, but not in unfavorable risk karyotypes.

A study at the M.D. Anderson Cancer Center showed that nonmyeloablative allogeneic stem cell transplant is a valuable therapy for older AML patients, with a CR rate of 44%.[13] Relapse-free and overall survival was superior in patients who had a consult from a transplant physician, also had a donor, and received a reduced-intensity transplant. Unfortunately, however, this approach could only be used in 5% of patients in the series.

### *Targeted Therapies for Patients with AML*

A number of drugs are now being evaluated in older patients with AML in an attempt to replace therapies that have significant toxicity and limited efficacy. These include targeted therapies like gemtuzumab and tipifarnib, and novel cytotoxic agents like the DNA methyltransferase inhibitors laromustine and clorfarabine.

Tipifarnib is a farnesyltransferase inhibitor which has been tested in AML patients based on the rationale that 10–30% of AML patients have mutations that activate *RAS*, and that tipifarnib may be able to interrupt that activated signaling pathway. Thus far, the benefits of tipifarnib have been modest in older, high-risk patients. Response rates were 6–20% in several major studies that evaluated different doses of the drug in this population,[14-16] and did not appear to correlate with *RAS* mutation status, farnesyltransferase inhibition, blast karyotype, or clinical features.[14] Tipifarnib offered no survival benefits compared to best supportive care.[14-16] Gemtuzumab ozogamicin, an anti-CD33 monoclonal antibody linked to the cytotoxin calicheamicin, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of AML patients 60 years or older who have relapsed or are intolerant to other therapies. This agent has been shown to have antileukemia effects in older AML patients, but its effect on survival outcomes are uncertain.[17,18]

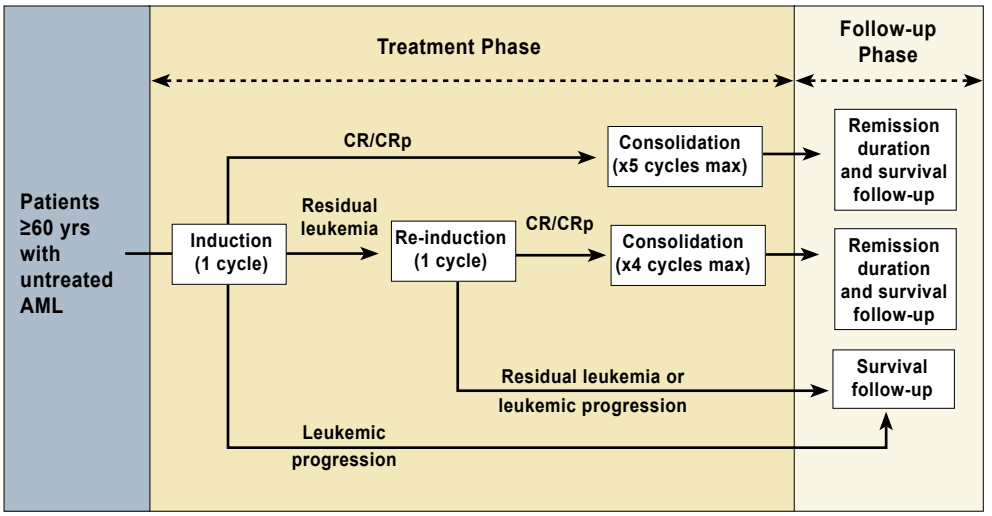


**Figure 2.** CLASSIC II: treatment protocol.

Induction: clofarabine 30 mg/m$^2$/day, day 1–5; re-induction and consolidation: clofarabine 20 mg/m$^2$/day, day 1–5.

CR=complete remission; CRp=complete remission with incomplete recovery of platelet count.

Given the biologic complexity of AML, it is naive to expect high response rates in all patients with a targeted therapy. It may be that a certain gene expression profile can predict which AML patients will respond to tipifarnib. Our challenge going forward will be to develop agents and design clinical studies which can detect the benefits of targeted drugs in small subsets of AML patients.

### *Novel Cytotoxic Agents for Treating AML in Older Patients*

Laromustine is a novel sulfonyl hydrazine alkylating agent. The largest study to date with this drug is a single-center trial in which older AML patients were treated with a single IV infusion of 600 mg/m$^2$ over 1 hour.[19] Patients who were eligible for this study had to have untreated de novo AML and have one other risk factor (ie, age >70, poor performance status, unfavorable blast karyotype, or some organ dysfunction). Patients with a prior history of MDS were excluded based on low response rates in a prior study. The median age of patients was 73, and half had an unfavorable blast karyotype. The overall response rate (ORR) in this study was 35%. When response rate was investigated based on risk factors, age of 70 years or above had no impact, but only 23% of patients with an unfavorable blast karyotype achieved a response. Laromustine had significant hematologic toxicity and 14% of patients died within the first 30 days on study.

Clofarabine is a promising new alkylating agent which showed an ORR of 48% in treatment-naive, elderly AML patients in the United Kingdom.[20] This led to the Classic II study in the U.S., which evaluated single-agent clofarabine (Figure 2).[21] Eligible patients had de novo or secondary AML, were 60 years or older with an adequate performance status (ECOG 0-2), and at least 1 adverse prognostic factor (age ≥70 years, ECOG performance status 2, antecedent hematologic disorder, intermediate- or unfavorable-risk karyotype).

Patients were treated with clofarabine at 30 mg/m$^2$ daily for 5 days, and then could receive reinduction or a consolidation dose (20 mg/m$^2$ daily for 5 days).[21] The ORR was 45%, with 40% of patients having CRs. Two-thirds of the responses occurred after the first cycle. Importantly, the ORR was consistent among the various risk group: 40% in patients 70 years of age or older, 38% in patients with an ECOG performance status of 2, 50% in patients with an antecedent hematologic disorder, and 43% in patients with an unfavorable blast karyotype. The 30-day mortality in this study was 10%.

In conclusion, older patients with AML have significant morbidity and a high early mortality due to disease-related complications even without cytotoxic therapy. There is no standard therapy for the majority of older patients with AML, making controlled studies difficult to design. Cure and prolonged disease-free survival will not be realized until we are able to develop treatments for patients with AML that are tolerable and effective at eradicating minimal residual disease.

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# The Role of Molecular Markers for Predicting Treatment Outcomes in Chronic Lymphocytic Leukemia

Kanti Rai, MD

## Emerging Treatment Approaches for Frontline Chronic Lymphocytic Leukemia (CLL)

CLL is a disease of the elderly. There is no standard of care for CLL, but a number of ongoing studies are comparing frontline regimens. Fludarabine-based regimens are a common inital treatment strategy. A large study in which 777 CLL patients were randomized to fludarabine, fludarabine plus cyclophosphamide, or chlorambucil showed higher CR rates for cyclophosphamide versus fludarabine (CR rate 38% vs 15% for fludarabine alone; ORR 94% vs 80% for fludarabine alone; *P*<.0001 for both comparisons).[1] The chlorambucil alone arm had the lowest response rates, with a CR rate of 7% and ORR of 72%. Although there was no difference in overall survival between any of the treatments, progression-free survival (PFS) at 5 years was significantly better with fludarabine plus cyclophosphamide (36%) than with fludarabine (10%) or chlorambucil (10%; *P*<.00005). Fludarabine plus cyclophosphamide was the best treatment for all ages, including patients older than 70 years. Similar results were seen in the phase III ECOG study E2997, in which 278 CLL patients were randomized to treatment with fludarabine plus cyclophosphamide versus fludarabine alone.[2] Treatment with fludarabine and cyclophosphamide was associated with a significantly higher CR rate (23.4% vs 4.6%; *P*<.001), ORR (74.3% vs 59.5%; *P*=.013), longer PFS (31.6 vs 19.2 months; *P*<.0001), but no survival benefit. Rates of hematologic toxicity were higher on the fludarabine plus cyclophosphamide arm, but there was no difference in incidence of severe infections (*P*=.812).

A single-arm phase II study of fludarabine, cyclophosphamide, and rituximab (FCR) as initial therapy

has shown high activity for this combination in 300 CLL patients.[3] At a median follow up of 6 years, the ORR was 95%, with CR in 72% of patients. Six-year overall and failure-free survival were 77% and 51%, respectively, with a median time to progression of 80 months. Only 2 patients (<1%) died within 3 months of starting therapy. Several baseline characteristics (eg, age ≥70 years, beta2-microglobulin ≥2 × upper limit of normal [ULN], white cell count ≥150 × $10^9$/L, abnormal chromosome 17, lactate dehydrogenase ≥2 × ULN) were associated with inferior response. Older patients were underrepresented in this study, where 62% of patients were less than 60 years of age and only 14% were 70 years old or older. Nevertheless, FCR induced CR in 51% of patients 70 years or older and has emerged as an important new treatment option in CLL. In a multivariate analysis of patients receiving fludarabine-based therapy at M.D. Anderson Cancer Center, FCR therapy emerged as the strongest independent determinant of survival.

Rituxmab has changed the way we treat patients with CLL. Two important studies presented at the 2008 ASH meeting—the CLL8 and REACH trials—showed that the addition of rituximab to fludarabine plus cyclophosphamide significantly improves outcomes.

The CLL8 study used the combination as first-line treatment for previously untreated patients. A total of 817 patients with previously untreated CLL were randomized to either the FC group (6 courses of fludarabine 25 mg/$m^2$ IV on days 1–3 plus cyclophosphamide 250 mg/$m^2$ IV on days 1–3, every 28 days) or the FCR group (regimen for FC group plus rituximab 375 mg/$m^2$ IV on day 0 at the first cycle and 500 mg/$m^2$ on day 1 for all subsequent cycles, every 28 days). PFS at 2 years was 76.6% in the FCR group and 62.3% in the FC group ($P$<.003); ORR was significantly higher in the FCR group than in the FC group (95% vs 88%). Patients in the FCR groups also showed an improved CR rate compared with those in the FC group (52% vs 27%). Although not significant, an overall survival benefit in the FCR group (91% vs 88% at 2 years; $P$=.18) was observed.

The REACH trial used the same drug regimen as the CLL8 study, but as second-line treatment in 552 patients with relapsed or refractory CLL who had received an average of 1 previous treatment. PFS was 30.6 months in the FCR group and 20.6 months in the FC group. ORR was significantly higher in the FCR than in the FC group (70% vs 58%); CR rate was superior in the FCR group to that in the FC group (24 % vs 13%).

Two recent trials have evaluated 2 newer options—alemtuzumab or bendamustine—in comparison to chlorambucil in frontline CLL. The alemtuzumab study randomized 297 patients, mostly eldery, to alemtuzumab or chlorambucil.[4] Alemtuzumab was associated with superior ORR, CR, and PFS outcomes, with an ORR of 83%, CR of 24%, and median PFS of 23 months, versus 55%, 2%, and 9 months for chlorambucil, respectively. Alemtuzumab was also effective in patients who had somewhat bulky lymphadenopathy, which has not been seen in the past with this agent; it also induced good responses in patients older than 65 years and in those with unfavorable cytogenetics such as 17p or 11q deletion. On the basis of these data, FDA approved alemtuzumab for first-line treatment of CLL.

**Table 2.** Bendamustine vs Chlorambucil in Front-line CLL

| | Bendamustine n=153 | Chlorambucil n=148 |
|---|---|---|
| **Median Age (range)** | **63 (46–77)** | **66 (38–78)** |
| % CR | 27 | 3 |
| % PR | 25 | 26 |
| % nPR | 10 | 3 |
| % ORR | 62 | 33 |

Adapted from Knauf et al. *Blood*. 2007;110:Abstract 2043.

Bendamustine is a purine analog and alkylating agent which has shown activity in CLL and several types of non-hodgkin lymphoma (NHL). A recent phase III randomized study compared bedamustine to chlorambucil in 305 patients (median age, 64 years).[5] Patients on the bendamustine arm were significantly more likely to achieve CR (Table 2), and median PFS and duration of remission were also significantly longer for bendamustine-treated patients. Median PFS with bendamustine was 21.7 months versus 9.3 months with chlorambucil ($P$<.0001), and median duration of remission was 18.9 versus 6.1 months, respectively ($P$<.0001). Bendamustine toxicities were manageable and the drug was generally well tolerated.

Several new studies are exploring the use of lenalidomide, the immunomodulator and thalidomide derivative, in CLL. This agent has shown success in the treatment of multiple myeloma and MDS, and is currently being tested alone and in combination with rituximab in CLL. Results from these studies are expected within the next 2 years.

## Molecular Markers in CLL

Four markers have emerged as important new indicators that can aid and augment other previously recognized clinical prognostic criteria. These are: ZAP-70, CD38, mutations in the immunoglobulin heavy-chain variable

region ($IgV_H$), and chromosomal abnormalities identified through fluorescent in-situ hybridization (FISH). All are associated with increased risk of progression and decreased survival.[6-10] In a seminal *New England Journal of Medicine* paper, 5 cytogenetic categories were defined in a statistical model: 17p-deletion, 11q-deletion, 12q-trisomy, normal karyotype, and 13q-deletion.[10] Patients in the 17p- and 11q-deletion groups had the shortest median survival times at 32 months and 79 months, respectively, compared with 114, 111, and 133 months for patients with 12q-trisomy, normal karyotype, and 13q-deletion, respectively. Patients with the 17p- and 11q-deletion had more advanced disease than those in the other groups, which is consistent with what is seen in the clinic, where the 17p-deletion is considered to be an abnormality of clonal evolution, typically occurring in patients who have had prolonged disease that has been previously treated.

The clinical utility of these prognostic markers remains an area of active debate. When all 4 markers are in concordance, indicating either bad or good prognosis, it is reasonable to use them to inform treatment choices. When they are not, however, it is unclear which indicators have the most clinical significance. The Cancer and Leukemia Group B (CALGB) has recently initiated several risk-adapted protocols in which patients are assigned treatment based on prognostic indicators. The results of these studies will be important in providing a framework that clinicians can use to tailor the optimal treatment regimen for their CLL patients. In the absence of this data, however, the most important tool for oncologists to determine the appropriate course of action for their patients is their own clinical judgment.

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# The Emerging Role of Novel Therapies for the Treatment of Relapsed Myeloma in the Elderly

Bart Barlogie, MD, PhD

Like many other hematologic malignancies, multiple myeloma disproportionately affects the elderly. Age over 65 years has been shown to be an adverse prognostic factor for survival in 2 large studies, one conducted by the International Myeloma Working Group and another conducted in Arkansas.[1]

The age-related difference in overall survival can be traced to differences at both a tumor and whole-cell level and the entire host, who is likely to develop substantial morbidities and comorbidities with age.

## Outcomes of Elderly Patients in the Total Therapy Programs

In the total therapy programs for newly diagnosed multiple myeloma patients, there is some difference in overall survival by age. This difference is most pronounced for total therapy 1, which includes remission induction with VAD (vincristine, doxorubicin, dexamethasone), high-dose cyclophosphamide with peripheral blood stem cell collection and EDAP (etoposide, dexamethasone, cytarabine

and cisplatin), a tandem transplant with melphalan, and interferon maintenance. With this regimen, median overall survival after start of therapy was significantly shorter for patients 65 years or older (*P*=.004). This difference remains but was not as pronounced for total therapy 2, which includes thalidomide and intensified induction and consolidation regimens (*P*=.007). Importantly, the treatment-related mortality with total therapy 2 did not show a marked difference between patients under and over the age of 65 years. The age-related difference in survival disappears with total therapy 3, which added bortezomib to the induction and the first-year maintenance regimen.

## Clinical and Molecular Characteritics of Elderly Patients in the Total Therapy Programs

An analysis of over 1,300 patients treated with the total therapies revealed that patients 65 years of age and older were more likely to have advanced disease (stage 3 by the International Staging System), higher levels of beta-2-microglobulin, a higher frequency of cytogenetic abnormalities, and elevated LDH at baseline. Patients over the age of 65 have also been shown to have a higher frequency of MDS-associated cytogenetic abnormalities as a secondary malignancy following treatment for their multiple myeloma.[2] However, when overall survival, event-free survival, and duration of CR were analyzed in a multivariate analysis of almost 2,700 multiple myeloma patients approximately a year after starting therapy, age did not emerge as a prognostic factor.

Gene expression profiling studies were performed on total therapy 2 and 3 patients who were at low and high risk for progression.[3,4] Interestingly, there was no difference in outcome by age (<65 years vs ≥65 years) within the expression profile groups. P53 status also appeared to supersede age as a prognostic indicator. My group recently tried to determine molecular fingerprints for multiple myeloma patients based on age. We determined the gene expression profiles of CD138-purified plasma cells from 50 patients under the age of 41, and 50 patients over the age of 70. Interestingly, 2 clusters emerged in this analysis: an "old" and "new" cluster. In the old cluster, osteoblast genes were underexpressed, whereas adipocyte genes were hyperactivated. Therefore, there seems to be a switch from an osteoblast-like phenotype to an adipocyte phenotype in multiple myeloma patients over the age of 70.

Older age is associated with poor outcome in univariate analyses of multiple myeloma patients. However, when considered in multivariate models which include factors such as metaphase hypergenetic abnormalities and gene array data, the impact of age on prognosis becomes less significant. Although there is an association between age and several traditional prognostic factors for myeloma such as beta 2-microglobulin and albumin, age does not appear to be related to gene array-defined molecular risk designation or P53 deletion status. However, when age extremes were investigated (patient age <41 years vs >70 years), there was an activation of adipocyte at the expense of osteoblast genes in the "old" myeloma cluster.

In the future we hope to validate the current observations that there are age-related plasma cell and stromal cell differences in multiple myeloma patients. We are anxious to identify crucial genes and signaling pathways that may point to age-linked differences in the pathogenesis of myeloma in the young, who may be more likely to develop de novo myeloma compared with older patients who may be more likely to have monoclonal gammopathy of undetermined significance that develops into myeloma. It is also possible that there may be a differential interaction between myeloma cells and the microenvironment as a function of age. More studies are needed to establish the clinical significance of molecular fingerprinting in predicting outcome and response to therapy in multiple myeloma patients.

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# Therapeutic Challenges for the Older Patient With Follicular Lymphoma

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The natural history of follicular lymphoma has improved in recent years. Data from the Southwest Oncology Group showed that, with the introduction of radioimmunotherapeutics and monoclonal antibodies like rituximab, we seem to finally be prolonging the survival rates of these patients.[1] Follicular lymphoma patients can be distinguished by the Follicular Lymphoma International Prognostic Index (FLIPI), which groups patients into risk categories based on 5 prognostic factors: age (>60 years vs ≤60 years), Ann Arbor stage (III–IV vs I–II), hemoglobin level (<120 g/L vs ≥120 g/L), number of nodal areas (>4 vs ≤4), and serum LDH level (above normal vs normal or below).[2] Moreover, 3 risk groups are defined: low risk (0–1 adverse factor), intermediate risk (2 factors), and poor risk (≥3 adverse factors). FLIPI risk group predicts overall survival, with poor risk patients having the lowest survival probability over time. Age, however, remains an independent risk factor in follicular lymphoma. Patients 60 years of age or older have lower survival probabilities within FLIPI risk categories.

The best approach for managing older patients with follicular lymphoma remains a topic of intense investigation. Watching and waiting is a perfectly acceptable approach. Initial treatment with a single alkylating agent like cyclophosphamide is also a tactic which can be used in some patients. Anti-CD20 monoclonal antibody rituximab in combination with cyclophosphamide-based chemotherapy regimens were the first to show prolonged survival in follicular lymphoma.[3-7] Rituximab as a single agent has also been evaluated in this population. In a study of 36 patients with newly diagnosed, advanced-stage, follicular grade 1 NHL, treatment with rituximab alone resulted in an ORR of 72%, with 36% CRs.[8] However, the median time to progression was only 2.2 years, making this approach acceptable only for follicular lymphoma patients who cannot tolerate more aggressive regimens.

There are a number of promising new agents currently being evaluated for the treatment of follicular lymphoma. These include new monoclonal antibody-based therapies, less toxic chemotherapy agents, immunomodulatory drugs, and agents which induce apoptosis.

## Novel Monocloncal Antibodies for the Treatment of Follicular Lymphoma

The success of rituximab has spawned an entire class of anti-CD20 monoclonal antibodies. The most extensively studied of these is ofatumumab, which binds to a different epitope on CD20 than does rituximab. In a phase I/II dose escalation study, ofatumumab (300–1,000 mg/week) had an ORR of 43% in 40 relapsed or refractory follicular lymphoma patients, the majority of whom (64%) had been exposed to rituximab.[9] The median duration of response to ofatumumab was approximately 2.5 years. An ongoing study is investigating ofatumumab in rituximab-refractory patients.

Another novel antibody under investigation in follicular lymphoma includes the anti-CD80 monoclonal antibody galiximab. CD80 is another important transmembrane glycoprotein which is involved in the activation and regulation of T cells and is transiently expressed on activated B cells and antigen-presenting cells. After promising results from a phase I/II trial,[10] galiximab was tested in combination with rituximab in relapsed follicular lymphoma patients.[11] The ORR was 66% with 33% CR.

At the 2008 ASH meeting, Czuczman and colleagues, myself included, presented results from the CALGB 50402 trial which showed that galiximab plus rituximab immunotherapy was well tolerated in previously untreated follicular lymphoma patients.[12] Of the 61 evaluable patients included in the study, only 13% had adverse events (grade 3). ORR was 70% (95% confidence interval [CI], 57–81.5%) and included 44% CR/CRu and 26% PR. Of particular interest was the association of FLIPI scores to ORR and CR rates. Patients who were FLIPI score 0–1 had ORR of 92% (CR 75%); those who were FLIPI score 2 had ORR of 80% (CR 48%); those who were FLIPI score 3–5 had ORR 55% (CR 27%). Although the FLIPI was originally developed in patients receiving chemotherapy alone, these data suggested that it is applicable and predictive of response to upfront immunotherapy. It was concluded that this regimen is promising for the treatment of untreated

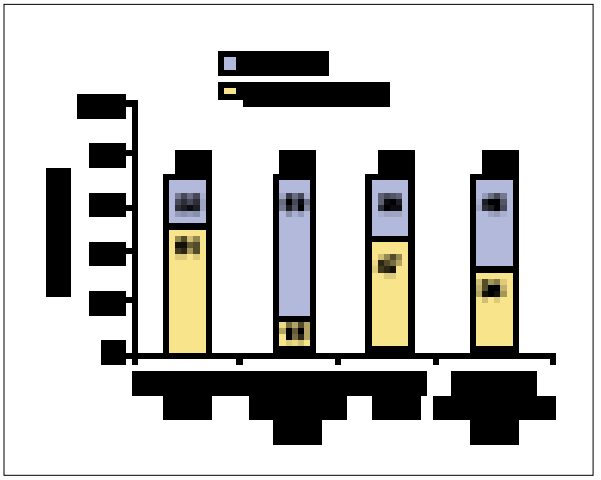

**Figure 3.** Overview of Y-90 Ibritumomab tiuxetan experience in relapsed/refractory B-cell non-Hodgkin lymphoma.

CR=complete response; CRu=complete response unconfirmed; PR=partial response.

**Table 3.** Bendamustine Plus Rituximab Versus R-CHOP Results

| | Bendamustine Plus Rituximab (n=166) | R-CHOP (n=149) |
|---|---|---|
| ORR | 93% | 93% |
| CR | 47% | 42% |
| SD | 3% | 4% |
| Primary refractory | 4% | 3% |
| PD/relapse | n=33 | n=43 |
| Deaths | n=13 | n=12 |

*315 patients evaluable for first interim analysis; median observation period 18 months.

CR=complete response; ORR=overall response rate; PD=progressive disease; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; SD=stable disease.

follicular lymphoma patients with low- and intermediate-risk FLIPI status.

The anti-CD22 monoclonal antibody epratuzumab has also shown activity in follicular lymphoma. When given to patients with postchemotherapy, relapsed/refractory, indolent NHL in combination with rituximab, a 54% ORR with a 24% CR was observed.[13] The median response duration was 13.4 months in follicular lymphoma patients and 29.1 months for the 10 patients who had a complete response; 4 patients had remissions that lasted for more than 4 years.

Another promising approach for the treatment of follicular lymphoma is radio-immunotherapy. A typical monoclonal antibody is thought to kill only the cells to which it binds. Radio-immunotherapy can potentially kill not only the cells that bind to the antibody but also neighboring cells. Response rates for the 2 available radio-immunotherapeutics—Y-90 ibritumomab tiuxetan and I-131 tositumomab—range at approximately 65–80% across trials (Figure 3).[14-18] Many of these responses occurred in patients who were refractory to prior chemotherapy, and the responses were durable.

## Bendamustine and Novel Approaches

Bendamustine is a chemotherapy drug developed in East Germany that has been in use for more than 40 years. It acts as both a DNA-alkylating agent and antimetabolite and is not cross-resistant with other alkylating agents. Bendamustine is approved in Europe for NHL, CLL, myeloma, and breast cancer; in the United States, it is approved for follicular lymphoma and CLL. In 5 single-agent trials, bendamustine showed activity in relapsed/refractory NHL, including in patients refractory to rituximab and those refractory to other alkylating agents.[19-23] Grade 3 or 4 hematologic toxicities included neutropenia (54%), thrombocytopenia (25%), and anemia (12%).[22] The most frequent nonhematologic adverse events included nausea and vomiting, fatigue, constipation, anorexia, fever, cough, and diarrhea.[22]

After the bendamustine plus rituximab combination therapy induced a median PFS of nearly 2 years and CR in 60% of patients (ORR 90%),[24] this regimen became the bar against which other regimens are evaluated. In the first results of a randomized comparison of bendamustine plus rituximab versus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), response rates were nearly identical between arms, as were PFS and overall survival outcomes (Table 3).[25] Approximately two-thirds of these patients were 60 years or older. PFS did not differ by patient age. The bendamustine-rituximab arm had a superior safety profile with no associated alopecia (vs 94% in the R-CHOP arm). The bendamustine-rituximab arm also had less grade 3/4 leucocytopenia (16% vs 41% for R-CHOP) and less infectious complications (23% vs 41% for R-CHOP). Thus, bendamustine-rituximab is a viable treatment option for older patients.

Other agents currently under investigation in follicular lymphoma include lenalidomide and a number of novel pro-apoptotic drugs. These and other new therapies appear to have antilymphoma activity alone and in

combination regimens, and are well tolerated by older patients with follicular lymphoma. However, in order to verify the safety and efficacy of these drugs in elderly follicular lymphoma patients, it will be critical to accrue more older persons to clinical research studies.

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# Unique Considerations in the Treatment of Aggressive Non-Hodgkin Lymphoma

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In general, elderly patients with aggressive lymphoma have less favorable outcomes than younger patients. It is difficult to determine which factors contribute to the poor prognosis of older patients, namely whether inferior outcomes are attributable to the comorbidities or poor performance status common in this population, or whether poor prognosis is related to the fact that older patients are less likely to receive intensive chemotherapy. The first task for a physician seeing an elderly patient with aggressive lymphoma is to determine whether there is really a contraindication to treating this patient with the CHOP regimen, since we know from experience and the literature that patients treated with CHOP have better survival outcomes. Standard treatment for aggressive NHL is R-CHOP. For patients who relapse, the treatment of choice, as recommended by the NCCN, is high-dose therapy with autologous stem cell rescue.[1] Unfortunately, however, these approaches are too toxic for many older patients.

## Tools for Assessing Treatment Choices in Older Patients

Accurately defining subsets of older patients who can tolerate more intensive therapy remains a primary objective in the lymphoma field. Patients unfit for intensive regimens have largely been excluded from clinical trials thus far, but efforts are underway to learn more about this patient population. Elderly patients with cancer are frequently not treated optimally, often due to the perception by the treating physician that they are too fragile to withstand standard treatment approaches.

A tool called the comprehensive geriatric assessment (CGA) was developed to try to address this issue. The CGA classifies older patients based on a number of different criteria including age, performance status, mental status, social situation, and comorbidities.[2-5] The assessment, which takes approximately 20 minutes to complete, can feasibly be administered in an inpatient or outpatient setting.[2-6] In a prospective study of 200 elderly patients, physicians were asked to classify their patients into 3 groups: fit, compromised, or frail[6] (Table 4). In the study, physicians categorized 64.3% of their patients as fit, 32.4% as vulnerable, and 3.2% as frail. They then administered the CGA, which classified more patients as unfit for chemotherapy then did the physicians' assessments. Future trials are needed to determine whether results of the CGA correlate with disease- and treatment-related endpoints.

## CHOP versus CNOP in Elderly Patients

Mitoxantrone has antilymphoma activity with potentially less cardiotoxicity than doxorubicin, an attribute which makes mitoxantrone particularly appealing for elderly patients. A number of studies have investigated the relative efficacy of CHOP versus CNOP (cyclophosphamide, mitoxantrone, vincristine and prednisone). In a meta-analysis of 9 randomized studies comparing CHOP and

**Table 4.** Design of Trials for Elderly Patients With Lymphoma: Gut Feeling vs Assessment-based

| Group 1 "Fit patient" | Group 2 'Compromised patient' | Group 3 'Frail patient' |
|---|---|---|
| Organ function | Organ function | Organ function |
| Functional status | Functional status | Functional status |
| Life expectation | Life expectation | Life expectation |
| Comorbidities | Comorbidities | Comorbidities |
| Risk of toxicity | Risk of toxicity | Risk of toxicity |
| **'Go-go'** | **Slow-go'** | **'No go'** |
| Treatment like younger patients | Special treatment protocols | Supportive care/ low-dose therapy |
| Classical protocols R-CHOP as control | New protocols | Palliative care/ supportive care |

CNOP in previously untreated patients with aggressive NHL, CNOP was significantly inferior to CHOP with regard to CR rate.[7] There was also a trend toward decreased overall survival with CNOP. The 2 regimens appeared equally myelosuppressive, and there was no evidence of increased incidence of symptomatic congestive heart disease with CHOP. However, gastrointestinal toxicities and alopecia were more common in patients treated with CHOP. This meta-analysis demonstrated that a regimen which includes CHOP remains the gold-standard for aggressive NHL treatment in those who can tolerate it.

## The Role of G-CSF in the Treatment of Elderly Patients

Supportive care with granulocyte colony-stimulating factor (G-CSF) may allow more patients to tolerate CHOP. In a randomized study designed to evaluate whether administration of G-CSF with CHOP or CNOP improves outcomes in elderly patients, 455 previously untreated patients with aggressive NHL were randomized to CHOP or CNOP with or without G-CSF.[8] No benefit of G-CSF was observed in terms of CR rate, time to treatment failure, or overall survival, but CHOP was superior to CNOP in all of these endpoints. The CR rates in the CHOP with or without G-CSF and CNOP with or without G-CSF groups were 60% and 43%, respectively ($P$<.001). Although G-CSF did not appear to significantly affect outcomes in this study of elderly patients, there was a trend toward improved survival for patients treated with CHOP plus G-CSF, and the cumulative proportion of patients receiving 90% or more of allocated chemotherapy was higher in patients receiving G-CSF ($P$<.05). These patients also had decreased incidence of severe granulocytopenia and infections.

Furthermore, a systematic review of 11 studies of more than 1,400 lymphoma patients was performed to investigate the potential impact of G-CSF prophylaxis in lymphoma therapy.[9] This analysis showed that G-CSF reduces the risk of neutropenia, febrile neutropenia, and infection in lymphoma patients. However, these improvements did not translate into better tumor control or prolonged overall survival. Another newer meta-analysis of almost 3,500 patients demonstrated that G-CSF prophylaxis was associated with reduced risk of febrile neutropenia (relative risk [RR] = 0.54; $P$<.001), infection-related mortality (RR=.55; $P$=.02), and early mortality (all-cause mortality during chemotherapy period; RR=.60; $P$=.002).[10] Average relative dose intensity was significantly higher in patients who received G-CSF ($P$<.001). There was insufficient data in this analyis, however, to assess the impact of G-CSF on disease-free and overall survival. Thus, although the overall utility of G-CSF prophylaxis in lymphoma patients is uncertain, this approach may have a favorable impact on infection-related and early mortality during therapy. G-CSF also appears to enable chemotherapy dose intensity, which has been shown to be very important in the treatment of lymphomas.

## Dose-intense CHOP in the Elderly

A landmark study in 689 patients ages 61–75 years demonstrated that biweekly CHOP (CHOP-14) is more effective than standard CHOP administered every 3 weeks (CHOP-21).[11] CHOP-14 was associated with higher rates of CR and a relative risk reduction of 0.66 ($P$=.003) for event-free and 0.58 ($P$<.001) for overall survival compared with CHOP-21. Importantly, the toxicities of CHOP-14 and CHOP-21 were similar. After R-CHOP became the standard of care for lymphoma, a follow-up trial by the same group investigated CHOP-14 with or without rituximab in patients aged 61–80 years.[12] Six cycles of R-CHOP-14 significantly improved event-free, progression-free, and overall survival compared with 6 cycles of CHOP-14 treatment, and now it is considered the preferred treatment for elderly patients in Germany. An ongoing study in France is also investigating R-CHOP-21 versus R-CHOP-14. The results of this study will aid us in the decision as to whether R-CHOP-14 should become the new standard of care for elderly patients with aggressive lymphoma. Other new approaches in this population include lenalidomide and bendamustine plus rituximab, a combination which is currently being evaluated in elderly lymphoma patients in Germany.

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