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Multiple myeloma: the death of VAD as initial therapy

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least one other pathogenic event is necessary for malignant transformation. Gene profiling data have not identified obvious candidates, though several recent published works suggest that Notch signaling is involved in the interaction between neoplastic plasma cells and their bone marrow microenvironment.³⁻⁵ More specifically, the Notch ligand JAG2 was found overexpressed in MGUS as a consequence of hypomethylation of the JAG2 promoter.³ It will be interesting to investigate the role of Notch signaling in the different TC groups defined by Bergsagel and colleagues. Another important finding of their study is that TC groups have different clinical behaviors in spite of the early occurrence of these pathogenic events in the course of the disease. This might suggest that pathogenic events that define these TC groups contribute not only to the early stage of the disease but also to further progression, providing clues for new thera-

peutic targets. Further validation of the gene profiles defined by the TC groups on other large independent cohorts of patients will be necessary to explore the questions raised by this study. ■

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of vincristine and doxorubicin in the VAD regimen, 2 drugs with negligible single-agent activity in myeloma. Was VAD merely a glorified and more toxic version of dexamethasone? Many thought so. Thus when thalidomide showed promising activity in relapsed myeloma, it was quickly combined with dexamethasone in an attempt to develop an oral alternative to the cumbersome VAD regimen. Three phase-2 trials established that the combination of thalidomide and dexamethasone (Thal-Dex) can achieve similar or better response rates compared with VAD as initial therapy for myeloma.⁴ As a result, the use of VAD as initial therapy has declined substantially.

In this issue of *Blood*, Cavo and colleagues appear to have placed the final nail in the coffin for VAD. In a matched case-control study of 200 patients, they show a significantly higher response rate with oral Thal-Dex therapy compared with intravenous VAD; 76% versus 52%, respectively. This difference in response rate is almost identical to the difference in response rate between Thal-Dex and dexamethasone alone observed in a recent randomized trial,⁵ confirming earlier suggestions that most of VAD's efficacy was due to dexamethasone. But Thal-Dex is not without issues either; deep vein thrombosis occurs in over 15% of patients, necessitating prophylactic anticoagulation.

Are we prematurely writing the obituary for VAD? I think not. Given the neurotoxicity of vincristine and its questionable activity in myeloma, it would be inappropriate to subject patients to such toxicity up front, thus potentially limiting the future use of thalidomide and bortezomib, both of which also have neurotoxic potential. Similarly, there is little reason to subject patients to the cumulative cardiotoxicity of doxorubicin when other alternatives are available. The paper by Cavo and colleagues adds more substance to this reasoning by demonstrating that VAD is simply less effective than Thal-Dex. As a testament to this, none of the 4 large randomized trials in newly diagnosed myeloma currently ongoing in the United States use VAD as the initial regimen. In fact, the fight is now on for the successor to Thal-Dex, with lenalidomide plus dexamethasone (Rev-Dex) and several bortezomib-based regimens vying to prevail.

Yes, it is time to finally say goodbye to VAD, at least as initial therapy for myeloma. ■

CLINICAL OBSERVATIONS

Comment on Cavo et al, page 35

Multiple myeloma: the death of VAD as initial therapy

S. Vincent Rajkumar MAYO CLINIC

In a matched case-control study of 200 patients, Cavo and colleagues show that thalidomide plus dexamethasone (Thal-Dex) yields significantly higher response rates compared with VAD as pretransplant induction therapy for multiple myeloma.

In recent years, the treatment of myeloma has undergone dramatic changes. After some 4 decades of mainly alkylator and corticosteroid-based therapy, we now have something to talk about in the form of new, active agents.¹ This includes thalidomide, an old drug with a notorious past reborn as an anti-neoplastic agent; bortezomib, a novel proteasome inhibitor; and lenalidomide (CC-5013), a potentially safer and more effective analogue of thalidomide. These discoveries have been associated with a better understanding of the bone marrow microenvironment, and assisted by a good dose of serendipity. The task at hand is to determine the best way of incorporating these active agents into the overall therapeutic strategy for myeloma.

Over the years, the paucity of effective drugs led to a dependence on autologous stem cell transplantation as the mainstay of therapy

for myeloma patients considered eligible for the procedure. Since its introduction in the 1980s,² the vincristine-doxorubicin (Adriamycin)-dexamethasone (VAD) regimen quickly became one of the most commonly used treatments for myeloma in preparation for stem cell transplantation. Patients with newly diagnosed myeloma deemed as candidates for a transplant would receive VAD for 4 to 6 cycles and then proceed to transplantation. VAD stood the test of time, and became the standard induction regimen for myeloma in major randomized trials. All this changed with the arrival of thalidomide.³

Despite its efficacy, VAD was plagued by the need for a central venous line and continuous intravenous infusion for 4 days every 4 to 5 weeks. This meant an increased risk of catheter-related sepsis and thrombosis. There were also substantial questions about the value

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CLINICAL OBSERVATIONS

Comment on Amadori et al, page 27

Divide and conquer: stomping leukemia cells by stimulating them to grow

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Treatment failure in older adults with AML is due to leukemia cell drug resistance as well as death due to infection. The EORTC and GIMEMA groups addressed these problems in a randomized trial using growth factors both during and after induction chemotherapy.

Combinations of pharmacokinetic, pharmacodynamic, cellular pharmacologic, cytokinetic, and other factors contribute to treatment failure in patients with acute myeloid leukemia (AML). The problem is particularly critical in the large group of older patients with AML in whom complete remission rates are about 50%, with long-term disease-free survival in less than 10% of patients entered on clinical trials. These results have not improved in the past 15+ years and it is likely that results in patients entered on trials are superior to the outcome in the larger universe of older patients with AML, given the selection criteria of performance status and adequate organ function imposed by such trials.

Given the ability to recruit large numbers of patients with hematologic malignancies in Europe (in striking contrast to what is now feasible in the United States), the large study from the European Organisation for Research and Treatment of Cancer (EORTC) and Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) groups reported in this issue of *Blood* employed an ambitious 2x2 factorial randomization, simultaneously addressing the supportive care problem of prolonged neutropenia as well as the more interesting question of recruitment of cytokinetically quiescent leukemia cells by simultaneous administration of growth factors with the chemotherapy. There is substantial in

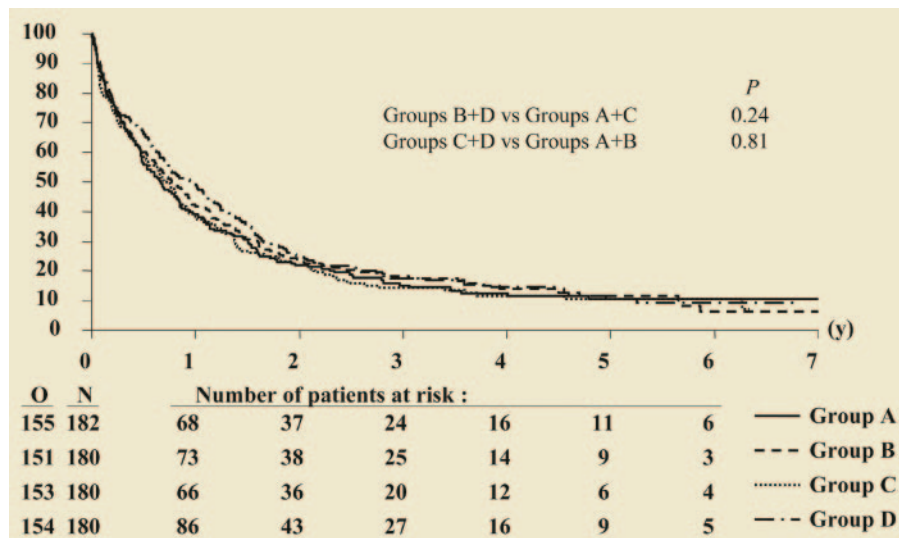
vitro data to support this “priming” approach, which is designed to coax the small but critical subpopulation of leukemia stem cells into cell cycle and then blow them to kingdom come.

As with other previously published randomized studies,¹⁻⁴ myeloid growth factors administered after the completion of chemotherapy produced modest shortening of the duration of neutropenia with no effect on complete remission (CR) rates, death during induction, CR duration, or overall survival. Although the CR rate was higher in the pooled

results from the 2 groups that received the growth factor as “priming,” this was due almost entirely to the group who received the granulocyte–colony–stimulating factor (G-CSF) both during and after the chemotherapy. There was, however, no effect on event-free survival, disease-free survival, or overall survival, and as shown in the figure, the overall results are unfortunately reminiscent of all other trials in older patients with AML.

The authors appropriately point out that most studies evaluating CSF priming also produced disappointing results, although there were some differences in study design, patient populations, and the timing and type of growth factors used. I hope that clinicians/statisticians will not succumb to the highly contagious metanalysis virus in an attempt to tease out a modest difference, because such an effort is unlikely to advance our understanding of the mechanism of treatment failure or to advance the treatment of AML.

It is unknown whether the biologic goal of leukemia cell recruitment was actually achieved and whether this might have correlated with response. Indeed, it is not really possible to determine whether the subpopulation of leukemia stem cells was perturbed by the stimulation or whether it continued to lie low, raising its head after the threat of chemotherapy had passed. AML is also a remarkably heterogeneous disease with new molecular markers such as FMS-like tyrosine kinase-3 (*FLT3*) mutations and partial duplication of the mixed-lineage leukemia gene (*MLL*) and



Duration of overall survival according to randomized treatment group. See the complete figure in the article beginning on page 27.