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Bruno Quesnel

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# inside blood

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● ● ● NEOPLASIA

Comment on Bergsagel et al, page 296

## Multiple myeloma: all roads lead to cyclin D

**Bruno Quesnel** CENTRE HOSPITALIER ET UNIVERSITAIRE (CHU) DE LILLE

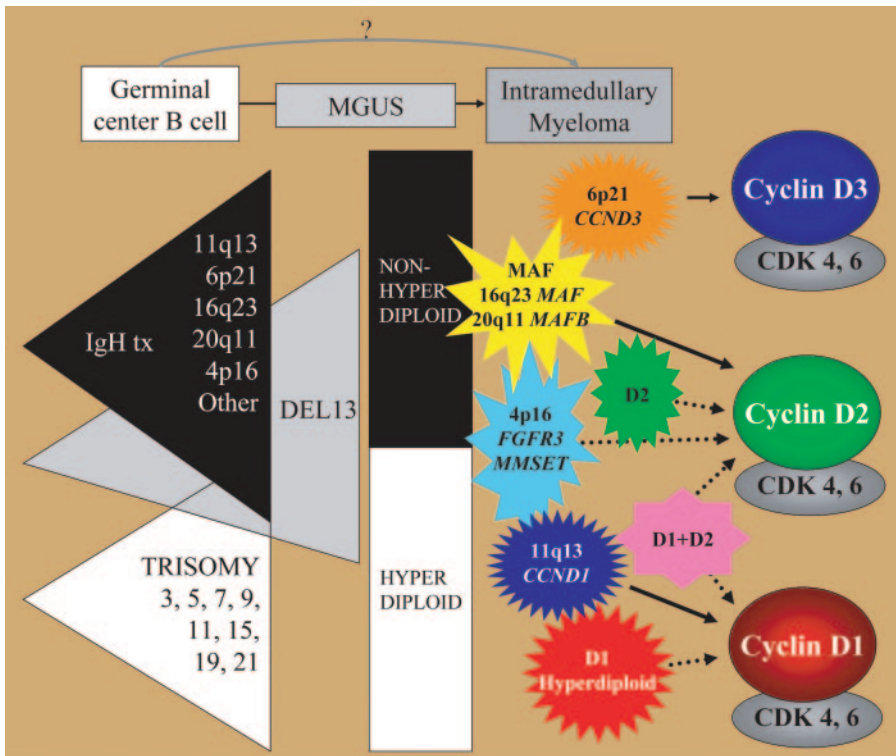
Early oncogenic events in multiple myeloma include IgH translocations and numeric chromosomal changes. Using gene expression profiling, Bergsagel and colleagues have identified several new groups that share dysregulation of cyclin D.

In contrast to acute leukemia, identification of early oncogenic events in multiple myeloma (MM) has remained somewhat elusive. Low proliferative capacities of MM cells and difficulties in isolating premalignant cells and establishing valid animal models explain this lack of a unifying model of oncogenesis in

MM. Cytogenetic studies have identified recurrent translocations involving immunoglobulin heavy-chain (IgH) and numeric changes including hyperdiploidy characterized by trisomy of nonrandom chromosomes, and deletions of chromosome 13.<sup>1</sup> Patients with MM seem to be divided into 2 subgroups:

one with hyperdiploid karyotypes with a low incidence of chromosome 13 abnormalities and one nonhyperdiploid group characterized by recurrent IgH translocations and a higher incidence of chromosome 13 deletions, suggesting that these 2 subgroups represent 2 oncogenic pathways. Mutations of *N-* and *K-RAS*, *FGFR3*, inactivation of *p53*, and dysregulation of *c-myc* seem to be involved later in the course of the disease. These findings draw a complex and only partial picture which until now has not led to precise identification of common mechanisms involved in MM ontogeny. Gene expression profiling techniques offer the opportunity to identify common oncogenic pathways and to define new subgroups in an unbiased approach.

In this issue of *Blood*, Bergsagel and colleagues have defined 8 groups of translocation/cyclin D (TC) MM, 4 based on recurrent translocations (4p16, maf, 6p21, 11q13) and 4 based solely on *CCND1* and/or *CCND2* expression (D1, D1+D2, D2, and none for absence of cyclin D overexpression). All these TC groups have distinct gene expression profiles and clinical evolution. However, they share overexpression of at least one of the 3 cyclins D (cyclins D1-D3). *CCND1* appears biallelically dysregulated in almost 40% of MM. Interestingly, monoclonal gammopathy of undetermined significance (MGUS) samples could be assigned into 5 of these TC groups. Bergsagel and colleagues propose a model of early oncogenesis in MM where the TC groups fit into the hyperdiploid or nonhyperdiploid pathway. An intriguing finding of this study and others exploring the role of cyclin D in MM is the contrast between the low proliferative index of MM cells and the apparently consistent finding of deregulated proteins involved in the G<sub>1</sub> phase. Methylation of p16INK4a and p15INK4b has been observed in MGUS and MM and this probably contributes together with cyclin D overexpression to disruption of the Rb/pathway.<sup>2</sup> However, at



Early oncogenic events in MM. See the complete figure in the article beginning on page 296.

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.<sup>3-5</sup> More specifically, the Notch ligand JAG2 was found overexpressed in MGUS as a consequence of hypomethylation of the JAG2 promoter.<sup>3</sup> 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.<sup>4</sup> 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,<sup>5</sup> 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.<sup>1</sup> 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,<sup>2</sup> 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.<sup>3</sup>

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