To the editor:

**Graft versus myeloma may overcome the unfavorable effect of deletion of chromosome 13 in multiple myeloma**

Partial or complete deletion of chromosome 13 (del13) is considered one of the most important prognostic factors for multiple myeloma (MM).1-4 The impact of del13 on the outcome of allogeneic stem cell transplantation is unknown. We describe 2 patients with unfavorable MM who benefited from a graft-versus-myeloma effect, resulting in sustained molecular remissions.5 Retrospectively a del13 was found in the diagnostic bone marrow aspirates of both patients.

The first patient progressed from monoclonal gammopathy of undetermined significance (MGUS; diagnosed in 1982) to MM (1991, IgAκ, stage IIIA). She was refractory to melphalan+ predimione, and in March 1992 at age 48 she received a partial T-cell–depleted (1 × 10^8 T cells/kg) BM transplant from her HLA-identical sister after conditioning with cyclophosphamide (120 mg/kg) and total body irradiation (12 Gy). This was complicated by transient acute graft-versus-host disease (GVHD), grade I. At the time of transplantation, her BM contained 55% myeloma cells. After achieving a partial remission (PR; disappearance of M protein, 8% residual BM cells), she relapsed 8 months after transplantation. Examination of diagnostic samples and BM aspirates at that time showed 3%, and 3% residual MM cells were detected by quantitative PCR more than 3 years after transplantation.

Since May 1994 she is in complete clinical and molecular remission as demonstrated by absence of M protein, normalization of BM, and quantitative allele-specific oligonucleotide (ASO)–PCR6 (sensitivity to detect 1 tumor of 1 × 10^6 normal cells). Molecular remission was demonstrated in 8 subsequent BM aspirates.

The second patient (stage IIIA, IgGκ) presented with bone pain and diplopia. His BM showed a 99% infiltration, labeling index 3%, and β2-microglobulin level of 5 mg/mL. The liquor was infiltrated with plasmablastic cells. He achieved a PR after induction with intermediate-dose melphalan but relapsed just before allogeneic (allo)-BMT. In the liquor a persistent M protein of 1 g/L was found after treatment with methotrexate and cytarabine intrathecally. Evaluation 6 months after transplantation showed a complete clinical remission. Residual myeloma cells however could be detected by quantitative ASO-PCR until 36 months after transplantation (Figure 1). Double-color FISH was performed on thowed cytocentrifuged BM cells, which had been prepared from diagnostic samples and had been stored at −20°C. A del13 was found in 99 of 100 myeloma cells of patient 1 and in 35 of 100 myeloma cells of patient 2.

The 2 patient histories demonstrate that alloreactivity may overcome the prognostic unfavorable impact of del13 in myeloma. The first patient is in molecular remission more than 10 years after allo-BMT and 8 years after DLIs. The second patient presented with a combination of adverse prognostic factors including a high β2-microglobulin level, high labeling index, and meningeal infiltration. He received a transplant in relapse after a very short period of remission. Remarkable, quantitative PCR became negative not until 3 years after transplantation.

Our results suggest that in patients with del13 a search for an HLA-identical family or unrelated donor is justified. The promising results of nonmyeloablative allo-SCT in MM7,8 justify inclusion of patients in such protocols as soon as unfavorable factors are identified after diagnosis.

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**References**


to the editor:

Not every polymorphism close to the AUG codon can be explained by invoking context effects on initiation of translation

The −1C>T change in the annexin V gene, which reduces the risk of myocardial infarction, cannot be explained as simply as your editorial note suggests. The demonstration by Gonzalez-Conejero et al. that −1T increases the efficiency of translation might be correct (the fourth paragraph of this letter discusses some concerns about the in vitro translation assay), but if so, the effect would not be explicable by invoking the Kozak context rules. The rules predict the opposite of what was seen; that is, translation should be more efficient with C rather than T in position −1, if that position scores at all.

GCCRCCaugG (R = purine) is the optimal context for recognition of the start codon in mammals. Within this motif, some positions are more important than others. Mutagenesis experiments with laboratory constructs showed that A or G in position −3 (3 nt upstream from the AUG codon, which is numbered +1 to +3) and G in position +4 make the strongest contributions. Only in the absence of −3R and +4G do mutations in positions −1 and −2 score strongly. Inasmuch as the annexin V start site conforms to the consensus motif in positions −3 and +4, the identity of the base in position −1 would be expected to affect translation only slightly, if at all.

The context rules, initially established by studying translation in cultured cells, can be replicated using in vitro translation systems, but the experiments must be designed carefully. Reaction conditions, such as the concentration of magnesium, can profoundly affect whether recognition of the AUG codon in vitro displays the same sensitivity to context as is seen in vivo. The coupled transcription/translation system used by many investigators, including Gonzalez-Conejero et al., makes it difficult to adjust magnesium levels and to be sure that the same amount of mRNA is generated from each allele. A small change in translational efficiency is believable when the reduction in initiation from the first AUG codon is accompanied by an increase in initiation from the next AUG downstream (eg, Figure 1 in Kozak) or when an assay is used that directly monitors the initiation step. One cannot be as confident, however, about a small (1-4-fold) difference in translational efficiency based on measurement of proteins precipitable by trichloroacetic acid.

In addition to these practical complications in testing for context effects, there are theoretical limitations. Because secondary structure downstream from the AUG codon can compensate for a less than perfect context, not every mutation within the consensus motif will score.

In some human and mouse genes, a mutation or polymorphism close to the AUG codon, usually in position −3 or +4, has been shown to reduce translational efficiency, with pathological consequences. Only one previous example involves a change in position −1: in a patient with ataxia with vitamin E deficiency, a C>T mutation in the alpha-tocopherol transfer protein gene causes a 2-fold decrease in translation, measured in vivo. In addition to these pathologies linked to mutations in the consensus motif, there is a growing list of human diseases wherein translation of a critical regulatory gene is perturbed by restructuring the 5′ UTR in ways that add or remove upstream AUG codons. Thus, the scanning mechanism for initiation of translation does provide a framework for understanding how some mutations cause disease.

It is possible that the demonstrated increase in plasma levels of annexin V protein associated with the −1T allele reflects an effect on mRNA stability or splicing. If followup studies rule out these alternative explanations and confirm that the −1T allele indeed augments translation, the reason could conceivably involve an effect on mRNA secondary structure. I do not think this particular polymorphism can be explained by invoking conventional context effects on AUG codon recognition.

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References

4. Kozak M. Recognition of AUG and alternative initiator codons is augmented by G in position +4 but is not generally affected by the nucleotides in positions −5 and +6. EMBO J. 1997;16:2482-2492.
8. Kozak M. Recognition of AUG and alternative initiator codons is augmented by G in position +4 but is not generally affected by the nucleotides in positions −5 and +6. EMBO J. 1997;16:2482-2492.
10. Kozak M. Recognition of AUG and alternative initiator codons is augmented by G in position +4 but is not generally affected by the nucleotides in positions −5 and +6. EMBO J. 1997;16:2482-2492.