For many years the gold standard for patients with MM not eligible for ASCT has been the combination of melphalan and prednisone (MP) or dexamethasone-based regimens. The overall response rate was < 30% with a CR rate of < 5%, a median duration of response of 1.5 years, and a median overall survival (OS) of ~3 years. Interestingly, for this population of patients, new combination regimens incorporating novel drugs such as MP-thalidomide (MPT), MP-bortezomib (MPV), MP-lenalidomide (MPR), or lenalidomide plus dexamethasone have resulted in an unprecedented CR rate of up to 15%, 30%, 24%, and 24%, respectively. However, the impact of these CRs on event-free survival (EFS) and OS in the nontransplantation setting has not yet established.

In this issue of *Blood*, Gay et al report on the impact of response to therapy on progression-free survival (PFS) and OS in 1175 newly diagnosed patients with MM, not eligible for ASCT and enrolled in 3 multicenter trials, treated with either MP alone (332), MPT (332), MPV (235), or MPV followed by VT maintenance (254). Concerning response, CR was achieved in 17%, VGPR in 19%, and PR in 35%. According to the treatment group, CR was attained in 49%, 31%, 15%, and 5% of patients treated with MP-VT, MPV, MPT, and MP, respectively. After a median follow-up of 29 months, PFS and OS were significantly longer in patients who achieved CR versus those who attained VGPR or PR. Of interest, the PFS and OS were virtually identical in patients who achieved VGPR and PR. Finally, the achievement of CR was an independent predictor of longer PFS and OS irrespective of age, International Staging System stage, and treatment arm.

There is no doubt that, in the transplantation setting, the achievement of IFE-negative CR is a crucial step forward for long-lasting response and survival in MM. Gay et al clearly demonstrate that the achievement of IFE-negative CR in elderly patients treated with MP plus novel antimyeloma agents has also a significant impact on PFS and OS. Interestingly enough, in a recent transplantation series, the achievement of VGPR did not result in a better outcome than the achievement of PR. It has been shown that approximately one-third of CRs achieved after ASCT in younger myeloma patients last for >10 years, representing the so-called “cure fraction” or “operational cure.” Although the achievement of a PFS of 67% at 3 years in elderly patients with MM in the study of Gay et al is encouraging, it must be considered that the follow-up is still too short with few patients at risk beyond 4 years from initiation of therapy, to know whether or not operational cures can be expected with primary therapy incorporating novel agents in elderly patients. Furthermore, with the availability of novel technologies, the achievement of IFE-negative CR should no longer be the ultimate goal in the treatment of MM. In this regard, the impact of sCR should be investigated. It has been recently reported that the achievement of CR with primary therapy including novel agents results in the emergence of oligoclonal bands in up to 60% of the patients. Whether this phenomenon is because of a higher tumor reduction or a more robust immune reconstitution as well as its potential prognostic influence are unknown. Finally, sequential MRD measurements with MFC or molecular studies could be helpful in determining from what level of MRD further treatment is or not needed. Ideally, the treatment approach in elderly patients with MM should include a triple-agent induction regimen such as MPT or MPV followed by maintenance incorporating novel agents along with sequential MRD studies to establish for how long treatment is still of benefit.

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**● ● ● LYMPHOID NEOPLASIA**

Comment on Baraniskin et al, page 3140

**PCNSL: biomarker better than biopsy?**

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In this issue of *Blood*, Baraniskin and colleagues report on microRNAs (miRNAs) as a possible biomarker for the diagnosis of primary central nervous system lymphoma (PCNSL). Levels of miR-21, miR-19, and miR-92a were significantly increased in cerebrospinal fluid (CSF) samples from PCNSL patients compared with controls with inflammatory CNS disease or other neurologic disorders.

The diagnosis of PCNSL is most commonly achieved via stereotactic brain biopsy. Contemporary imaging methods (CT, MRI, PET) fail to reliably differentiate inflammatory processes, solid-tumor metastases, and primary or secondary CNSL. A misinterpretation of findings can lead to a delay in initiating therapy on the one hand, or to unnecessary...
The success of stereotactic biopsy, while not yet achieved general acceptance in clinical practice, may be the only feasible source of tumor-derived RNA for future clinical studies. The article by Baraniskin et al advances the field of diagnostic markers in CNSL. Perhaps the analysis of miRNAs in the CSF of patients with suspected PCNSL will expand the diagnostic tools at our disposal, especially in patients in whom biopsy appears too risky or when histologic findings are equivocal. However, as these data are generated from a small number of patients, it will be up to future studies to validate the diagnostic utility of miRNAs in the PCNSL patient population. Finally, there is the intriguing possibility that miRNAs derived from primary brain tumors like PCNSL may also circulate in blood, which could offer a readily accessible source of tumor-derived RNA for future study.

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**Comment on Berckmans et al, page 3172**

**Salivary microvesicles clot blood**

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The capacity of saliva to clot blood has been documented in the scriptures (Luke 16:21), folklore, and in the medical literature of the 1920s when Hunter described the ability of saliva to clot blood and proposed it as a means to attenuate bleeding from gastric ulcers.1 In 1938, Glazko and Greenberg reported that saliva contains a cell-derived, protein-based thromboplastin,2 which was later identified as tissue factor.

As with all science, answers beget more questions. In mice, removal of the salivary glands decreases wound healing.9 Is the poor wound healing the result of an absence of salivary tissue factor? Do the levels of salivary tissue factor change with aging or disease? Would strategies aimed at increasing salivary tissue factor reduce mucosal bleeding in patients with thrombocytopenia or gingivitis, or even those with gastric ulcers? These are questions for the future. Meanwhile, the work by Berckmans and colleagues provides some basis for why the wound-licking reflex may be beneficial. The clot-promoting activity of saliva may be offset by harm, including the introduction of oral bacteria into the wound.10

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PCNSL: biomarker better than biopsy?

Gerald Illerhaus and Tracy Batchelor