Research has indicated that HLC analysis can provide prognostic information when performed early in a treatment regimen, at the end of consolidation therapy (Section 18.4) or at the time of maximum response. From a study of 44 MM patients treated with carfilzomib, lenalidomide and dexamethasone, Bhutani et al. [3] reported that normalisation of the HLC ratio after 2 cycles of therapy was significantly associated with achieving a sCR (p=0.001). In a multivariate model that initially included monoclonal immunoglobulin, dFLC, normalised sFLC ratio, difference between involved and uninvolved HLC concentration (dHLC) and normalised HLC ratio; only dHLC (<2.6 g/L vs. ≥2.6 g/L) remained as an independent factor after 2 treatment cycles.

A preliminary analysis of 70 patients treated with bortezomib suggested that the HLC ratio was a more sensitive monitoring tool than the monoclonal immunoglobulin and suppression of the uninvolved HLC isotype (HLC pair suppression) was associated with poor PFS and OS.

Scheid et al. [5] studied the prognostic value of HLC measurements 6 months post-induction in 292 transplant-eligible MM patients (212 IgG, 86 IgA). Patients who achieved a HLC-CR (defined as a normal HLC ratio) had a superior OS compared to those who achieved lesser degrees of HLC response (86.5% vs. 71.4% at 60 months, p=0.039). D’Souza confirmed the prognostic value of a HLC-CR in patients who had not achieved a VGPR or better, prior to transplant.

A greater number of studies have investigated the prognostic value of HLC analysis at the time of maximal response. Ludwig et al. [1] analysed outcomes in 156 patients with IgG or IgA MM. Patients with HLC ratios that remained abnormal at maximal response (PR or better) had a significantly shorter survival than those achieving a normal HLC ratio (HR 2.8, CI 0.99 - 8.3; p=0.03) (Figure 20.11A). Similar findings were reported by Suehara et al. [7] and Abe et al. [8]. In a separate study of 65 patients at maximal response, Ludwig and colleagues [1] compared immunofixation electrophoresis (IFE), BMPC infiltration, sFLC ratio, HLC concentrations and HLC ratio, and concluded that HLC pair suppression was the most powerful predictor for OS (Figure 20.11B). Drayson et al. [9] studied the prognostic value of IgA HLC analysis at maximal response in 195 IgA MM patients treated in the UK, MRC IX myeloma trial. At maximal response, an abnormal HLC ratio was associated with shorter PFS in both the intensive (p=0.002) and non-intensive (p=0.032) treatment arms. HLC pair suppression was also associated with shorter PFS in all patients achieving a CR (p=0.061). By contrast, classical immunoparesis of either IgG or IgM was not associated with PFS (p=0.525 and p=0.964, respectively). Koulieris et al. [10] found that HLC ratio normalisation was predictive of improved PFS (p=0.046) irrespective of the treatment used. In contrast, D’Auria et al. [10] reported that normalisation of HLC ratios in myeloma patients achieving CR had no impact on PFS, but the number of patients was small (n=25).

Fouquet et al. [12] compared the reduction in HLC pair suppression with the depth of response in 107 IIMM patients following treatment with pomalidomide and dexamethasone. For patients achieving a VGPR or better, 75% had improved levels of the uninvolved HLC pair (defined as a 50% increase from the time of maximum response), compared to 31% and 13% for patients achieving a PR or SD, respectively (p=0.005). Therefore, recovery of the uninvolved HLC pair correlates with depth of response. Similar findings were reported by Harutyunyan et al. [13] and Michallet et al. [14]. Harutyunyan et al. [13] also demonstrated that MM patients with an uninvolved HLC concentration within the normal range showed a longer PFS than those with concentrations below the normal range (45 months vs. 11 months, p=0.0019). Similar results have been published by others.

Ludwig et al. [15] examined HLC pair suppression of patients at best response. They observed that HLC pair suppression of >50%
at best response correlated significantly with subsequent survival (49.0 vs 71.9 months, HR: 1.581, p=0.035). Expanding on these results, Michallet et al. \cite{17} reported that HLC pair suppression of >50% remains prognostic of PFS in patients who achieve a CR.

**Figures**

**Figure 20.11. The prognostic value of HLC analysis at maximum response.**

(A) Overall survival of MM patients achieving a partial response or better, stratified at best response according to HLC ratios. Blue line: patients with normal HLC ratio; red line: patients with abnormal HLC ratio. Reprinted by permission from Macmillan Publishers Ltd: Leukemia \cite{2}, copyright 2013. (B) Overall survival was significantly shorter in patients with HLC pair suppression than patients with no HLC-pair suppression (median 4.8 years vs. 8.5 years, respectively; p<0.02). (This research was originally published in Blood \cite{1} © the American Society of Hematology).

**References**


multiple myeloma patients in the prospective phase III GMMG-MM5 trial. Presented at ASH 2017:1784a


