Does Heparin Have An Anti-Myeloma Effect? An Analysis On Individual Data From Three Randomized Studies of GIMEMA, Nordic and Turkish Myeloma Study Groups

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Abstract

Background and aim: The anti metastatic effects of heparin have been known for many decades. Such effects are dependent on the protease activated receptor expression (PAR-1 and/or CD24) by the cancer cells. The genes controlling PARs are located on chromosome 5q13. Recurrent amplification of chromosome 5q and 5p have been shown to increase survival (Avet-Loiseau H et al 2009 and Tapper W et al 2011) in myeloma. Low molecular weight heparin (LMWH) either for prophylaxis or treatment of venous thromboembolism, is frequently used in the treatment of myeloma. With an aim to separate the effect of heparin from the response achieved following Melphalan and Prednisolone (MP) plus Thalidomide, this study was initiated.

Patients and methods: Individual data on 797 patients who were randomized to MP(n:393) or MPT(n:404) and published by the GIMEMA, Nordic, and the Turkish Myeloma Groups were analyzed using the SPSS 15.0 windows version. Except for the Nordic trial, LMWH was given as routine for the MPT patients. Patients who received anticoagulation as routine or following a thrombotic event were assigned to the LMWH group. Response equal to and more than partial response was included in the analysis. Comparisons were made using the Chi-Square or Mann Whitney U tests. Assessment of risk factors for response was done by the Backward-Stepwise Logistic Regression analysis. Survival analysis was performed using the Kaplan-Meier test.

Results: Treatment groups (MP vs MPT) were well balanced according to prognostic factors. LMWH was given as prophylaxis (n:124, n:4) or as treatment (n: 38, n:16) in the MPT and MP groups respectively. Patients who received LMWH in the MP group exerted similar characteristics to MP patients, but more patients in the MPT+LMWH group had advanced ISS (p=0.007) compared to MPT patients. Response (≥PR) was observed more frequently among the patients who received MP and LMWH than those who did not receive LMWH (38.4 % vs 70.6%, p=0.002). Similar effect was not observed in the MPT group. Within the MP and MPT groups responders had lower b2mg (3.8 vs 4.2, p=0.068) and 3.9 vs 4.5, p=0.028). Higher s-albumin (3.7 vs 3.4 , p=0.002) was associated with better response only in the MP group. When age, creatinine, b2mg, ISS, gender, and anticoagulation were introduced into the logistic regression model including all patients, LMWH (odds ratio (OR): 1.948, 95 % CI: 1.319-2.877,p=0.001) and b2mg (OR:0.966, 95 % CI: 0.939-0.998, p=0.007) were found to be independent risk factors. Logistic regression performed for MP or MPT groups revealed LMWH to be significant in the MP arm (OR: 4.168, 95 % CI: 1.288-13.492, p=0.017) but not in the MPT arm (OR:1.031, 95 % CI: 0.65-1.745, p=0.938). Within the MPT arm, creatinine (n:160) (OR:0.455, 95 % CI: 0.219-0.908,p=0.033) and advanced ISS (OR:0.766,95 % CI:0.582-1.038,p=0.065) were additional risk factors. Survival was extended when LMWH was introduced to patients who were in the MPT group (p=0.048).

Conclusion: In this study, based on individual data from three large randomized trials comparing MPT and MP, we found the addition of LMWH to be significantly associated with a better response in MP patients and improved survival in MPT patients. Although the cytogenetic and molecular profile of the patients are unknown and this is a retrospective analysis, improvement of response and survival following introduction of LMWH to the MP or MPT treatment suggests an anti-myeloma activity of LMWH.