Clinical and population-based studies in multiple myeloma and monoclonal gammopathy -with focus on infections

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av

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I. Cecilie Hveding Blimark, Ljupco Veskovski, Jan Westin, Stig Rödjer, Mats Brune, Martin Hjorth, Erik Holmberg, Per-Ola Andersson, Ulf-Henrik Mellqvist
Melphalan 100 mg/m2 with stem cell support as first relapse treatment is safe and effective for myeloma patients with long remission after autologous stem cell transplantation. *Eur J Haematol 2011:87(2):117-22.*

II. Sigurdur Y Kristinsson, Min Tang, Ruth M Pfeiffer, Magnus Björkholm, Lynn R Goldin, Cecilie Hveding Blimark, Ulf-Henrik Mellqvist, Anders Wahlin, Ingemar Turesson, Ola Landgren.
Monoclonal gammopathy of undetermined significance and risk of infections: a population-based study.
Haematologica 2012:97(6):854-8.

III. Cecilie Hveding Blimark, Erik Holmberg, Ulf-Henrik Mellqvist, Ola Landgren, Magnus Björkholm, Malin L Hultcrantz, Christian Kjellander, Ingemar Turesson and Sigurdur Y Kristinsson.
Multiple Myeloma and Infections: A Population-Based Study on 9,253 Multiple Myeloma Patients.
Haematologica 2014 Epub 24 Oct.

IV. Sigurdur Y Kristinsson, Erik Holmberg, Cecilie Hveding Blimark
Treatment for High-Risk Smouldering Myelom
N Engl J Med 2013; 369(18):1762-3

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Multiple myeloma is a haematological disorder of the bone marrow. It is preceded by the benign precursor monoclonal gammopathy of undetermined significance (MGUS). In multiple myeloma, a progression leading to expansion of malignant plasma cells occurs, causing skeletal lesions, anemia and renal insuffiency. Multiple myeloma is incurable, but the disease can be controlled with chemotherapy and other immunosuppressive drugs. It is known that both conditions have compromized immune responses, which lead to an increased risk of infections. However, there is no population-based data on the occurrence and type of infections in patients with plasma cell disorders compared to the normal population. Considering the cumulative immunodeficiency in patients with multiple myeloma, caused by multiple cytotoxic and immunomodulating therapies, there is a demand for less toxic treatments in the relapse setting, aiming to reduce morbidity and mortality in infections. Recent studies have suggested that immunomodulating treatment is beneficial even in smouldering multiple myeloma. There is a lack of population-based incidence data in smouldering multiple myeloma patients with high risk of progressing to multiple myeloma, and there is a need of identifying patients with smouldering multiple myeloma that could benefit from up-front treatment.

In **paper I** we investigated the treatment with intermediate-dose melphalan (Mel 100) and stem cell support in multiple myeloma patients relapsing after high dose melphalan and autologous transplantation (ASCT) in 66 patients. With an overall response of 62%, limited toxicity and a progression-free survival of 8.5 months, we conclude that Mel 100 is a viable therapeutic option in relapsed patients and the best efficacy was seen in patients with long-lasting response after ASCT.

In **paper II and III** we studied the risk of infections in MGUS and multiple myeloma patients compared to matched controls. Using population-based data from Sweden, in **paper II** we estimated the risk of infections among 5 326 MGUS patients compared to 20 161 matched controls. We found that patients with MGUS had a 2-fold increased increased risk (hazard ratio (HR) 2.1; 95% confidence interval (CI) 2.0-2.3($p<0.05$)) of developing any infection at 5-year follow up, and at 10-year follow up the risk was very similar (HR=2.2; 95% CI 2.0-2.3). Patients with M-protein concentration over 2.5 mg/dl had the highest risk of infections. In **paper III** we compared the risk of infections in 9 253 multiple myeloma patients to 34 931 matched controls. Overall, multiple myeloma patients had a 7-fold (HR =7.1; 95% CI 6.8-7.4) risk of developing any infection compared to matched controls. The increased risk of developing a bacterial infection was 7-fold (7.1; 6.8-7.4), and for viral infections it was 10-fold (10.0; 8.9-11.4). Multiple myeloma patients diagnosed in the more recent calendar periods had significantly higher risk of infections compared to patients diagnosed earlier ($p<0.001$). We could show, that in patients who died within the first year of diagnosis, 22 % of deaths were infection-related. Our findings provide novel insights into the mechanisms behind infections in patients with plasma cell disorders, and may have clinical implications and could give support to preventive interventions.

In **paper IV** we estimated the risk of progression to symptomatic multiple myeloma in a cohort of smouldering multiple myeloma patients with high-risk features using population-based data from the Swedish Myeloma Registry. The 2-year risk of progressing was 56% and this cohort count for 29% of all smouldering myeloma patients and should be considered for clinical early treatment trials.

Keywords: multiple myeloma, MGUS, infections

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