Secondary Immunodeficiency
– in lymphoproliferative malignancies
PROGRAM

13:30 Welcome and introduction
Grifols Nordic
Vanda Friman (Chairman)

13.45 Basic immunology and the development of the B-cell
Ola Winqvist

14.30 Multiple myeloma and infections
Cecilie Blimark

15.15 Chronic lymphocytic leukemia and infectious complications
Pertra Langerbeins

16.00 Paus

16.15 Replacement immunoglobulin treatment in the antibody deficiency, secondary to CLL and MM
Helen Chapel
Fatima Dhalla

17.15 Panel discussion
Chairman, speakers and audience

18.00 Buffé dinner

SPEAKERS
In order of appearance

Vanda Friman (Chairman)
Associate professor, Department of Infectious Diseases, Sahlgrenska University Hospital Gothenburg, Sweden

Ola Winqvist
Professor, Translational Immunology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden

Cecilie Blimark
Med Dr, PhD, Department of Internal Medicine, Hematology Section, Sahlgrenska University Hospital, Gothenburg, Sweden

Petra Langerbeins
Med Dr, German CLL Study Group, Department of Internal Medicine, University Hospital of Cologne, Germany

Helen Chapel
Professor, Clinical Immunology, University of Oxford, United Kingdom

Fatima Dhalla
Med Dr, Clinical Immunology, University of Oxford, United Kingdom
Dr Vanda Friman is Associate Professor at the Department of Infectious Diseases at Sahlgrenska University Hospital, Gothenburg, Sweden. She is senior consultant for patients with secondary Immunodeficiencies i.e. patients with hematologic disorders and organ transplant patients. Dr Friman is also in charge of the Centre for Primary Immunodeficiency at the Department of Infectious Disease.

She is a member of the Board of the Swedish Association for Primary Immunodeficiency and member of the National Expert Group for Infections in patients with secondary immunodeficiencies. She is also acting chairman of the Committee on Prevention of transmission of infections within the organ allocation organisation Scandiatransplant.
In order to understand secondary immunodeficiencies, their development and therapeutic rationales some understanding of basic immunology is necessary. In the lecture the basic understanding of innate and adaptive immune system will be recapitulated. Antigen processing and presentation and the concept of adjuvants will be discussed in order to support broader understanding of vaccination regiments. T cell immunology and tolerance and T cell help will be discussed. B cell immunology from bone marrow maturation till circulating subsets, functionality, immunoglobulins and tolerance will be brought up. The concept of T cell and T cell independent responses will be clarified. Immunological mechanisms behind biologicals including antibody dependent cellular toxicity (ADCC) and complement activation will be introduced. The purpose of the lecture is to give an overview and a recapitulation of basic immunology useful for the understanding and handling of patients with secondary immunodeficiencies.
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Cecilie Hveding Blimark, MD, PhD, is working as a senior consultant in haematology at Sahlgrenska University hospital where she leads the Multiple Myeloma team. She is employed at Regional Cancer Centre West, responsible for the Multiple Myeloma Programme in Western Sweden. She is active in the Nordic Myeloma Study Group and the Swedish Myeloma Group, and on the board of the National Multiple Myeloma Guidelines. She has acted as PI in several clinical studies Since 2011 Dr Blimark is head of the Swedish Multiple Myeloma Registry, a prospective observational study of all multiple myeloma patients in Sweden, surveilling treatment and survival of patients with plasma cell disorders.

Her main field of research include clinical and populations-based studies on multiple myeloma, with focus on infections.

Multiple myeloma and infections

Multiple myeloma is a haematological disorder of the bone marrow, causing skeletal lesions, anemia and renal insufficiency. The median age at diagnosis is 71 years. It is preceded by the benign precursor monoclonal gammopathy of undetermined significance (MGUS). Multiple myeloma is incurable, but the disease can be controlled with chemotherapy and other immunosuppressive drugs. It is known that both conditions have compromised immune responses, which lead to an increased risk of infections. The different immunosuppressive treatments add to the risk of infections in multiple myeloma. Large population-based studies have estimated the risk of infections in multiple myeloma patients to be increased 7-fold compared to the normal population and MGUS patients have an increased 3.4-fold risk of dying in infections compared to controls.

Several studies have found an increased risk of upper respiratory bacterial infections, and in Sweden, infectious diseases seen more common in myeloma patients are; bacterial pneumonia, septicemia and meningitis, and the viral infections Herpes zoster and influenza.

The multiple myeloma-related immunodeficiencies involve B-cell dysfunction, like hypogammaglobulinemia, as well as T-cell-, dendritic cell-, and NK-cell abnormalities. Secondary hypogammaglobulinemia is reported to be present in about 25-40 % of MGUS and multiple myeloma patients whereas a reduction of one or more polyclonal immunoglobulins is seen in more than 90% of patients with myeloma. Hypogammaglobulinemia is known to increase the risk of life threatening infections especially caused by encapsulated bacteria.

The recent advances in treatment, have prolonged life in remission and in relapse phase in multiple myeloma. However, managing multiple relapses and salvage therapies can lead to a cumulative immunosuppression and a higher risk of infections.

In current guidelines for infection prophylaxis in plasma cell disorders multiple myeloma patients with 3 or more febrile infections per year and a coexisting hypogammaglobulinemia are recommended intravenous gammaglobulins (IVIG) as empirical treatment.
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Petra Langerbeins
(Cologne, Germany)

Dr. Petra Langerbeins studied medicine at the University of Cologne from 2001 to 2008. In 2005 she started her scientific work on prognostic markers of chronic lymphocytic leukemia (CLL) at the German CLL Study Group, earning a medical degree in 2009. In 2008 she began her medical training at the Department I at the University Hospital of Cologne under the direction of Professor Michael Hallek. Her clinical activities include hematological and oncological patient care as well as the general CLL second opinion consultation. She also works as a study physician at the German CLL Study Group, initially as a coordinating physician, then as a Principal Investigator of randomized Phase III trials. Her clinical research is focused on early CLL stages, prognostic CLL-markers, and novel drugs.

Chronic lymphocytic leukemia and infectious complications

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the western countries with an age-adjusted incidence of 4.1/100,000 inhabitants. Despite tremendous advances in treatment and survival, infectious complications are the main cause of morbidity and mortality with an infection-related mortality ranging from 30 to 50%. The pathogenesis of infections is multifactorial and complex. The risk of infections increases with advanced stage of disease. Several pathways of the immune system are impaired by the disease itself including defects in cell-mediated immunity, complement defects, neutrophil or phagocytic dysfunction, and hypogammaglobulinemia. Immunosuppression is further increased with administration of CLL-specific treatment, mostly chemoimmunotherapy. The spectrum of infections is various and includes bacterial, viral, and fungal infections. The most common involved site is the respiratory tract, followed by the urinary tract, and blood-stream. Strategies for prevention of infections include immunoglobulin therapy, vaccination, antimicrobial prophylaxis, and administration of growth factors. In early stage, treatment-naïve CLL patients the risk of infections is mainly related to hypogammaglobulinemia. Those patients should be considered for periodic immunoglobulin therapy. Heavily pretreated patients appear to have the greatest risk for serious infections, and should be considered for appropriate antimicrobial prophylaxis. Novel targeted drugs with high efficacy seem to have a less toxic profile than the classic chemoimmunotherapy and the risk of infections might be reduced with these hardly immunosuppressive agents.
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Helen Chapel
(Oxford, United Kingdom)

Professor Helen Chapel is a Professor of Clinical Immunology at the University of Oxford. She has been clinical immunology consultant at the Oxford Radcliffe Hospitals since 1978 and has a particular interest in primary immune deficiencies and their treatment. She has published on the several clinical phenotypes of common variable immunodeficiency disorders, as well as patient outcomes of immunoglobulin therapies for replacement and immunomodulation. She started the ESID summer school in 1999 and continued to serve on the faculty till 2015, as well as to teach at other PID schools elsewhere. She has been a member of the IUIS PID committee and is Medical Vice-president of IPOPI.

Fatima Dhalla
(Oxford, United Kingdom)

Dr Fatima Dhalla graduated from Imperial College in 2008 having studied medicine and Immunobiology and Pathology as an undergraduate. After her acute medical training she started her specialty training in Clinical Immunology in Oxford, where she held a position as an Academic Clinical Fellow allowing her to pursue basic and clinical research alongside her training. She has recently begun a PhD in Oxford, funded by the Wellcome Trust, during which she will be studying the epigenetic regulation of self antigen expression by thymic epithelial cells in the process of central T cell tolerance induction. Her clinical and academic interests include immune deficiencies, both primary and secondary, as well as thymic developmental biology.
Replacement immunoglobulin treatment in the antibody deficiency, secondary to chronic lymphocytic leukaemia and multiple myeloma

Immunoglobulin (Ig) therapy for CLL or MM patients with “infections” has been approved in Europe for over 3 decades, following RCTs in both diseases, but there was no more precise indication for the selection of CLL patients who were likely to benefit. Investigation in the 1990s showed that some untreated CLL patients had low serum immunoglobulin levels and this was then used in some centres as a surrogate for failure of antibody production to select patients for Ig therapy. MM patients had been shown to benefit from Ig therapy in plateau phase, when neutrophil counts were normal and they failed to respond to Pneumovax immunization, but there has been little published since the haematological treatments for these conditions improved.

Having considered the types of infection with the two previous speakers, we will discuss the nature of the underlying immunodeficiencies at various stages of these two diseases, the newly proposed indications and appropriate testing for antibody failure. The results of Ig therapy in various patients with secondary antibody failure due to CLL or MM in our centre will be reviewed, with illustrative cases, in order to demonstrate efficacy (or otherwise) and to consider improved criteria for the selection of patients most likely to benefit from Ig therapy.

Notes
Grifols is a global healthcare company with a 75-year legacy of improving people’s health and wellbeing through the development of life-saving plasma medicines, diagnostic systems, and hospital pharmacy products. The company is present in more than 100 countries worldwide and is headquartered in Barcelona, Spain.

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