Chronic myeloid leukemia and cancer

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt förvar i Unod T9, Hörsal D, 9 tr, Norrlands Universitetssjukhus, fredag den 24 november, kl. 13:00. Avhandlingen kommer att förvaras på svenska.

Fakultetsopponent: Professor, Bertil Lindahl, Institutionen för medicinska vetenskaper, Medicinska fakulteten, Uppsala Universitet.
Chronic myeloid leukemia (CML) is a relatively rare hematological malignancy with a constant incidence of approximately 90 new cases each year in Sweden (0.9 cases/100 000 inhabitants). The etiology is largely unknown but high doses of ionizing radiation are a known but rare risk factor. The treatment options were for a long time limited to treatment with chemotherapies, interferon's and allogeneic hematopoietic stem cell transplantation and the median survival were only about four years. Since the beginning of the 21st century a new way of treating CML have been introduced, the tyrosine kinase inhibitors (TKI), leading to a rapid decrease in leukemic cells and symptoms. Due to the TKIs, the overall 5-year survival is nowadays approximately 85 % and CML patients have time to develop other diseases, including other malignancies. The aims of this thesis was to investigate the present and future prevalence of CML and the prevalence of other malignancies prior and subsequent to the diagnosis of CML, malignancies among first-degree relatives of persons with CML. In addition, the incidence of autoimmune and chronic inflammatory diseases among patients with CML was also investigated.

Methods: From the Swedish CML register, data over nearly all Swedish CML patients from 2002 and forward were obtained for paper II-IV. For paper I the Swedish cancer register (SCR) was used to identify all Swedish CML patients since 1970 and the Swedish cause of death register to identify an eventual date of death for these patients. With a constant incidence and the relative survival rates for CML patients between 2006 and 2012 as a model, the present and future prevalence was calculated. For paper II, III and IV, data from the SCR were used to identify other malignancies than CML. For paper II information about autoimmune- and chronic inflammatory diseases were retrieved from the Swedish national patient register. For paper II and IV, five, year of birth, gender and county of residence-matched controls were randomly selected from the Swedish register of the total population. To calculate odds ratio (OR), conditional logistic regression was used. To calculate the risk of a second malignancy for paper III, Standardized incidence ratio (SIR) were used. In paper IV, first-degree relatives (FDR) i.e. parents, siblings and offsprings, for both cases and controls where retrieved from the Swedish multi-generation register where persons born later than 1932 and registered in Sweden at some time since 1961 are registered.

Results: As shown in paper I, between 1970 and 2012 the 5-year overall survival for CML patients increase remarkably from 0.18 to 0.82. The prevalence increased from 3.9 to 11.9 per 100 000 inhabitants in Sweden between 1985 and 2012. By assuming no further improvements in relative survival as compared to the survival rates between 2006 and 2012, the prevalence by 2060 is expected to increase to 22.0 per 100 000 inhabitants which corresponds to 2 587 CML patients as compared to 1 137 CML patients in 2012. In study II more than 45 000 person years of follow up were evaluated in 984 CML patients diagnosed between 2002 and 2012. With an OR of 1.47 (95 % CI 1.20–1.82) and 1.55 (95 % CI 1.21–1.98), respectively, the prevalence of prior malignancies and autoimmune diseases were significantly increased as compared to matched controls. No association between CML and chronic inflammatory diseases was shown. In 868 CML patients diagnosed between 2002 and 2011, 52 malignancies were found in the SCR, in paper III. When compared to expected rates in the background population, a significantly increased risk of second malignancies with a SIR of 1.52 (95 % CI 1.15–1.99) was shown. In paper IV, 984 CML patients were identified, although only 800 patients where analyzed, due to a birth date before 1932. Among them, 287 FDR were identified and 20 930 FDR of matched controls were included in the analysis. 611 malignancies were retrieved; no significant increase of malignancies in FDR of CML patients was shown (OR 1.06; 95 % CI: 0.96–1.16).

Conclusion: Since CML patients nowadays have a high survival rate, the calculations in this thesis shows that the prevalence of CML will almost double by 2060. CML patients have an increased risk of developing malignancies prior and subsequent to the diagnosis of CML, suggesting a hereditary or acquired predisposition to develop cancer. Since there is no familial aggregation of malignancies in CML patients, a hereditary predisposition to develop cancer is unlikely to be part of the pathogenesis of CML, leaving an acquired predisposition more likely.

Keywords
Chronic myeloid leukemia, Prevalence, Malignancies, Odds ratio, Standardized Incidence Ratio, Outcome, Autoimmune diseases, Survival