

# Epidemiology and risk factors

## 362 SECONDARY HAEMATOLOGICAL MALIGNANCIES AND PURINE ANALOGUE TREATMENT: A RETROSPECTIVE ANALYSIS OF CLADRIBINE

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Secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are well-recognized complications following chemotherapy (CT) and/or radiotherapy, mainly with alkylating containing regimens, and/or after high dose CT followed by autologous peripheral stem-cell reinfusion.

Recently, some reports (Morrison 2002, Leleu 2009, Carney 2010, Treon 2009) suggested that the use of purine analogues (mainly Fludarabine) may be associated with increased risk of secondary MDS/AML (crude rate 1.6 - 10.8%). The risk of developing MDS/AML using other purine analogues such as cladribine (2-CDA) is not well described.

We retrospectively analyzed 312 patients (pts) receiving 2-CDA as part of their treatment from 1993 until 2007 to evaluate the incidence of secondary hematological malignancies.

**Material and Methods:** 195 pts with hairy cell leukemia (HCL) received one single cycle of 2-CDA delivered subcutaneously for five or seven days at doses 0,1-0,14 mg/kg. 117 pts with indolent non Hodgkin lymphoma (Waldenström, follicular lymphoma [FL], chronic lymphocytic leukemia [CLL], small lymphocytic lymphoma [SLL]) received 4-6 cycles of 2-CDA at a dose of 0,1mg/kg daily for 5 days, alone or in combination with other alkylating agents and/or antiCD-20 monoclonal antibody (rituximab).

Pts with HCL received a maximum of 3 cycles of subcutaneous 2-CDA.

All pts with indolent malignant lymphomas received additional therapies including subsequent alkylating containing regimens and/or autologous bone marrow transplantation.

All pts with at least 3 years of follow up were considered.

**Results:** Median follow-up time was 6.2 years (range 3-16) for all pts. Due to large percent of censoring, median survival time was not reached. The crude incidence of observed secondary AML/MDS was 0.96%, including 1 AML and 2 MDS, that occurred after 2.7, 4.4 and 1.9 years in 3 pts (median age 63years) with HCL, SLL and FL respectively. Based on 1862.3 patient-years, the yearly incidence rate was 0.0016.

**Conclusion:** Our results suggest that 2-CDA could be safely delivered without increased risk of secondary MDS/AML. The relative low crude incidence of second hematological malignancies (0.96%) in our study may be related to the relative low dosage of 2-CDA delivered in patients with HCL or indolent lymphoma.

## 363 THE LYMPHOID CANCER FAMILIES STUDY - A RESOURCE FOR IDENTIFICATION OF GENETIC FACTORS CONTRIBUTING TO LYMPHOMA, LYMPHOID LEUKEMIA, AND MYELOMA: PHASE 1 - RECRUITMENT

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**Introduction:** Although most lymphoid cancers are sporadic, the occurrence of multiple cases within the same family may indicate the existence of genetic susceptibility factors common to these disorders. By creating a collection of DNA samples with medical, family history and lifestyle information from consenting subjects and family members, we hope to identify genetic factors involved in susceptibility to lymphoid cancer.

**Materials and Methods:** Proband with a family history of lymphoid cancer were identified from a database begun in 1981 by the Lymphoma Tumour Group at the BC Cancer Agency, and by ascertainment of probands through local hematologists. Eligible subjects are mailed an introductory package including an explanatory letter, information and consent form, and family history questionnaire (FHQ). A pedigree is constructed from completed FHQ and a phone interview is conducted to obtain more detailed information about cancer diagnoses, treatment histories, and vital statistics of family members. Living affected and unaffected family members of participating subjects are invited to join the study. Participation consists of providing a DNA sample, permission to access medical records and stored tissue samples if applicable, and completing an epidemiological/lifestyle questionnaire. Pedigrees are then assessed to determine suitability for genetic mapping studies.

**Results:** To date 144 families have been ascertained. Introductory packages have been mailed to 445 eligible subjects; 252 individuals from 73 families have consented and are at various stages of participation. DNA samples have been collected from 168 participants including 22 saliva samples and 146 blood samples. Epidemiological/lifestyle questionnaires have been completed by 123 participants.

**Conclusions:** We have established a DNA sample and medical history collection of families with multiple cases of lymphoid cancer. Recruitment is in progress. This collection, likely applied in collaboration with other researchers in the field, will help to identify genetic risk factors for lymphoid cancers

## 364 WITHDRAWN

## 365 SURVIVAL OF THE PATIENTS WITH NON-HODGKIN LYMPHOMAS: RETROSPECTIVE STUDY OF THE 40 YEARS SINGLE CENTER EXPERIENCE

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**Background:** The aim of the study was to compare the long term results of the non-Hodgkin lymphoma (NHL) treatment in different decades of the last 40 years.

**Materials and methods:** 1567 patients with histologically confirmed NHL were treated in our clinic in the time from 1970 till 2010. The therapeutic regimens were performed according to contemporary protocols including chemotherapy, local irradiation or combination of both. First group (n=212) was treated in the years 1970-1979, the second (n=338) – in the years 1980-89, the third (n=427) – in the years 1990-1999, the fourth (n=590) – in the years 2000-2010. The results of the treatment were evaluated according to the disease specific survival parameter (DSS) for the each group in general and for aggressive vs indolent as well as local (clinical stage I-II) vs generalized (stage III-IV) subgroups in particular.

**Result:** Five years DSS in the decade groups in general showed 50,8±3,6%, 59,5±2,8%, 65,4±2,5%, 79,5±2,6% respectively. The historical subgroups of the *local aggressive* NHL demonstrated significant differences in the 5-years DSS between all decades (27,1±5,5%, 53,1±4,9%, 66,7±4,5%, 80,1±4,2%; log-rank test, P<0,03), the difference between the third and the fourth decade subgroups was highly significant (P<0,004). The historical subgroups of the *generalized aggressive* NHL demonstrated significant differences in the 5-years DSS between second, third and fourth decades (38,9±16,2%, 34,2±5,9%, 54,1±4,8%, 73,9±5,6%; P<0,05). The subgroups of the *generalized indolent* NHL demonstrated no significant differences in the 5-years DSS between decades (57,1±5,1%, 69,0±4,9%, 66,7±5,1%, 73,2±6,2%). However, the 10-years DSS (20,2±4,5%, 29,9±5,7%, 40,8±7,6%, 54,8±9,8%) was significantly higher for the third and the fourth decades compared to the first decade group (log-ranktest, P<0,05). The increase of the 5-years as well as 10-years DSS was statistically significant for the patients of the age 59 and younger only in the last two decades in this subgroup of NHL (5-years DSS 65,9±5,1%, 80,2±3,0%; 10-years DSS 54,1±3,7%, 67,2±8,4%, P=0,00001). No significant differences between decades were shown for the decade groups of the *local indolent* NHL (83,9±6,3%, 98,4±5,0%, 83,0±5,6%, 89,6±5,7%).

**Conclusion:** The results of the NHL treatment in our center during the last 40 years demonstrated significant improvement of the survival in the subgroups of aggressive NHL (local and generalized). The improvement of the DSS in the subgroups of indolent generalized NHL was statistically significant in the last two decades compared to the years 1970-1979. No changes of the DSS took place in the subgroups of the local indolent NHL during the four analyzed decades.

## 366 WITHDRAWN

## 367 NON HODGKIN LYMPHOMA (NHL) IN CHILE. A REVIEW OF 207 CONSECUTIVE ADULT NHL CASES BY A PANEL OF FIVE EXPERT HEMATOPATHOLOGISTS

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**Introduction:** Information on the subtype distribution of non-Hodgkin lymphoma (NHL) in South America is scanty. The International Non-Hodgkin Lymphoma Classification Project study group reviewed 207 consecutive, untreated NHL cases in Chile diagnosed at 5 cancer centers in Santiago and 1 in Viña del Mar.

**Patients and Methods:** All cases were reviewed and reclassified by 5 pathologists independently according to the World Health Organization Classification of NHL and a consensus diagnosis was reached in each case.

**Results:** A diagnosis of NHL was confirmed in 195 of 207 cases (94%), and B-cell NHL constituted 88% of the NHL cases. Diffuse large B-cell lymphoma was the most common subtype of NHL at 38.5%, and follicular lymphoma comprised 25.1%. There was a high percentage of marginal zone B-cell NHL of MALT type (10.3%), and extranodal NK/T cell NHL of nasal type (2.5%). Extranodal presentation was seen in 74/195 cases (38%) and the most common presentation was in the stomach (37.6%). The most common gastric lymphoma was DLBCL (54.5%), followed by MALT (41%).

**Conclusions:** There is a high proportion of gastric NHL in Chile. Overall, the distribution of NHL subtypes is between that of western and eastern countries, which is a reflection of the mixed races and social development in Chile.

### 368 CHARACTERISTICS OF 917 NON-HODGKIN'S LYMPHOMA PATIENTS IN SERBIA ACCORDING TO THE WHO CLASSIFICATION OF LYMPHOID NEOPLASMS – LIRA NATIONAL REGISTER-BASED STUDY

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**Introduction/background:** The purpose of this prospective study, the largest unselected series in our country and region, was to illustrate the clinicopathological features of non-Hodgkin's lymphoma (NHL) classified according to the World Health Organization (WHO) classification of lymphoid neoplasms.

**Material and methods:** An analysis was conducted and clinical features of histological subtypes were established in 917 patients (age > or = 19 years) with NHL who were treated at 6 major centers representative of Serbia.

**Results:** There were 507 (55.3%) males and 410 (44.7%) females, 96.4% of them aged >30 years. B symptoms were present in 50% of the patients, while 33.3% had stages I-II (Ann-Arbor staging). B cell lymphomas formed 95.7% of the cases whereas T cell lymphomas formed 4.3% of the total. Indolent lymphomas accounted for 49.2% and aggressive ones for 50.8% of all NHLs. Among indolent lymphomas extranodal ones (MALT B cell lymphoma) were the most common subset (49.2%). Among the aggressive lymphomas diffuse large cell lymphoma (DLCL) was the most common subtype (80.7%). Among the T cell lymphomas, peripheral T cell lymphomas and anaplastic large cell lymphomas of the T/null-cell type were the most common subtypes (33.2%). The most common extranodal presentation was the gastrointestinal tract (29.4%). DLBCL was the predominant histological subtype (65.2%) in the patients with extranodal places NHL.

**Conclusions:** This is the first report of a large series of malignant lymphomas in Serbia using the WHO classification. It appears that there are no significant differences between NHL in Serbia and other large series as far as clinical and extranodal presentation is concerned.

### 369 META-ANALYSIS OF TREATMENT-RELATED RISK OF SECOND MALIGNANT NEOPLASMS AFTER HODGKIN LYMPHOMA: UPDATED DESIGN AND PROGRESS

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**Introduction:** Second malignant neoplasms (SMN) are a major late treatment effect for Hodgkin lymphoma (HL). Consequences of choice of first-line treatment for SMN risk remain unclear. A Cochrane systematic review on this question is being performed, based on our previous analysis performed in 2000-2004.

**Material and methods:** Individual patient data are being collected from randomised controlled trials addressing 5 currently relevant aspects of treatment choice: additional radiotherapy (RT), RT field, RT dose, chemotherapy (CT) cycles, intensified CT. Inclusion is restricted to trials employing ABVD-like chemotherapy and involved-field radiation as standard treatment. SMN rates will be analysed meta-analytically. For

planning, the numbers of person-years of observation and expected numbers of SMN were estimated for each treatment comparison using published incidence curves of SMN after HL.

**Results:** In a comprehensive search using Medline and the Cochrane database, 3901 references identified by electronic search were screened by 2 reviewers, yielding 578 relevant articles and 21 eligible trials. Trialists have been contacted and we expect to receive most of the data during 2011. We used published information about patient numbers, recruitment periods and median follow-up in the eligible trials and published time-dependent SMN incidences from 3 large cohort studies to estimate the total numbers of person-years and SMN per treatment comparison.

| Treatment comparison* | trials | patients | median follow-up <sup>#</sup> | person-years | SMN <sup>§</sup> |
|-----------------------|--------|----------|-------------------------------|--------------|------------------|
| Additional RT         | 6      | 1 850    | 4.9 yr                        | 9 009        | 57               |
| RT field              | 4      | 2 405    | 6.3                           | 15 135       | 97               |
| RT dose               | 3      | 2 974    | 6.8                           | 20 894       | 134              |
| CT cycles             | 3      | 2 412    | 6.9                           | 16 703       | 107              |
| Intensified CT        | 8      | 3 613    | 4.6                           | 16 278       | 104              |

\* 3 multi-arm trials contribute 2 comparisons each, thus some counts overlap  
<sup>#</sup> as published; weighted average over trials

<sup>§</sup> cumulative risks of 2.8%, 6.8% and 11% at 5, 10 and 15 years assumed

Estimated SMN numbers generally agreed well with reported numbers per trial where available.

**Conclusions:** The total numbers of patients and expected SMN are comparable with those in our original systematic review. The estimated numbers of SMN suggest that the proposed meta-analysis has the potential to detect relevant differences in SMN risk between treatment options, if they exist. Final results are expected in 2012.

### 370 HODGKIN LYMPHOMA IN JORDAN

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**Background:** Lymphoma is the fourth most common newly diagnosed cancer in Jordan, a small country with a population of 5.85 million.

The contribution of Hodgkin lymphoma (HL) to the overall lymphoma burden in Jordan, and the relative frequencies of its major subtypes, have not been hitherto well characterized.

**Objective:** to characterize the clinico-pathological features of Hodgkin lymphoma, and the relative contribution to the overall lymphoma burden, in patients referred to King Hussein Cancer Center (KHCC), the major cancer tertiary referral centre in Jordan.

**Patients and Methods:** A retrospective analysis was conducted of adults (>=18 years) lymphoma patients referred to KHCC, between 1/1/2003 and 31/12/2010. Clinical features and histological subtypes were prospectively established for all patients registered in the Lymphoma Service database. Pathology review and submission of original paraffin blocks were mandated for all patients.

**Results:** Over the 8 year period of 2003-2010, 1329 lymphoma patients were referred to KHCC and registered in the Lymphoma Service Database, of whom 477 (35.9%) were diagnosed with Hodgkin lymphoma. Among this group, all 477 patients were adults 18 years or older (100%), as children are treated in a different department. The median age was 35 years, (with an age range of 18-77), and 5% of patients were above the age of 60. 290 (61%) of the patients were males, 187 (39%) were females, with a male to female (M:F) ratio of 1.55:1.

276 (57.8%) of the HL cases had a diagnosis of nodular sclerosis Hodgkin lymphoma (HDNS), making it the most common histological subtype. 120(25.2%) had mixed cellularity Hodgkin lymphoma (HDMC), 9 (1.9%) had lymphocyte-rich Hodgkin lymphoma (HDLR), and 6 (1.2%) had lymphocyte-depleted Hodgkin lymphoma (HDLD). The ration of HDNS to HDMC was 2.3:1. Nodular lymphocyte predominance Hodgkin lymphoma (NLPHD) cases were 33, and constituted 6.9% of the HL cohort.

**Conclusion:** To our knowledge, this is the biggest series to of Hodgkin lymphoma to have ever been reported in Jordan. HL appears to constitute a bigger share of the lymphoma burden in Jordan, as opposed to Europe and the US. Clinico-pathological features, however, appear to be closer to those described in the West, with the possible lower prevalence of HDLR and HDLD. The prevalence ratio of HDNS to HDMC also appears closer to figures from the West as opposed to some other developing countries.

### 371 THE RELATIONSHIP BETWEEN VITAMIN D LEVELS, LATITUDE AND RACE AND PRIMARY CNS LYMPHOMA

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We have previously shown a difference in incidence rates between African Americans and Whites using the SEER data for primary CNS lymphoma (PCNSL). Recently there has been some thought that latitude and vitamin D might be related to the development of PCNSL.

We therefore looked at SEER data from the different sites as well as the levels of vitamin D in cases from the University of Iowa and Mayo Clinic. From the SEER data, there was no difference in incidence in regard to latitude in the ten year time period between 1992-2002. As we had previously shown, there was a higher rate among whites than in AA everywhere except for rural Georgia and Iowa where AA had a higher incidence. For AA, urban areas had a consistent rate of occurrence while the rural areas had only occasional spikes. Why this occurs is unknown.

For the vitamin D levels, there were 25 patients which were included in the Vitamin D serum analysis. Median total 25(OH)D in the 25 patients was 22 (range 7-43). 16 of the 25 patients (64%) were vitamin D deficient. Of these 25, 17 have progressed and 14 have died.

Median follow-up was 35 months (range 9-83).

Deficient vitamin D patients had moderately worse OS (HR = 1.49, 95% CI: 0.50-4.47,  $p=0.48$ ) but not statistically significant.

**Results:** were similar for event-free survival: (HR = 1.35, 95% CI: 0.50-3.69,  $p=0.55$ ).

**Conclusion:** we could not find a difference in rates of PCNSL in relationship to latitude. Urban areas have a higher incidence of PCNSL for AA than rural areas. Vitamin D deficiency appears to be common in our series. A wider series should be evaluated for this.

### 372 THE SPECTRUM OF T-CELL NEOPLASMS WITH LEUKEMIC PRESENTATION IN TAIWAN

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**Introduction/Background:** Lymphoma types vary in different geographic regions. In the West, the incidence of T-cell neoplasms among non-Hodgkin lymphomas is lower at 5-10%, while it is higher in the East including Taiwan, where it is nearly up to 20%. The frequency and disease spectrum of T-cell neoplasms with leukemic presentation may also vary in different geographic regions.

**Materials and Methods:** We retrospectively searched the pathology file of our institution located in Tainan, southern Taiwan from 2000 to 2009 for T-cell neoplasms with leukemic presentation.

**Results:** Among 717 cases of non-myeloid leukemias/lymphomas, there were 136 (19.0%) T-lineage neoplasms. Of the 136 neoplasms, 17 (12.5%) cases were leukemic at presentation, half (8/16) of these cases with concurrent lymphoma. These 17 patients were 12 males and 5 females with a median age of 46 (range, 17-82). These neoplasms included 7 (41%) T-cell large granular lymphocytic (T-LGL) leukemias, 4 (24%) T lymphoblastic lymphoma/leukemia (T-LBL), 4 (24%) adult T-cell lymphoma/leukemia (ATLL) and one case (6%) each of T-cell prolymphocytic leukemia (T-PLL) and peripheral T-cell lymphoma/leukemia, unspecified (PTCL-U). Marked leukocytosis with WBC count greater than  $100 \times 10^3/\mu\text{l}$  was noted in the T-LBL group. Mild to moderate leukocytosis was noted in the other entities. Of note was that the WBC counts of the 2 patients with T-LGL leukemia were within normal ranges. Interestingly, one case of T-LGL leukemia showed markedly irregular contours of the neoplastic cells resembling flower cells in ATLL, while non-floral cells with minimal nuclear irregularity was noted in one ATLL at chronic phase. The outcome of these patients was dichotomous. At one end with a very poor prognosis were those with T-LBL, ATLL at acute phase, PTCL-U and T-PLL. At the other end with a favorable prognosis included cases with T-LGL leukemia and ATLL at chronic phase.

**Conclusion:** Our study revealed a wide spectrum of T-lineage neoplasms with leukemic presentation in Taiwan. Although Taiwan is not endemic for human T-lymphotropic lymphoma virus type I (HTLV-1) infection, sporadic cases of ATLL including those at chronic phase do occur. The prognosis of patients of T-cell neoplasms with leukemic presentation depends largely on the specific tumor type, emphasizing the importance of clinicopathological correlation to reach a correct diagnosis according to the World Health Organization classification of lymphoid neoplasm.