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Post-treatment parenthood in survivors after Hodgkin lymphoma

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Background: Post-treatment parenthood (PtP) is an important dimension of the treatment and quality of life in young patients with Hodgkin's lymphoma (HL).
Methods: In 2002 276 males and 221 females treated for HL at the Norwegian Radium Hospital from 1971–99 completed a questionnaire in men assessing their attempts and success to achieve PtP and in females recording the number of completed pregnancies. 3 principal therapeutic groups were constructed: 1: Radiotherapy (RT) only (Rad), 2: Chemotherapy only (Chem), 3: RT and chemotherapy in combination (RaCh). Chemotherapy was divided in 3 groups (low, medium, high) according to the regimens' expected gonadotoxicity (GT). RT was subgrouped depending on whether infradiaphragmatic RT was given or not. Data were analysed by Kaplan-Meier and log rank tests using birth of 1. child post-treatment as primary endpoint.
Results: Of 121 males who attempted PtP, 84 were successful and had 1–5 children after their treatment. 70 females achieved PtP (1–4 children). 18 of the males had used assisted reproduction techniques (ARTs), 9 of them becoming a father. 3 of the females had used ARTs, one of them achieving pregnancy.
With a mean observation time of 16 years successful attempts of PtP were recorded in 85% (29/34) of the males in the Rad group, in 67% (10/15) in the Chem group and in 63% (45/72) in the RaCh group, with significant difference between the success rate in the Rad group compared to the two other groups ($p = 0.04$ vs Chem, $p = 0.02$ vs RaCh). In the females there was a similar significant difference between the Rad group and the two other groups ($p = 0.01$ vs Chem, $p = 0.02$ vs RaCh).
For both the males and the females there were no differences in PtP between the two subgroups of RT. In males there was a significant difference in PtP between all three groups of chemotherapy, with highest success rate in the low GT group, and the lowest success rate in the group with high GT. In females there was a significant difference in achieving PtP between the low and the high GT group.
Conclusions: In this study 69% of males who attempted PtP were successful with only 11% of them using ARTs. The success rate for female patients seems lower, though the exact rate of success is not yet available. In both males and females the chance of PtP was significantly highest in the Rad group and the low GT group.

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Ovarian toxicity after high dose chemotherapy without total body irradiation and without busulfan

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Given the known gonadic late effects of total body irradiation (TBI) in children, new conditioning regimens have been built without TBI. High doses (HD) of alkylating agents, have been used to avoid the side effects of TBI, particularity on endocrine functions. In girls, few conventional chemotherapies are known to produce ovarian toxicity. Conversely, in childhood, HD Busulfan even in prepubertal period is a major cause of ovarian failure. We report here the analysis of ovarian function in girls previously treated in our department with HD chemotherapy containing neither Busulfan nor TBI before autologous HSC for malignant tumors. These girls were minimum 13 year (Y) old at the time of ovarian evaluation and had survived over 6 months post transplant. Sixty two girls received different conventional chemotherapies before entering the consolidation phase for several types of pediatric tumors. Several HDC regimens have been used: containing:
1. HD Melphalan
2. HD cyclophosphamide
3. HD Thiotepa
4. HD Carboplatine.

The cumulative doses of drugs as well as previous radiotherapic and surgical damages have been studied for each case. Their median age at the transplant was 13 Y (2–32 Y): 32 were prepubertal and 30 had regular menses. The median time lapse post transplant was 5 Y.
Results: only 54 patients were analysed since 8 girls had a known ovarian failure secondary to castration. Among them, 31 had normal development and 23 had amenorrhea (17 secondary). At the last evaluation their median age was 18.5 Y (13–33 Y). Univariate analysis showed that the patient's age, the use of Thiotepa in the HDC, the use of Ifosfamide in the conventional chemotherapy, and the sarcoma's group were significant risk factors of ovarian failure. Conversely, BCNU/CCNU, the use of HD Melphalan and the neuroblastoma group demonstrated few gonadal damage. Obviously age at transplant and diagnosis are linked ($p = 0.0001$). After logistic regression: previous exposition to Ifosfamide, HD Thiotepa and the age at transplant appeared as 3 independent risk factors of ovarian failure for girls transplanted after conditioning without Busulfan or TBI. The incidence of ovarian toxicity for girls treated without TBI and without Busulfan is 42%. Preservation of fertility by ovarian cryopreservation, before treatment, must be considered in all patients at high risk of infertility: the girls transplanted after 13 Y of age and previously treated with HD alkylating agents, especially Thiotepa.

Oral presentations (Mon, 31 Oct, 9.15–11.15)
Leukemias and lymphomas in adults and children

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Mucosa associated lymphoid tissue (MALT) lymphoma: excellent outcome in 130 patients treated with radiation alone

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Introduction: Mucosal associated lymphoid tissue (MALT) lymphoma is the 3rd most common non-Hodgkin's lymphoma. It often presents in an early stage and may involve a variety of extra-nodal sites. We reviewed the long-term experience of treating MALT patients with radiation alone (RT) at a single cancer center.
Methods: All 130 patients with MALT lymphoma that were treated with RT alone in our center between 1985 and 2004 were identified. All cases were pathologically confirmed. We retrospectively reviewed the clinical data and treatment results.
Results: There were 76 (58%) men and 54 (42%) women with a median age of 61 years (range 24–90 years). The stomach was the most common primary site of involvement with 76 (58%) cases. Other primary sites of involvement included orbital adnexa (20 cases, 15%), skin (7, 5%), salivary gland (6, 5%), breast (5, 4%), oral sites (4, 3%), thyroid (3, 2%), subcutaneous tissue (2), lung (2), meninges (2); other sites were involved in 3 patients. 110 patients were presented in stage I, 6 in stage II, 9 patients were in stage IV and 5 patients presented following relapse. All patients were treated to the involved field with a median dose of 30 Gy (range 21–43 Gy).
Median follow up was 36 months (range 6–205). 5-year freedom-from-treatment failure (FFTF) with all events included was 91%, 5-year overall survival was 96% and 5-year cause-specific survival was 99%. Only one patient remained refractory to RT, 6 relapsed in another extra nodal site, 2 transformed to diffuse large B-cell lymphoma and one patient relapsed in an irradiated site. Patients with gastric MALT had a better FFTF compared to those with non-gastric sites ($p < 0.04$) and patients with early-stage (I-II) had better FFTF than those with relapsed or advanced stage ($p < 0.001$). No acute side effects (grade 3 or 4) were recorded, and no significant long-term side effects were detected thus far (maximal follow of 17 years).
Conclusions: This is the largest reported series of MALT lymphoma patients treated with RT alone. The outcome of these patients using low-dose RT and limited fields is excellent and safe. RT alone should be considered the treatment of choice for most non-gastric sites (excluding lung) and for all patients with gastric MALT lymphoma that have exhausted their antibiotic option or are unlikely to respond to it.

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Primary mediastinal large B-cell lymphoma (PMLBL) in children/adolescents; data of European and American groups

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Introduction: PMLBL is a rare sub-type of non-Hodgkin's lymphoma (NHL), especially in paediatric patients (pts) for whom optimal treatment is still to be established.
Methods: We identified the pts with PMLBL in the French LMB89, the international French-American-British FAB LMB96, the German-Austrian-Swiss BFM 86–90–95 and the Italian AEIOP LNH 92–97 databases, covering periods between 1984 and 2003. Treatment regimen was either the LMB or the B-BFM strategy for mature B-cell NHL. Radiotherapy was not part of the first line strategy

Results: We identified 116 pts, which represents about 2% pts. 56% were female. Age was from 1.4 to 19.7, median 15y. There were 40 events: 1 toxic death, 17 no complete remission with the protocol and 22 relapses. 25 pts died. One major difficulty was the interpretation of a residual mediastinal mass. Prognostic factors were: LDH level >500 in the BFM series, and the association of size>10 cm+LDH > Nx2 in the FAB LMB96 series.
Conclusions: PMLBL is rare in children and national series are small, not allowing to draw clear conclusions. Data from the different databases will be extracted, merged and presented. The pooling of these data should enable a better description of these pts, and improve the analysis of events and prognostic factors, and will be the basis for a collaborative prospective study.

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Chemotherapy followed by low dose radiotherapy in childhood Hodgkin disease; retrospective analysis of results and prognostic factors

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Purpose: To report on treatment results and prognostic factors of young patients with Hodgkin's disease treated with chemotherapy (CT) followed by low dose radiotherapy (RT).
Materials and Methods: This retrospective series analysed 166 patients under 18 years of age, treated from January 1985 to December 2003. Median age was 10 years (range 2–18). The male to female ratio was 2.3: 1. Adenomegalia was the most frequent complaint (68%), and the time of symptom duration was smaller than 6 months in 55% of the patients. In histological analysis Nodular Sclerosis was the most prevalent type (43%) followed by Mixed Celularity (41%). The disease was restricted to two nodal group (stage II) in 60% and to adjacent groups in 55% (stage III). The most frequent site of metastasis ware bone marrow (38%) and lungs (42%). Standard treatment consisted of chemotherapy (drug combination varied according to the current treatment protocol). Radiotherapy consisted of 21 Gy dose in 17 fractions in the majority of patients (90.2%), delivered to involved field or mantle field. 13.86% patients did not receive RT. Median follow-up was 101 months (mean 109, range 29–237).
Results: The Overall Survival (OS) and Event Free Survival (EFS) in 10 years were 89% and 82%. Survival according to clinical stage was 94%, 94%, 91% and 72% for stages I to IV ($p = 0.0215$). Ten years OS was 91% for patients who received RT and 76% for patients who did not ($p = 0.001$). Multivariate analysis showed presence of B symptoms and low platelet count to be associated with a worse prognosis.
Conclusions: This study shows that combining chemotherapy and low dose RT is effective in treating childhood HL, providing high cure rates (89% in 10 years), and disease control. So far it is not possible to exclude RT from treatment. And yet, attention to platelet count should be payed in order to improve survival. B symptom presenting children may be involved in more aggressive protocols so survival can be improved.
As the disease is highly curable, any data of long term follow-up should be presented in order to better direct therapy, improving outcome and lowering side effects.

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Suggestion of TNM staging system for the angiocentric T-cell and nasal type NK/T cell lymphoma

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Background: To do comparative analysis of outcome of angiocentric T-cell and nasal type NK/T cell lymphoma after radiotherapy (RT) for appropriate staging of prognostic value.
Patients and methods: Between February 1989 and March 2001, 60 patients, with newly diagnosed angiocentric T-cell and nasal type NK/T cell lymphoma of Ann Arbor stage I and II involving the head and neck, underwent RT. There were 42 males and 18 females and the median age was 45 years. Twenty-five of them were treated with combined chemoradiotherapy (CRT), while 35 with RT alone. The tumors in the nasal cavity or paranasal sinuses were classified as the nasal cavity group (NC group; 35 cases), and those found in other regions as the non-nasal cavity group (NNC group; 25 cases). The median follow-up period was 74 months.
Results: The 5-year survival rate (5YSR) was 69%. The NC group was superior to the NNC group in 5YSR without significance (75% vs. 60%; $p = 0.40$). When the tumors were restaged by the AJCC TNM system of nasal cavity cancer in the NC group, patients with T1–2 tumors have not reached the time of median survival, whereas median survival time of T3 and T4 tumors was 50 and 10 months, respectively ($p = 0.013$). In the NNC group, however, Ann Arbor stage was relatively accurate in predicting the treatment outcome. The 5YSR of Ann Arbor stage I and II was 76% and 31%, respectively ($p = 0.060$).
Conclusions: Our results suggest that TNM stage of the nasal cavity cancer might be appropriate in predicting the treatment outcome in the NC group of the angiocentric T-cell and nasal type NK/T cell lymphoma rather than Ann Arbor system.

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N-CoR is a target of a serine protease specifically activated in acute promyelocytic leukaemia (APL)

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Acute promyelocytic leukaemia (APL), which is caused by fusion protein PML-RAR, is characterized by accumulation of immature myeloid cells arrested at the stage of promyelocytic development. APL tumour cell exhibits disintegration of nuclear domains known as PODs (PML oncogenic domains) while treatment of APL patients with retinoic acid (RA) results in clinical remission associated with reorganization of PODs. We recently identified that PML-RAR promotes accumulation of mis-folded nuclear hormone receptor co-repressor (N-CoR) in Endoplasmic Reticulum (ER). Here, we report that N-CoR is proteolytically processed in APL tumor cell, while N-CoR in non APL cells showed no sign of processing. Cellular lysate of APL tumor cell NB4, as well as that of human APL primary cell, contain an activity that cleaved the N-CoR protein.
Expression analysis using RNA prepared from APL and non APL cells revealed selective expression of the activity in APL tumor cell. It is likely that mis-folded N-CoR in the ER becomes a target of cellular protease that is activated in response to accumulation of mis-folded protein. Biochemical purification of the activity from the NB4 cell and its spectrometric analysis revealed that the N-CoR cleaving activity is a serine protease. Through small scale screening of known protease inhibitors, we identified a specific agent capable of inhibiting the activity and the processing of N-CoR in NB4 cell. Treatment of NB4 cells with the protease inhibitor, as well as with retinoic acid (RA) stabilizes the N-CoR protein, suggesting a role of N-CoR in the differentiation of promyelocytic cells. Indeed, down regulation of N-CoR through RNAi abrogated RA induced differentiation of NB4 cells. Targeting the N-CoR cleavage activity with its inhibitor promotes apoptosis and differentiation of NB4 cells, suggesting a crucial role of the protease in malignant transformation of APL tumor cell.
We have identified a previously uncharacterized protease that appears to be crucial for transformation of promyelocytic cells. Moreover, we have identified an agent capable of inducing differentiation and apoptosis of APL tumor cells through targeting the cleavage of N-CoR protein. These finding will improve our understanding about the pathogenesis of APL and will lead to the designing and development of newer diagnostic and therapeutic measure.

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Ocular adnexal lymphoma is highly associated with Chlamydia psittaci

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Background: Ocular adnexal lymphomas (OAL) are mostly of low-grade MALT type. Recently, an association between *C. psittaci* and OAL was suggested (Ferreri AJM et al. J Natl Cancer Inst 2004;96:586). We conducted this study to confirm the relationship between *C. psittaci* and OAL.
Methods: Between 1993 and 2004, a total of 33 OAL cases were identified in Asan Medical Center, Seoul, Korea. DNA was extracted from formalin-fixed, paraffin-embedded OAL tissues, and then touchdown enzyme time release-PCR was performed to identify three Chlamydia species (*C. psittaci, C. tracomatis,* and *C. pneumoniae*). DNA extraction and PCR for Chlamydia species were also performed in 21 cases with non-neoplastic ocular adnexal disease (NNOAD).
Results: In all OAL cases, histologic type was low-grade MALT lymphoma. The median age was 42 yrs (range, 22 to 73 yrs). Male to female ratio was 1.1. *C. psittaci* was highly associated with OAL: *C. psittaci* was found in 78% of OAL cases, while it was observed only in 23% of NNOAD cases