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Prognostic markers in nk/t cell lymphoma and peripheral t cell lymphoma (PTCL): should treatment be guided by histology or prognostic scores?

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Background: T-cell lymphomas have traditionally been treated uniformly but are clinically distinct in behavior. We aimed to compare the frequencies, clinical characteristics, and prognostic factors of T-cell lymphoma subtypes and implications for treatment.
Materials and Methods: We reviewed 192 consecutive patients with systemic T-cell lymphoma from 1992−2008. All patients had histological review and are classified based on the WHO classification system.
Results: Extra-nodal-NK/T-cell lymphoma and PTCL comprised 37% and 63% of all cases. Of the PTCL cases, histology was PTCL-NOS in 53 (42%), anaplastic large cell (ALCL) in 33 (26%), angioimmunoblastic T-cell in 22 (18%) and others in eleven patients. A low International Prognostic Index (IPI) score was associated with significantly better overall survival (OS) for PTCL but score $\geqslant$2 was associated with a uniformly poor prognosis in PTCL (40 mths vs <9 mths). IPI was not useful in determining outcome in NK/T-cell lymphoma. Histology wise, ALCL was associated with a better 3 year OS of 60% as compared to other subtypes of PTCL (36−40%; p = 0.189). Compared with PTCL, extra-nodal NK/T-cell lymphoma was associated with a significantly inferior rates of complete remission (CR) (OR 1.74; 95% CI 1.50−1.97) and OS (HR 1.610; 95% CI 1.05–2.47). Further analysis into this subtype showed the nasal variant (n = 50) differed significantly from extra-nasal variant (n = 21) in terms of stage at presentation (stages I/II) (OR 1.45; 95% CI 1.29−1.62), with better CR rates (OR 1.67; 95% CI 1.51−1.82) and OS (HR1.50; 95% CI 0.75−2.99).
Conclusions: In this large series of T-cell lymphoma patients, extranodal NK/T-cell lymphoma especially extranasal variant is associated with a poor outcome when compared to PTCL. PTCL with low IPI scores may be treated with conventional chemotherapy but poor risk PTCL and NK/T-cell lymphoma regardless of IPI score are in dire need of novel strategies.

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Role of salvage radiation therapy in Hodgkin Lymphoma with relapsed or progressive disease despite autologous stem cell transplant

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Background: Hodgkin Lymphoma (HL) patients (pts) who have relapsed or progressed following autologous hematopoietic stem cell transplantation (ASCT) have poor prognosis. The efficacy of salvage radiotherapy (RT) in terms of local control and survival was analysed through a chart review.
Methods and Patients: Among 347 pts with recurrent/refractory HL who received ASCT from 1986−2006, 163 had post-ASCT progression or relapse. Of these, 56 received salvage RT and form the basis of this report (progression: 13; relapsed: 43). The M: F ratio was 1.3:1. Median age at salvage RT was 32 yrs (range, 19.4−61.6). Disease was confined to lymph nodes in 32 pts while 24 had both nodal and extranodal disease (frequently in bone, 18/24 pts). RT alone was given in 34 pts (61%), while RT and chemotherapy (CT) was given in 22 (39%). Median interval from ASCT to relapse was 0.5yrs (range 0.1−5.5) and from ASCT to salvage RT was 0.8 yrs(range 0.1−5.6). All the involved sites were radiated in 39 pts (70%) while 17 (30%) were radiated at symptomatic sites only. The median RT dose was 35 Gy (range, 8−40.3), and 84% pts received 30−40 Gy. RT technique was extended field in 20 pts (36%), and involved field in 36 (64%). Survival was calculated from the start date of RT. Disease progression in the RT volume was regarded as *local* failure, while progression outside RT volume was judged as *systemic* failure.
Results: The median follow up from RT was 31.3 mo (range 0.2−205.5). Overall response rate was 84% (CR: 36%, PR: 48%). The median overall survival (OS) was 40.8 mo (95% CI, 34.2−56.3). The 5-year OS was 32% (95% CI, 17−49). The 2-year PFS was 16% (95% CI, 8−27), the 2-year *local* PFS was 69% (95% CI, 57−81), while the 2-year *systemic* PFS was 17% (95% CI, 0.09−0.31). The 1-year PFS was significantly higher in pts where all diseased sites were irradiated (49%) compared to those where only the symptomatic site was treated (19%, p = 0.01). Among 20 alive pts, 9 had systemic progression, 5 had both systemic & local progression, 1 had local progression and 5 were disease free (at 5.6, 6.3, 6.4, 7.5, and 17.1 yrs). Of these 5 long term survivors, 3 were in continuous CR following salvage RT, 2 had relapsed after RT and received further therapy (one with 2nd course RT, other with RT+CT), but both > 5 years beyond last treatment were disease free.
Conclusion: RT results in high rates of local disease control in chemotherapy refractory HL. However, pts who fail ASCT have a poor prognosis with systemic progressive disease in the majority. In selected cases RT provides a local control rate of 70% at 2 yrs and occasionally leads to long-term survival.

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Hodgkin lymphoma treatment with ABVD in the US and the EU: neutropenia occurrence and impaired chemotherapy delivery

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Background: In newly diagnosed patients with Hodgkin lymphoma (HL) the effect of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD)-related neutropenia on chemotherapy delivery is poorly documented.
Materials and Methods: Two similarly designed prospective observational studies conducted in the US (115 community practices) and the EU (Belgium, France, Germany, Spain, UK; 66 clinical centres), observed HL patients who started a new course of ABVD in 2002−2005. Patients were followed over the first 4 cycles of treatment. Datasets were merged and definitions reconciled to gain information on US and EU treatment patterns and the incidence of grade 4 chemotherapy-induced neutropenia (CIN; absolute neutrophil count [ANC] <500/mm^3), febrile neutropenia (FN; ANC <1000/mm^3 and fever/infection), chemotherapy delivery and colony-stimulating factor (CSF) use. Univariate associations between variables were explored in the pooled dataset.
Results: The age range was 19−83 years (median 36; 49% female) in 68 US patients and 18−74 years (median 34; 38% female) in 47 EU patients. US patients had slightly higher body surface area (median 1.9 m^2 vs. 1.8 m^2), a higher incidence of stage III/IV disease (42% vs. 30%) and were more often pre-treated with radiotherapy (9% vs. 0%). Typically, 4 cycles (US 41%, EU 34%) or 6 cycles (US 56%, EU 55%) of ABVD were planned. In the EU and in the US, median planned dose intensities (expressed on the basis of actual body weight) met the ABVD standard of bleomycin, 5 units/m^2/week; doxorubicin, 12.5 mg/m^2/week; dacarbazine, 187.5 mg/m^2/week; vinblastine, 3 mg/m^2/week. Observations during cycles 1−4 are shown in the Table. The relative risk (RR) of CIN was 0.35 for patients with vs. without primary CSF prophylaxis and the RR of dose delays was 1.55 for patients with vs. without CIN. Other univariate associations considered were not statistically significant.
Conclusions: In this population of HL patients CIN and FN occurrence was substantial. Chemotherapy delivery was suboptimal in 18−22% of patients. Use of primary CSF prophylaxis in ABVD patients was more common in the US than the EU and appeared to reduce CIN rates.

CSF prophylaxis, neutropenic events and chemotherapy delivery

Parameter	US (N = 68)	EU (N = 47)
Primary CSF prophylaxis	37%	4%
CIN occurrence	24%	32%
FN occurrence	12%	11%
Dose delays > 3 days[1]	41%	57%
Dose reductions > 10%[b]	22%	9%
Average relative dose intensity[a] $\leqslant$ 85% of standard ABVD	22%	18%

[a]Per cycle; [b]Excluding vinblastine

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Chronic fatigue in Hodgkin lymphoma survivors – does it affect mortality?

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Background: Long-term survivors after Hodgkin lymphoma (HLSs) are at increased risk of chronic fatigue (CF). It is not known whether CF in

cancer survivors impacts negatively upon somatic health. The primary aim of the present study was to examine mortality and causes of death in HLSs included in a questionnaire survey in 1994 which explored the presence of CF after a mean observation time since diagnosis of 12 years [1], and to compare their survival to that of controls (Ctrs) from the general population. Secondarily we explored the mortality in HLSs with or without CF and in the non-responders, using HLSs without CF as reference group in the survival analysis.
Methods: In 1994, 557 disease-free HLSs were included. In 2008 the HLSs were allocated to three groups: 1) responders without CF (n = 329), 2) responders with CF (n = 113), and 3) non-responders (n = 98). A control group was drawn from the general population using five Ctrs per patient, matched on age and sex (n = 2785). Dates and causes of death for all subjects were retrieved from the National Statistics for Causes of Deaths. Observation time was calculated from January 1st 1994 until date of death or a cut-off of January 1st 2007. Kaplan-Meier plots were used for univariate analyses and Cox models were fitted to adjust for multiple covariates.
Results: By January1st 2007, 149 (27%) of the HLSs had died compared to 197 (7%) of the Ctrs. HLSs had almost five times higher mortality compared to Ctrs (HR = 4.93; 95% CI: 3.91−6.21). Responders with CF had an increased risk of mortality by 4.85 (95% CI: 3.02−7.77), responders without CF had a mortality risk of 4.35 (95% CI: 3.16−6.00), whereas non-responders had the highest mortality risk of 9.45 (95% CI: 5.44−16.41), all groups compared to Ctrs. The non-responders had a two-fold increased mortality compared to HLSs without CF (HR:2.05, 95% CI:1.37−3.07), whereas there was no significant difference in mortality in HLSs with CF compared to those without CF. Among HLSs, 83/149 of deaths were caused by malignant diseases (21/149 due to recurrent Hodgkin lymphoma) and 36/149 by cardiovascular diseases.
Conclusions: After a median of 23 years since diagnosis HLSs had a near five-fold increased mortality risk compared to Ctrs. The highest mortality risk was found among the non-responders from the 1994-survey, whereas there was not found increased mortality risk in HLSs with CF compared to those without CF. The former findings indicate that health problems probably are underestimated among non-responders in cross-sectional questionnaire surveys.

References

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9227 POSTER

Involved node radiotherapy (INRT) and modern radiation treatment techniques in patients with Hodgkin lymphoma

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Background: To assess the clinical outcome of the involved node radiotherapy (INRT) concept and the use of modern radiation treatments (intensity modulated radiotherapy (IMRT) or deep-inspiration breath-hold radiotherapy (DIBH)) in patients with localized supra diaphragmatic Hodgkin lymphoma.
Material and Methods: All but two were early stage Hodgkin lymphoma patients and were treated with chemotherapy prior to irradiation. Radiation treatments were delivered using INRT concept according to the EORTC guidelines. IMRT planning was performed using CadPlan® v.6.3.6, (Varian Oncology Systems, Palo Alto, CA) with dose constraints assigned to a virtual volume located behind the PTV and/or the origin of the coronary arteries. For breath-adapted technique, a dedicated spirometer to DIBH radiotherapy (Spiro Dyn'RX system®, Dyn'R, Muret, France) was used with video-glasses that allow a visual monitoring of the patient. The DIBH technique was implemented with a 3-dimensions conformal radiotherapy.
Results: 50 patients with Hodgkin lymphoma (48 patients with primary Hodgkin lymphoma, 1 patient with recurrent and 1 with refractory disease) entered the study from January 2003 to August 2008. 32 were treated with IMRT and 18 with DIBH. The median age was 28 years (range 17 to 62). 34 (68%) patients had stage I-IIA and 16 (32%) had a stage I-IIB. All but 3 patients received 3 to 6 cycles of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD). The median radiation dose to patients treated with IMRT and DIBH technique was respectively 40 Gy (range: 21.6−40 Gy) and 30.6 Gy (range: 19.8−40 Gy). The median mean dose delivered to coronary artery origin, the median heart V30 and the median lung V20 were respectively with IMRT and DIBH 34.5 Gy and 27.4 Gy, 15.5% and 2%, 28.6% and 21%. The median follow-up was 38 months (range: 9−74 months). The 3-year progression-free survival and overall survival were 92% and 98% respectively. Recurrences were observed in 4 patients, 2 were in-field recurrences and 2 were at a distance from radiation fields with visceral recurrences. There was one grade 3 lung acute toxicity (transient pneumonitis).
Conclusion: Our results suggest that patients with localized Hodgkin lymphoma can be safely and efficiently treated using the INRT concept and modern radiation treatment techniques such as IMRT and DIBH.

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Involved-Field Radiotherapy (IFRT) after induction chemotherapy with 4−6 cycles of ABVD in early stage (I/IIA) Hodgkin Lymphoma: long term results of a single institution

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Background: Combined-modality treatment with induction chemotherapy, followed by IFRT in early stage Hodgkin's disease, appears to be beneficiary for the patients in terms of survival rates and quality of life in general.
Materials and Methods: We analyzed the data of 150 patients, with early Hodgkin's disease (stage IA/IIB) who underwent adjuvant IFRT after 4−6 cycles of ABVD, during the period 1996 to 2000, in our department. All patients were retrospectively analyzed for acute, chronic side effects and clinical results.
Results: The 5 year disease free survival rate (DFS) was 87.5%. Of the 19 (12.5%) patients who relapsed, 7 (5%) relapsed in the irradiated field (infield relapse). Five year overall survival rate was 93%. Only 1 patient presented with Acute Myelogenous Leukemia (AML). The clinicaly recorded acute side effects (fatigue, dermatitis, esophagitis, nausea, diarrhea, neutropenia) were mild and acceptable.
Conclusions: Our findings indicate that, IFRT after chemotherapy with ABVD, presents as a highly effective and safe treatment for early stage Hogkin's disease, though a larger number of patients has to be studied in order to achieve results of higher statistical significance.

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Polymorphisms of glutathione S-transferase mu 1(GSTM1), theta 1 (GSTT1) and pi 1 (GSTP1) in outcome of Hodgkin's lymphoma patients

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Background: The chemotherapic regiments for Hodgkin's lymphoma (HL) patients include alkylating agents, anthracyclines and cyclophosphamide; that are metabolized by enzymes of the glutathione S-transferase system. The *GSTM1*, *GSTT1* and *GSTP1* genes are polymorphic in humans. The *GSTM1* and *GSTT1* may be homozygous null in 10−60% of individuals of distinct populations, which result in a lack of the proteins. The variant allele Val of the *GSTP1* Ile105Val polymorphism, found in 10% of healthy individuals, was associated with a decreased enzyme activity. In a unique study, HL patients with at least one *GSTM1* or *GSTT1* null had a significant better disease-free survival compared to those with undeleted genes. In another study, the variant Val allele of the *GSTP1* Ile105Val polymorphism was associated with an improved free survival in HL patients. In this report, we studied the impact of genetic polymorphisms of the *GSTM1*, *GSTT1* and *GSTP1* genes in outcome of Brazilian HL patients.
Material and Methods: Our analysis included 110 consecutive patients (median age: 27 years, range: 17−63; 58 males, 52 females; 67 at stages I / II, 42 at stages III / IV) treated with ABVD or BEACOPP. Genomic DNA was analysed by the multiplex-PCR or PCR-RFLP for identification of the *GSTM1*, *GSTT1* and *GSTP1* genotypes. Disease free survival (DFS) and overall survival (OS) were calculated using the Kaplan-Meier estimate probabilities. Differences between survival curves were analysed by the log-rank test.
Results: At 120 months of follow-up, the DFS in patients with the *GSTM1* null genotype was higher than in those with undeleted gene (95% *vs* 68%, P = 0.03). The DFS was not influenced by the *GSTT1* (P = 0.30) and *GSTP1* (P = 0.38) genotypes. The OS was higher in patients with the *GSTT1* gene than in those with the null genotype (80% *vs* 72%, P = 0.006) and in patients with the Val allele (Ile/Val plus Val/Val) than in those with the Ile/Ile genotype (93% *vs* 78%, P = 0.04) at 120 months of follow-up, but was not influenced by the *GSTM1* genotype (P = 0.80). Similar results were found when patients were stratified by the age and stage of the tumour.
Conclusions: Our results suggest that the *GSTs* polymorphisms interfere in outcome of HL patients treated with ABVD or BEACOPP. However, ongoing studies of toxicity, pharmacokinetics and proteins should clarify whether carriers of the distinct genotypes should receive distinct doses of chemotherapic agents. Financial support: FAPESP and CNPq