''Focus on...'' session: radiotherapy and early stage

025 RADIATION DOSE FOR LOCAL CONTROL IN NON-HODGKIN LYMPHOMA L: BRITISH NATIONAL LYMPHOMA INVESTIGATION RANDOMISED TRIAL.

P. Hoskin[1], L. Lowry[2], P. Smith[2], W. Qian[3], S. Falk[4], K. Benstead[5], T. Illidge[6], M. Robinson[7], A. Jack[8], D. Linch[9]
[1]Cancer Centre, Mount Vernon Hospital, Northwood, United Kingdom, [2]Haematology Trials Group, CRUK & UCL CTU, London, United Kingdom, [3]Clinical Trials Unit, MRC, London, United Kingdom, [4]Oncology, Oncology and Haematology Centre, Bristol, United Kingdom, [5]Clinical Oncology, General Hospital, Cheltenham, United Kingdom, [6]Academic Health Sciences, Christie Hospital, Manchester, United Kingdom, [7]Clinical Oncology, Weston Park Hospital, Sheffield, United Kingdom, [8]HMDS, St James Institute, Leeds, United Kingdom, [9]Cancer Institute, UCL, London, United Kingdom

Introduction: This multicentre randomised phase III trial was designed to investigate lower dose radiation schedules in non Hodgkins lymphoma for both indolent (I-L) [24Gy in 12 fractions] and aggressive (Ag-L) [30Gy in 15 fractions] compared to a standard 40-45 Gy in 1.8 to 2Gy fractions.

Methods and materials: Patients >18 yrs requiring radiotherapy for non Hodgkin's lymphoma where the aim of treatment was local control were eligible. Randomisation was stratified by histological subtype. Central review of pathology was mandated and achieved in 85%. Primary end point was overall response rate (ORR) within the irradiated field and the study was powered to detect a 15% difference in ORR with a 90% power and 5% significance level.

Results: Between April 1997 and January 2005, there were 1001 randomisations from 40 centres; 361 I-L and 640 Ag-L. 81% received RT as part of primary radical treatment. Amongst the I-L 69% received RT alone for cure of localised disease and in Ag-L 80% had RT in a combined modality schedule with chemotherapy and 12% received RT alone for cure of localised disease. Compliance with the protocol treatment was >95%.

In the I-L group the 1 month ORR was 95% in the high dose (HD) arm and 92% in the low dose group (LD) [Difference 3%, 95% CI -5% to 6%]; in the Ag-L arm the 1month ORR was 92% in both arms [Difference 0% 95% CI -4.5% to 4.5%]. The complete response rates (CR) were 79% and 82% respectively [95% CI -8% to 6%] for I-L; 83% and 82% respectively [95% CI -6% to 8%] for Ag-L. At median follow up of 5.6 years, 5-year freedom from local progression (FFLP) rates fir I-L are 78.9% (HD) and 75.6% (LD) [p=0.37], and in Ag-L 83.5% (HD) and 82.2% (LD) [p=0.66]. No significant differences in overall survival (OS) were seen. No difference is seen on subgroup analysis in those patients having radical treatment alone, those with aggressive lymphoma receiving consolidation RT after chemotherapy, or those who received rituximab as part of their induction chemotherapy. Acute and late toxicity rates were low in both arms; erythema in the irradiated field was reduced in the lower dose arms (29% vs. 41%, p<0.001).

Conclusion: There was no difference in ORR, FFLP or OS between the two dose levels tested; 24Gy in I-L and 30Gy in Ag-L lymphoma should be the standard of care.

026 SHOULD RADIATION THERAPY (XRT) BE THE STANDARD THERAPEUTIC APPROACH FOR STAGE I FOLLICULAR LYMPHOMA (FL)? A COMPARATIVE EFFECTIVENESS ANALYSIS OF THE NATIONAL LYMPHOCARE STUDY (NLCS)

J. Friedberg[1], M. Byrtek[2], B. Link[3], C. Flowers[4], M. Taylor[2], J. Hainsworth[5], J. Cerhan[6], J. Hirata[2], T. Miller[7]
[1]James P. Wilmot Cancer Center, University of Rochester, Rochester, United States, [2]Biostatistics, Genentech, South San Francisco, United States, [3]Oncology, University of Iowa, Iowa City, United States, [4]Oncology, Emory University, Atlanta, United States, [5]Oncology, Minnie Pearl Cancer Center, Nashville, United States, [6]Epidemiology, Mayo Clinic, Rochester, United States, [7]Hematology/oncology, University of Arizona, Tucson, United States

Background: The NLCS is a multi-center, observational study on therapy and outcome for patients (pts) with newly-diagnosed FL in the USA. Using NLCS, we compared the effectiveness of widely disparate therapeutic regimens used for stage 1 FL.

Methods: Of 472 pts with stage 1 FL in NLCS, incomplete staging occurred in 56% due to lack of bone marrow biopsy (39%), incomplete imaging (4%) or both (13%); this incompletely staged group had more progression events (34% vs. 17%; p<0.01) than rigorously staged pts and was excluded from further analysis. Therefore, 206 (106 female) stage I FL pts with complete staging were analyzed.

Results: Median age was 61 (range 25-86); and grade was: 1 (44%); 2 (26%); 3 (18%); NOS (12%). 18% of pts had extranodal disease. There was no difference in outcome in PET-staged (n=128) compared with CT-staged patients. Therapeutic modalities included watchful waiting (WW) (N=34, 17%), rituximab alone (N=26, 13%), rituximab + chemotherapy (N=62, 30%), XRT only (N=56, 27%), chemotherapy + XRT (combined modality) (N=21, 10%); 3 pts received other therapies. Baseline characteristics were similar between all treatment groups with the exceptions that WW and XRT groups had less pts with B symptoms (p=0.04) and grade 3 histology (p=<0.01) compared with R-Chemo and combined modality. With a median follow-up of 49 mos, 34 progression events (6 deaths) occurred. Analysis of PFS used Cox regression adjusted for grade, age ≥ 60, LDH > normal, and hemoglobin < 12 g/dl. There was no difference in PFS in patients treated with XRT (HR 0.9; CI 0.3-2.2) compared to WW; however patients treated with other modalities had statistically better outcome (HR 0.3; CI 0.1-0.9) compared to WW.The only specific therapeutic modality with statistically improved outcome in PFS compared to WW was R-chemo (HR 0.2; CI 0.05-0.6). Patients treated with combined modality therapy also had excellent outcome, but estimated effect could not be calculated due to small numbers.

Conclusions: Complete staging with a bone marrow biopsy and CT imaging allows accurate prediction of stage 1 outcome; there is no added prognostic benefit to PET staging. The excellent outcome observed with over 4 years of follow-up incorporating systemic immunochemotherapy challenges the dogma that XRT alone is optimal; indeed pts observed did as well as patients treated with XRT. As prospective randomized trials are unlikely to be conducted in stage 1 FL, the NLCS dataset provides evidence that an observation approach, rituximab-containing chemotherapy, and combined modality approaches are reasonable and effective options that may be considered for stage 1 FL pts.

027 FOLLICULAR LYMPHOMA: CURABILITY BY RADIOTHERAPY IN LIMITED STAGE NODAL DISEASE? UPDATED RESULTS OF A RANDOMIZED TRIAL.

M. Engelhard[1], M. Unterhalt[2], M. Hansmann[3], M. Stuschke[1]
[1]Radiation Oncology, University Hospital Essen, Essen, Germany, [2]Biometrics, University Hospital Munich, Munich, Germany, [3]Pathology, University Hospital Frankfurt, Frankfurt, Germany

Aims: Follicular lymphoma WHO grade I or II (FL) in early stage nodal disease can be treated effectively by radiotherapy alone. The extent of optimal target volumes remains controversial with a high rate of relapse (RLS) out-field after Involved field irradiation, but higher toxicity and potentially risks of secondary neoplasia after large field techniques. Therefore, this study aimed to determine adequate age-adapted irradiation volumes in FL patients (pts) [randomized trial (RD)] and to evaluate standardized radiotherapy in elderly FL pts [prospective observation trial (OBS)].

Methods: In FL stage I-II and limited stage III disease, pts up to 65 years (ys) were randomized to Extended field (EF) or Total lymphatic irradiation (TLI), basic dose 30 Gy, boost 10/14 Gy (lymphoma size dependent). Pts aged 66-75 ys were treated with EF, pts > 75 ys with involved field (IF) radiotherapy.

Results: A total of qualified 255 pts were recruited. In the RD trial, 202 pts, median age 54 (23-65) ys, were randomized to EF or TNI. In the OBS trial 53 pts, median age 70 (64-84) ys, were treated with EF (79%) or IF (21%). In the updated combined analysis of all 255 pts, overall survival is 97%, median observation period of 51 months. Relapse- and progression-free survival are 60% and 59% at five years with a plateau after six years. Complete remissions (CR) were obtained in 92% of all pts. RLS occurred in 24% of all pts, median interval 24 months. In the RD pts, differences in RLS rates and probabilities between treatment arms emerge and the required number for unblinding will shortly be reached.

First RLS sites of all 255 pts were correlated with extent of radiotherapy: RLS developed predominantly as new manifestations (92%, 79% new site alone), more often out-of field (73%), and were in 68% located on the opposing side of the diaphragm. RLS was mostly entirely nodal (76%), rarely bone marrow (8%), or extranodal (10%).

In 65% of all RLS, histology was obtained, revealing transition into secondary diffuse large B-cell lymphoma (DLBCL) in 30% of these pts (19% of all RLS, 5% of all study pts), 15 (7-96) months from diagnosis. Second tumors were observed as solid tumors (n=6), sarcoma and AML (one case each) and possibly MDS (n=2) after 36 (4-119) months.

Conclusions: In early stage nodal FL, standardized RT induced high rates of CR with excellent survival, and relapse is rare beyond six years. However, the predominance of relapse in new and out-of field nodal sites is suggestive of early occult dissemination, warranting consideration in new treatment concepts.

028 TREATMENT OF LIMITED-STAGE DLBCL CAN BE EFFECTIVELY TAILORED USING A PET-BASED APPROACH

L. H. Sehn[1], K. J. Savage[1], P. Hoskins[1], R. Klasa[1], T. Shenkier[1], R. D. Gascoyne[2], T. Pickles[3], J. Morris[3], D. Wilson[4], F. Benard[4], J. M. Connors[1]

[1]Medical Oncology, BC Cancer Agency, Vancouver, Canada, [2]Pathology, BC Cancer Agency, Vancouver, Canada, [3]Radiation Oncology, BC Cancer Agency, Vancouver, Canada, [4]Functional Imaging, BC Cancer Agency, Vancouver, Canada

Background: Since 2005, patients in British Columbia (BC) with limited-stage DLBCL (stage I/II, no B-symptoms, mass < 10cm) have been treated according to a PET-based algorithm. Following 3 cycles of R-CHOP, patients undergo FDG-PET/CT scan; PET-negative patients receive one additional cycle of R-CHOP, while PET-positive patients receive IFRT. We present an update of this ongoing experience.

Patients and Methods: Using the BC Cancer Agency Lymphoid Cancer database we identified all patients with limited-stage DLBCL treated with this PET-based approach between Mar 2005 and June 2010. Patients with primary CNS, primary testicular and transformed lymphoma were excluded. Clinical characteristics of the 134 patients identified are as follows: median age, 64 y (range 22-88); 57%, male; 57%, stage I; 43%, stage II; 3%, PS>1; 11%, elevated LDH; 51%, at least 1 extranodal site; 32%, mass size ≥ 5cm. Stage-modified IPI risk score: 20%, 0; 49%, 1; 23%, 2; 8%, 3-4. Median follow-up is 30 mos (range 3-68).

Results: After 3 cycles of R-CHOP: PET-negative, 103 patients (77%); PET-positive, 30, (22%); PET-indeterminate, 1, (1%). Elevated serum LDH (p=0.02) and mass size ≥ 5cm (p=0.001) were predictive of PET status, whereas stage-adjusted IPI was of borderline significance (p=0.08). Of the 103 PET-negative patients, 100 completed treatment with one additional cycle of R-CHOP, 2 received IFRT due to physician choice and 1 died of toxicity before receiving any more treatment. 7/103 PET-negative patients have relapsed (3 initially localized at original site, 2 local and distant, 2 distant only). 3/7 PET-negative relapses were delayed, occurring between 2.5-4 years post initial diagnosis. 29/30 PET-positive patients received IFRT, 1 patient received 1 additional cycle of R-CHOP alone due to concern about toxicity. 9/30 PET-positive patients have relapsed, all with disease distant from the original site, 1 with follicular lymphoma. The one patient with an indeterminate PET scan completed therapy with IFRT and remains in remission. The 3-year estimated time-to-progression (TTP) is 85% overall (92% and 60% for PET-negative and PET-positive patients, respectively). The 3-year overall survival is 93% overall (96% for PET-negative and 83% for PET-positive patients). On univariate analysis, age, stage, PS, and PET status were significant predictors of TTP. On multivariate analysis controlling for age, stage, PS, LDH, presence of extranodal involvement, mass size ≥ 5cm, and PET status, only age, PS and PET status remained independent predictors of TTP.

Conclusion: The majority of patients with limited-stage DLBCL will be PET-negative after 3 cycles of R-CHOP and have an excellent outcome following abbreviated R-CHOP alone, although delayed relapses have been observed. PET-positive patients who complete therapy with IFRT have a high rate of distant relapse. Alternative approaches may be warranted in this subgroup.

029 6-YEAR FOLLOW-UP OF THE MINT STUDY SUGGESTS A ROLE FOR RADIOTHERAPY TO BULKY DISEASE.

M. Pfreundschuh[1], E. Kuhnt[1], L. Truemper[1], A. Osterborg[1], M. Trneny[1], L. Shepherd[1], D. Gill[1], J. Walewski[1], R. Pettengell[1], U. Jaeger[1], P. L. Zinzani[1], O. Shpilberg[1], S. Grass[1], N. Murawski[1], V. Poeschel[1], M. Loeffler[1]
[1]MabThera International Trial (MInT) Group, Saarland University Medical School, Homburg, Germany

Background: The results of the MInT trial, a randomized comparison of 6 cycles of a CHOP-like regimen with or without rituximab in young good-prognosis patients (aaIPI=0,1; stages II-IV and I with bulky disease) with radiotherapy to sites of initial bulky disease and/or extranodal involvement were published with a median follow-up of 34 months (Lancet Oncol 2006; 379-91).

Methods: Between 05/2000 and 10/2003 823 patients were recruited of whom 396 received CHOP-21, 361 CHOEP-21, 34 MACOP-B, and 32 PMitCEBO with or without rituximab.

Results: Toxicity, incidence of adverse events, severe adverse events and second neoplasms in the CHEMO and the R-CHEMO arms were not significantly different. After a median follow-up of 70 (0.03-117) months, R-CHEMO compared to CHEMO patients had increased 6-year event-free (74.0% vs 55.7%; p<0·0001), progression-free (79.9% vs 63.8%; p<0.001) and overall survival (89.8% vs 80.0%; p=0.001). In a multivariate analysis event-free survival was affected by the addition of rituximab (HR 0.49; p< 0.001), age-adjusted IPI (HR 1.73; p<0.001), and bulky disease (HR 1.43, p=0.004). Similar effects were observed for PFS and OS, dividing R-CHEMO patients into a very favorable (aaIPI=0, no bulky) with a 100% OS after 6xR-CHOP-21 and a less favorable subgroup (aaIPI=1 and/or bulky disease). Outcome of aaIPI=1 patients with 6xR-CHEMO in MInT was similar to R-ACVBP and better than 8xR-CHOP in GELA's LNH03-2B trial (Blood 2010; 116 [21]: abstract #109], where no radiotherapy was given.

Conclusions: Addition of rituximab to a CHOP-like regimen results in a significant improvement of outcome in young patients with good-prognosis diffuse large B-cell lymphoma, with significant survival benefit maintained during a 6-year follow-up. The superiority of 6xR-CHOP-21 in MInT compared to 8xR-CHOP-21 in LNH03-2B suggests that this might be due to radiotherapy to areas with bulky disease, which was given in the MInT, but not in the LNH03-2B trial. While reduction of treatment in a randomized study like the FLYER trial of the DSHNHL is justified for young patients with very favorable DLBCL, further progress, e.g. by dose densification (UNFOLDER trial of the DSHNHL) and/or dose escalation is still warranted for the less favorable subgroup. Comparison of aaIPI=1 patients in MInT and LNH03-2B underlines the need of a randomized trial to define the role of radiotherapy to bulky disease, which is addressed in the ongoing UNFOLDER trial of the DSHNHL. *Supported by Roche, Deutsche Krebshilfe and KML.*

030 ACVBP VERSUS ACVBP PLUS RITUXIMAB FOR YOUNG PATIENTS WITH LOCALIZED LOW-RISK DIFFUSE LARGE B-CELL LYMPHOMA: A STUDY BY THE GROUPE D'ETUDE DES LYMPHOMES DE L'ADULTE

N. Ketterer[1], B. Coiffier[2], C. Thieblemont[3], C. Fermé[4], J. Brière[5], O. Casanovas[6], S. Bologna[7], B. Christian[8], E. Van Den Neste[9], C. Récher[10], D. Bordessoule[11], C. Fruchart[12], M. Fournier[13], H. Tilly[14], C. Haioun[15]
[1]Oncology, CHUV, Lausanne, Switzerland, [2]Hematology, CHLS, Lyon, France, [3]Hematology, Hôpital St Louis, Paris, France, [4]Hematology, IGR, Villejuif, France, [5]Pathologie, Hôpital St Louis, Paris, France, [6]Hematology, CHU, Dijon, France, [7]Hematology, CHU, Vandoeuvre, France, [8]Hematology, Hôpital Bon Secours, Metz, France, [9]Hematology, UCL St Luc, Bruxelles, France, [10]Hematology, CHU, Toulouse, France, [11]Hematology, CHU, Limoges, France, [12]Hematology, Centre François Baclesse, Caen, France, [13]Biostatistics, GELARC, Lyon, France, [14]Hematology, Centre Henri Becquerel, Rouen, France, [15]Hematology, Hôpital Henri Mondor, Créteil, France

Introduction: In a prior study, we demonstrated that ACVBP + consolidation was superior to 3 cycles of CHOP + radiotherapy in young patients (pts) with localized aggressive lymphoma (Reyes F et al. N Engl J Med 2005;352:1197). This randomized trial compared in these pts ACVBP *vs.* ACVBP + a short course of rituximab (R-ACVBP).

Methods: untreated pts between 18 and 65y with stage I/II DLBCL and no adverse prognostic factors according to the aa-IPI were eligible. ACVBP consisted of 3 induction cycles given every 2 weeks: doxorubicin (75 mg/m^2) day 1, cyclophosphamide (1.2g/m^2) day 1, vindesine (2 mg/m^2) day 1 and 5, bleomycin (10 mg) day 1 and 5, prednisone (60 mg/m^2) day 1 to 5 followed by consolidation with metothrexate, ifosfamide, VP-16 and cytarabine. R-ACVBP consisted of the same regimen combined with 4 doses of rituximab (375 mg/m^2) on day 1, 15, 29 and 43. Primary objective was EFS.

Results: From 01/04 to 03/08, 223 pts were randomized, 113 in ACVBP and 110 in R-ACVBP arm. Characteristics were: median age 49y (18-65), stage I 63%, extranodal involvement 45%, bulky disease 4%. CR was 94% in ACVBP and 97% in ACVBP arm (*ns*). With a median follow-up of 43 months, the 3-y EFS was 82% (95% CI, 73% to 88%) in ACVBP and 93% (95% CI, 87% to 97%) in R-ACVBP group (*P*=0.0487). The 3-y PFS was 83% (95% CI, 74% to 89%) and 95% (95% CI, 89% to 98%) respectively (*P*=0.0205). OS did not significantly differ with a 3-y estimates of 97% (95% CI, 90% to 99%) for ACVBP and 98% (95% CI, 92% to 100%) for R-ACVBP (*P*=0.686). In multivariate analysis, a longer PFS was associated with R-ACVBP arm (*P*=0.0302) and lower β2-m level (*P*=0.0164). The same proportion of pts (27%) experienced at least 1 SAE in both groups. There were 4 deaths in each arm, with 1 treatment-related death in R-ACVBP (*pneumocystis jiroveci* pneumonia).

Conclusion: the addition of only 4 doses of rituximab to ACVBP significantly improves EFS and PFS in younger pts with low-risk localized DLBCL.