ASH Summaries – 2010

After some positive feedback last year, I will again put my ASH summary notes on the Anglia Cancer Network website. Please remember these are my own summaries, and often my interpretations of data. They must not be taken as a definitive account of ASH – I am sure I will have missed some things and misinterpreted others. I have decided to stick to areas where I feel I have more expertise, so I am only putting lymphoma / CLL notes on the website and I am keeping my AML / ALL / MDS notes to myself!

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High Grade NHL

1. GELA – ACVBP + HD MTX vs R-CHOP21. aaIPI 1 <60 (quite tight). No RT. 380patients – 73 centres ORR similar around 90%, but EFS at 3 y = 81% vs 67% → OS 92% vs 84% at 3 years. Death no progression = 7 in each arm. Progressions 21 vs 44. Toxicity was higher as expected in exp arm, but toxic death 5 vs 3. 2 x CNS relapse in R-CHOP (2/?120) – none in expt. arm.

Very interesting data, but Pfreunschuh pointed out that control arm not good. ? reflects RT plan??

2. Pfeundschuh – 6 year f-up of MiNT. Large trial. aaIPI 0-1. 6 x cycles. Without R, CHOEP was best chemo. With R- all v. Similar (apart from PMitcebo – numbers small, but signif. Worse). All comers, OS at 6 years 89% with rituximab vs 80%. Note – they used RT for initial bulk. Multivariate – bulky, IPI, no R = worse. If take IPI 0 with no bulk – 90% EFS at 6 years with 100% OS at 6 years. (FLYER – currently looking at 4 vs 6 cycle qu. (All get 6 R) – so far 200 pt interim. 2 y EFS = 98% with OS = 99.5% (1 x swine flu death).

Then compared 411 R-CHOP pt from Mint with aaIPI1 (some had bulky – excluded from GELA) and compared with GELA and showed at 3 year comparison, EFS, PFS and OS with MINT = to R-ABCVP. ? why GELA R-CHOP did relatively badly? No defence from GELA!!

3. Schmidt – another analysis of CNS risk from 6 German trials (2,200 patients). Id 56 Relapse median at 7 months but v. Wide range. With R-chemo – risk increases with aaIPI 0,1 = 0.5%,

2 = 4% and 3 = 10%. Also found LDH a RF in multivariate. No discussion of previous risk groups identified from RICOVER 60 trial, but obviously significant overlap with IPI. Overall, the incidence in these 2,200 German patients (56 / 2200, i.e.2.5 % overall) was similar to some datasets at ASH (NCCN incidence around 3%), but MUCH lower than other datasets presented at ASH (e.g. Japanese data approx 8%, (no IT was used)) . Could the 14 day cycles of chemo have a lower CNS incidence?? Could the IT use that was used in some patients (and high dose therapy in some MEGACHOEP patients) have reduced the overall incidence???). Claims no risk association with specific extranodal sites (not consistent with other ASH data). Note, the current protocol for the next German trial includes 4 x IT MTX and ivHDMTX for highest risk groups (given pre 1st R-CHOP and post completion of R-CHOP).

4. BC data using gem/cis at relapse for DLBL and HL. Retrospective database. Using since 2002– 152 DLBL and 83 HL. Rather poor presentation with little split on R vs no R. ? how many R with salvage? Also no data on ITT with no plan for salvage (who could get up to 6 cycles). For whole cohort, 38% had auto, 6% allo. 2y OS 28% for no transplant vs 47% for transplant (was this ITT?). BUT key fact – if primary refractory (? How did they define exactly) – 2 year OS = 2%!

HL data much better with 2 year OS for whole cohort = 85%. Ongoing trial of R-DHAP vs R/gem/cis.

5. Coiffier – Romidopsin – licence for cutaneous T-cell – 130 patients use for all comers relapsed T cell.iv on D1, 8, 15 4 weekly cycle. Can carry on (1 patient 3 years on therapy). ORR 40%, CR 15%.

6. Looking at predictive power of PET2 and PET4 using a new method looking at SUVmax reduction (66% and 70%). GELA trial patients (aaIPI2,3). Using standard IHP method, still had significant no. of PET2 and PET4 that were + that had good PFS like neg. However, if used SUV max reduction – PET2 + and PET4+ both very predictive of PFS and OS , - far fewer patients called as +ve. Argument as to why need pre-treatment PET.

7. Anthracycline resistance in DLBL. SNP assessment of genes in oxidative stress pathway in 330 patients in SWOG trials. Very interesting – MPO (key generator of ROS) and aldoketase reductase (AKAIC3) (metabolises doxorubicin to inactive doxorubicinol) found to have SNP that have poor OS – i.e. don't generate enough ROS, or break down doxo too efficiently. A lot of validation work still required, but good to remember that non-tumour aspects of host biology also have a role in outcome.

8. Anaplastic large cell. From 3 GELA trials, i.d. 64 ALK+ and 74 ALK-. Much comparative analysis between groups, but bottom line is NOT ALK that is critical, but age and B2M are key determinants of outcome. Age>40 and B2M>3 = poor outcome. Beware making autograft decisions based on ALK!

9. miRNA risk score in DLBL. This is certainly an interesting novel area, but early days. Did miRNA array and correl with outcome with 7 relapse and 8 long CR. ID 59 discriminatory miRNA and reduced to 29. Then test set of 40 patients. If combine with IPI – very predictive. However, need much bigger validation.

10. Long term f-up of original Intergroup R-CHOP / CHOP trial. Numbers in each arm are small (90), but overall, longer term f-up does NOT support maintenance R in DLBL if R given with chemo. No apparent benefit for R in low risk (contrasts with MinT which was much bigger). Ongoing fall off the OS curve with 9 y OS of R-CHOP = 44% (60% of all relapses occurred within 2 years. Later deaths due to many things – I saw Coiffier present something similar with the long term follow up of the 1st R-CHOP GELA trial – don't see a real survival plateau, but constant gradual fall off)

11. SWOG bexxar trial in DLBL. Give after 6 x R_CHOP then 2 CHOP. Overall results not really better than would expect. ? if being pursued anymore in high grade?

12. SWOG R-CHOP + avastin. 5% early deaths 2/73 sudden. 5/73 = GI perforation. 5 / 73 = VTE. 3/73 = SVT. 18% had fall in EF. Overall poor results and abandoned. (note side study looking at urine VGEF – appeared to predict worse OS independent of IPI). Relief that we decided not to join a similar study in the UK (the early phase data with avastin in DLBL was very poor!)

13. EBV surveillance post solid organ transplant. Paris data. Very interesting – In 2004 put in surveillance EBV PCR every month post cardiac transplant. $<10^5$, observe. 10^5-10^6 – reduce IS If stays + then 1 x ritux., $>10^6$ – reduce IS and give ritux. X 1 dose. 37 reactivations 32 patients RIS→4 got ritux. 5 patients straight to ritux. In this period they have only had one PTLD and that patient left the region and was not having f-up EBV PCR. In same previous period saw 13 PTLD (1.8/year). (note 6/6 patients transplanted when EBV IgGneg seroconverted). Cardiac rejection data looks OK.

14. GELA phase II R-mini CHOP x 6 in the >80. Cyclo 400mg / m2, doxo 25mg/m2, vinc 1mg cap and pred 40mg/m2. Well tolerated. ORR 75% with 40% CR. Cause of death, 6% with PD. 2 year OS = 58%. Median 4 nights in hospital. Not all had G-CSF. DFS = 56%, i.e PD / relapse = fatal.

15. BC group – RT to PET+ LN at end of therapy. Id 196 pt from database treated with R-CHOP 6 to 8 (all stages, but 61% stage ¾). Good mix of poor prog patients (40+% bulky>10cm). If residual disease at end of Rx → PET scan. RT (30 to 40Gy) to PET +. Overall, 121pt pet neg, 8 indeterminate and 66 Pet + (average SUV = 3.5). Of the 66, 51/66 received RT (all but 5 patients = single field). OS for PET + RT v.similar to PET neg. (3 y OS 77% - 84%) but PFS 80 – 84% vs 42% for pet + no RT. NOT given diffs in OS between pet + groups. And not given % that went pet negative after RT. This practice is appealing, as options so limited for more frail non-transplantable patients, but unclear how we would use this with younger patients.

16. MSK PMLCL. Use an R-CHOP → ICE protocol with no RT. 3 year PFS of 78% and 3 year OS of 88% (n=54). These figures appear worse than NIH data (EPOCH) from Lugano, but still not seen that published. Of the 11 that relapsed, 6 / 11 died. Interim PET NOT predictive of relapse in their experience.

17. SGN35 – phase 2 in ALCL. Neuropathy. Iv (30 minutes) every 3 weeks up to 16 cycles. 58 pt with relapsed ALC NHL. 87% ORR. Of first 30 patients analysed, 17/30 = CR! Remarkable data for a very promising drug.

18. CORAL data trying to look at results by subgroup of DLBL pathology and treatment. Overall cohort, little between DHAP and ICE BUT if look at GC PFS 64% vs 42% (was significant, i.e. R-DHAP appeared better) compared with non-GC (35% vs 45% not significant).

POSTERS

1. Japanese study looking at CNS relapse with DLBL. Excluded any patient that had any CNS prophylaxis. 1492 patients treated with R-chemo and NO IT / CNS MTX from 2003 to 2006 at 48 hospitals. 1099 pt had 6-8 cycles, therefore assume wide range of stage and IPI (no details). 1221 treated with R-CHOP. Overall cumulative 5 year CNS risk was 8.4% (6.3% in whole cohort in written abstract). Looked at RR for different sites and found breast (RR x10), adrenal, bone (paranasal and peritoneum RR=2 but p=0.09).

2. Japanese look at hepB reactivation. Found 51 hepB + with R-CHOP. 6/51 reactivated. No prophylaxis, but followed hepB PCR and treated with entecavir when +. All 6 became PCR negative within 3 weeks.

3. Relapsed / refractory DLBL with ofatumumab. Ineligible for auto, or post auto. ORR=11%. 81 patients. 4/81 = CR. Poor data, but alot to expect from a monotherapy antibody. The GA101 data looks a little better perhaps, with responses in the 20%+ range as monotherapy (GA101 has less clear dose-response relationship in high grade compared with low grade)

4. ATLL – UK experience. 84 cases. Overall do BETTER if also use antivirals (not randomised)

5. BC group looking at prognosis of refractory / early relapse DLBL in the R-CHOP era. From 1126 <70 treated with R-CHOP, they found 73 patients (i.e. around 7%). 33 = true primary refract and 40 who after initial PR/CR relapsed within 3 months. Of the 73, 36/73 made decision for palliation only. Of 37 treated with full intent, 10 got to transplant with 3/10 alive > 1 year. Of 27 who failed to get to transplant, 3/27 alive >1 year. OVERALL, of 33 primary refractory, only 1/33 alive > 1 year. And 5 /40 early relapse alive > 1year.

6. Miami group managing PTLD post liver transplant. Monoclonal DLBL, Pre-2006 they had a mixed approach of RIS +/- rituximab. Of 6 patients, only 1 survivor beyond 3 years. After 2006 they went straight to R-Chemo. Since adopting that policy, 10/10 have survived. PFS also markedly different between the cohorts. Small numbers, but ?liver PTLD needs this more aggressive treatment from the outset???

7. Pralatrexate for relapsed PTCL. Do see responses and small numbers of CR. May allow transplant.

8. CNS prophylaxis in DLBL from NCCN sites. Wide variation. Of 989 patients, 117 received CNS prophylaxis. Looked at % chance depending on 'reason'. 36% with high risk site (testes, bone, paranasal, orbit, blood etc.) received prophylaxis. Of all prophylaxis given 30% patients had HDMTX. No clear consistency of reasons behind HDMTX, but clear centre bias. Of 617 patients with 1+ high risk feature, CNS relapse = 20 cases, i.e. around 3%. No clear evidence that receipt of prophylaxis was protective (figures not given).

9. Italian look at frail elderly DLBL. Overall, 28% 5 year OS and in multivariate analysis, key determinant are 1. If rituximab was included in thx, 2. High IPI, 3. Bad PF, 4. Respiratory co-morbidity

10. Roswell Park compared outcomes of MCL with blastoid MCL treated with R-CHOP or R-hyperCVAD approaches + autograft. Paired 30 patients with each other. Clearly blastoid much shorter PFS and OS (19 months vs 57 months)

11. Monash CNS lymphoma. Compared +/- RT and showed very similar data to Addenbrookes. OS same, but early PFS much better if RT (49% vs 12% at ?2years). In patients who had RT, no relapse beyond 2.7 years.

12. Nashville – Another frail elderly DLBL study. Showed that if can get doxorubicin >30mg / m2 / cycle = marker of ORR and PFS (similar to younger cohort). Compared with younger, much more likely to be admitted (54% vs 34%) at least once. Also 73% dose reduction on standard R-CHOP compared with 18% of younger.

13. Rasburicase in lymphoma. (Chicago) Showed a single 4.5mg dose achieved rapid complete reduction in urate in 28/30 patients. Other 2 achieved with repeat dosing.

14. Italian CNS. Attempt to add alkylator (thiotepa) to HDMTX / cytarabine protocol, but to balance, reduced cytarabine to 1g / m2 D2 and D3. Results from 1st 20 patients very much worse than trial CR / PFS and OS ALL about ½ of what expected. Conclusion – cytarabine very important and dose below 2g could be ineffective.

15. MDACC compared burkitts treated with R-hyperCVAD with previous cohort with only hyperCVAD And no rituximab. 5 year OS 75% vs 50%. OF 56 patients, 3/56 relapse, 9/56 died in CR, 4/56 tMN (3, 3.5, 3.5, 7 years post). Now using R-hypercvad for high risk DLBL. 1st 45 patients, 2 year OS = 78%)

16. Korean study looking at Breast lymphoma. Identified 25 cases. Found higher chance of relapse at extranodal or CNS site compared with matched nodal cases. Unsure about the validity of this study.

17. HIV lymphoma consortium looking at DLBL in HIV. Pooled data from 2 trials comparing R-CHOP vs CHOP, then R-EPOCH strategies. If just compare R-CHOP (n=100) with R-DA-EPOCH (n=50) the results appear strikingly better for R-DA-EPOCH with 2 year OS 87% vs 66% in low IPI and 62% vs 36% in high IPI. There is an on-going head-to-head trial in immune-compromised DLBL. Will this data translate to immunocompetent population. Could have huge resource implication. Our experience with EPOCH is that is relatively easy to deliver, but 5 days inpatient stay + line access etc....

18. Interstitial pneumonia in DLBL. Large Taiwan cohort. Est incidence 5%. Risk = lymphocytes <1 and use of rituximab. (? Role for septrin prophylaxis in spec cohorts?)

19. BC study of DLBL pathology. Comparison of c-myc expression in immunohistochemistry and genetics / gene expression profiling. Find c-myc translocations in 10% of patients. NO

correlation with Ki-67.Of 18 translocation patient, 13/18 had high myc protein detectable by immunohistochemistry. High BCL2 protein and high C-MYC = bad.

20. DLBL of stomach. Japanese study looking at outcomes with 6xR-CHOP vs 3 x R-CHOP+IFRT vs surgical approaches. No evidence that need surgery or RT.

21. Spanish PET with R-CHOP-14. Again reinforces that ½ patients PET negative after 2 cycles and very strong NPV (94%). Again stress, early + in DLBL = 50%, and 2/3 of these will be PET NEG by the end. EFS of entire pet neg cohort = 95% compared with 40% if pet+ at the end (worth remembering that a reasonable number of pet + at the end of treatment will not relapse).

22. GOELEMS relapse schedule (R-vinorelbine / ifos / mitox / pred). N= 50. Treating patients who had relapsed from at least a PR that lasted at least 30 days, claim ORR 66% and 43% CR). 11 went to autograft and 11 had additional 3 cycles consolidation . PFS better with more treatment (either auto OR extra cycles of salvage) BUT if could get to auto, then better than 3 x extra cycles.

23. CNS prophylaxis. Cleveland clinic identified 121 patients that had received IT MTX from 1998 to 2008. Then id 73 patients that met inclusion criteria (high risk for anatomical reasons) and had all received IT MTX as part of first line. Median = 3 injections (1-6). 5/73 had CNS relapse (3x lepto and 2 x parenchymal). Median = 18 months post (6-43) diagnosis. 2/5 had renal involvement at dx. (2/68 non-CNS relapse). The authors feel this supports the use of IT MTX. ? does IT therapy affect the time of CNS relapse?? In this study with IT MTX, NO CNS relapse before 6 months (contrast Nordic study with HD MTX / ara-C and no IT MTX, ALL CNS relapses within 6 months).

24. Nordic aaIPI 2,3 R-CHOEP-14 x6→1x HDara-C→1xHDMTX. Poor prognostic groups with many high risk CNS features. N=156. 3 year OS = 80%. 7/156 = CNS relapse (i.e. around 5%). ALL CNS relapse within 6 months of diagnosis. Authors conclude CNS relapse rate was LOW considering the population but think high frequency of early relapses reflects lack of EARLY CNS prophylaxis.

25. Korean PET in T cell NHL – interim pet negative also very strong NPV

26. Fully resected DLBL – Koreans identified 18 patients treated with R-CHOP x 3 (16) and x4(2) with no RT. Median f-up 27 months, but so far 100% DFS and OS. Small numbers and short follow-up but encouraging.

27. CMC-544 + rituxmiab. Note, very encouraging results in relapsed indolent NOT seen in relapsed DLBL, where ORR = 15% with 2/34 = PR and 2/34 = CR.

28. DUTCH – Looking at EATL and risk profiles (n=41). Find LDH / B sympt / secondary subtypes. Create split low and high risk. Low risk – numbers small but OS around 30% long term. High risk, median OS = 2-3 months with no survivors beyond 18 months.

29. Pulmonary CT abnormalities – as high as 24% of patients on R-CHOP. Approx 5% develop symptomatic interstitial pneumomnitis. ? how many infective (PCP) vs rituximab effect? The incidence was <1% in pre-rituximab era.

30. Flu vaccine efficacy in patients with active haem malignancy. Overall meaningful responses are relatively uncommon (around 20% of patients vaccinated)

31. Comparison of flow vs morphology for lymphoid CNS disease (Ontario). 5 colour flow. From 609 cases, 24 + by morphology and 47+ by flow. No samples were morphology +, but flow negative. Therefore conclude that 5 colour flow approx doubles the chance of detecting clonal cells in CSF. (? Do these low levels of cells have the same clinical impact as morphology + ---No clinical correlative data given)

LOW GRADE NHL

1. European Mantle Cell. 500 patient trial. R-CHOP vs R-CHOP / R-DHAP alternating. Both x 6 then autograft. Note different conditioning. ORR both around 90% but CR 40% vs 55% with cytarabine. Both arms around 78% had auto. With 97% CR post auto BUT EFS post auto separates by pre-auto chemo arm (median = 49 months vs not reached). Relapse = 49 vs 22 patients. Key is state of remission going into auto, with PR R-CHOP = worse. OS same between arms with median 33 months follow-up. (note MRD data – elsewhere but much better post cytarabine).

2. MRD talk from same European Mantle cell. Much higher MRD neg in cytarabine arms at every stage, but after auotgraft CHOP arm increases much more. After auto, MRD neg 88% vs 65%. MRD neg at any stage is clearest separator of PFS. If MRD neg for whole year after autograft, 94% chance of remaining in CR with MRD negative for next year.

3. Great mantel cell latency paper. Female patient CML allo in 1996 developed male mantle cell NHL recently. Contacted donor and found they had developed MC within 2 weeks of recipient!! ID 7 patients from records with MCL who had had prior surgery > 2 years pre and went to old pathology (e.g. LN taken at time of prostate surgery) in each case found 'in situe' MCL (up to 13 years pre from breast tissue) that was t(11;14).

4. Galituximab. I think this Ab will struggle. Anti-CD80. First randomised double antibody trial (R+placebo vs R+Gal) for relapsed non-ritux refractory FL. Stopped trial at 337 patients as recruitment failing. ORR abd OFS a little bette (? Stats) trend towards OS benefit...

5. Vaccination in FL – maybe it is back on the agenda! Construct anti-idiotype vaccine with fused hybridoma approach. Randomised trial in patients responding to first chemo. Found if FL is IgM, then appears to benefit in PFS 53 months vs 28 months p=0.001. IgG don't benefit over control

6. CMC-544. This is anti-CD22-calicheamicin (Pfizer). This looks very interesting! Phase II. Relapsed indolent. 76% R-refract. 2+ prior thx. 53 patients (45 FL) iv infusion every 4 weeks. Median = 2 cycles (1-8). 45% gd ¾ low plt. Plt recover. FL – 60% ORR, 22% CR. Of 21 FL

beyond a year, only 4/21 relapsed / progressed. FLIPI seems very predictive. ? what the current trials are with this drug.

7. R-CHOP 14 vs R-CHOP 21 in Indolent lymphoma (Japanese). No difference, apart from higher peripheral neuropathy in 14 day cycle.

8. Zevelin first line (German multi-centre). FL 59 patients. Excluded BM >25% and LN > 10cm. Overall the data did not seem as good as Bexxar. Toxicity OK and ORR 83%, but PFS of 25 months. Higher FLIPI seemed to do worse. Presenter feels this still should be an option for some. Note all patients treated within 3 months of Dx. Bexxar patients had to be stable for 12 months prior to thx. ? Bexxar pt were biologically better patients?

9. Hagenbeek – FIT update. 66 months median f-up. Overall curves are still well separated. No diffs in initial rituximab treated patients. Note 6 tMN vs 1 in control and 16 2nd cancers vs 9. Both not quite significant.

10. PET in a small number of paired FL patients in PRIMA. Looks like if have PET avid disease, then remaining pet + at the end of therapy is strongly predictive of relapse. No breakdown yet in maintenance arm, so uncertain whether rituximab in any way protective.

11. Relapsed indolent (StIL group) looking at BR vs FR (note 90mg/m2 D1/2 / 4 weekly schedule). 219 patients. Post 2006, R maint added to both arms. Very clear benefit in ORR (83% vs 52%), CR (38% vs 16%) and PFS (30 months vs 11 months). OS not yet different. R maint also appears to favour ritux maint subset (both OS and PFS with very good P value) but dataset small.

12. Coiffier – relapsed follicular (still R-sens): R vs R + bortezomib. Small improvement in PFS. Not very convincing benefit for bortezomib in this cohort

POSTERS

1. Italian Hairy cell – 95% get CR / PR. Predictor of response (wcc, spleen, unmutated), but once obtain remission, in multivariate, only remission status correlate with PFS. Different 2CDA schedules - no difference between them in results.

2. Weill-Cornell Hairy Cell. If look with flow, find other LPD 12/115. 8/12 = other LPD, 4/12 = plasma cell neoplasm.

3. Relapsed HCL – combine oral F with rituximab. 13 patients. Aim 4- 6 cycles. 2 year PFS = 92% with 2 year OS = 100%.

4. Combination of rituximab + epratuzumab – anti CD22. In treated FL. ORR 84% with CR in 1/3.Small numbers but looks interesting.

5. Extreanodal MALT CBL vs CBL + rituximab. 113pt in each arm. 5 year EFS = 68% vs 50% but both arms 5 year OS = 88%.

6. Italian R+CBL vs CBL+pred for untreated FL. CBL dosing schedule different from UK, but reasonable doses. As expect, all parameters better for R+CBL.

7. Long term f-up of bexxar monotherapy for relapsed / refractory indolent AND transformed NHL. 60 patients treated 1996 to 1998 – i.e. very long follow up. 4 MDS (all fairly early), 7 hypothyroidism, 9 cancers (7 were skin). 12 CR and of these 5 / 12 = still in CR, i.e 10% long term CR from one treatment. 12 patients (20%) still alive >10 years post (for a relapsed / transformed cohort, this seems impressive).

8. Weill-Cornell. 1st line fludarabine x 3 then bexxar (FL). 38 pt with 50% in ongoing CR > 10 years.

9. MAG with waldenstroms. Look back at 61 French patients treated with either CBL or rituximab. Conclude R has much higher chance of MAG symptoms improving and much lower relapse.

10. Pabinostat in relapsed / refract Waldenstroms. Ongoing ph2. 27 patients enrolled. ORR 60%

11. French single institution MCL using cytarabine for 10 years. Fit= R-DHAP→auto. Less fit R-CVP+ cytarabine, frail = s/c cytarabine. Numbers small (54), but with fit cohort. Best figures if get the autograft. In the >65, PFS and OS better in s/c cytarabine group!! (27 vs 17 months and 37 vs 29 months) BUT only 14 vs 6 patients.

12. Frech FCR for Waldenstroms. 1st line 15 pt and 2nd line 40 patients. Overall ORR 90% (may be delayed). 2/55 tMN and 2/55 transformation to HG NHL. Cytopenias a significant issue in 10/55

13. French Mantle cell phase II using 4 x R-DHAP then R-BEAM. Data looks good. Supports the notion for trial of anthracyline-free strategy.

14. Grade IIIa FL in USA. Identified 300+ cases from multi-institution study. 48 W+W, 30 R-CVP and 245 R-CHOP. No apparent PFS difference between R-CVP and R-CHOP although clinicians are clearly favouring R-CHOP over CVP / W+W strategy.

15. PRIMA update. 3 year PFS now 78% vs 60%. By end of 2 years, 1/3 of no-Ritux and ½ of ritux groups convert PR to CR. After 2 years, CR = 75% vs 55%. Multivariate = age, FLIPI, R-CVP and no rituximab = RF for early progression.

16. SAKK – ongoing R-maint to 5 years. Interim analysis for safety – nothing to report.

17. BC – in 2006 adopted R-CVP→R for follicular. Data almost identical to PRIMA. Comparing 3 year PFS with historical 83% vs 62% with OS 93% in both time periods at 3 years

18. Using bortezomib in multiply relapsed NHL – remember VZV / HSV prophylaxis

19. Israeli meta-analysis of antracyclines in FL. Overall, they conclude appear to improve response and PFS, but no clear evidence that first line use improves OS.

20. Rituximab in Castlemans – early use appears to dramatically reduce the chance of developing NHL (300 fold!)

21. HepC and low grade lymphoma. Treatment with anti-virals can have a sustained response to viral load and lymphoma. Claim 9/13 pt treated with ribavirin and peg-interferon has CR / PR.

22. French group looking at Hep C and low and high grade NHL. They conclude that high grade should get R-CHOP and then anti-virals. Low grade should have trial of antivirals +/- rituximab.

23. Second cancers after benadmustine (amalgamation of German trials). Rates look similar to other chemo. 0.5% tMN, 7% solid organ GI / GU / skin / lung.

24. Spanish – looked at large FL data set in rituximab era with FLIPI2. Found spread from diagnosis of 5 year OS 94% vs 84% vs 64%. Useful as this is fairly up to date survival info in the R-era.

CLL

Education

RR 5-7.5 if 1st degree relative. Linkage to 2q21 but no gene as yet identified. Probably large number of SNPs that each contribute small relative risk. Acquired genetic factors. 13q much more than just miR16 etc. 14% of 13q delete RB locus →poor outcome. TP53 gene. Note mutation may not assoc with deletion in all cases, but can act as dominant NEGATIVE by virtue of protein function.

BCR – increasingly realising that restricted sets dominate. E.g.1-69 and 4-34. When map aa sequence of CDR3, even finding identical sequences between different patients. Strongly suggestive of Ag drive in CLL - ? unmutated – polyreactive Ag, vs mutated for more targeted Ag.

Tumour microenvironment highly supportive of CLL cells. Can demonstrate in co-culture assays. Also concept of 'nurse-like cells' – theory behind using plerixifor + Rituximab.

Younger patients with CLL. Of 15,490 cases dx in USA in 2009, 11% were <55. Mayo data base of 593 pt <55, found 10 year OS = 60% vs 98% for age-matched controls. Younger patients travel more, and more likely to go into tertiary centres and trials. Of MDACC 3744 CLL patients from 1970 to 2009, 37% were <55. Median age of the combined 6 largest immunochemo trials was 60. In the MDACC FCR trial, 112 pt were <55, with ORR 96% and 5 year OS = 87%. Median time to treatment failure = 7.5 years! CLL8 data strongly supports MRD as predictor of remission duration.

Consolidation options R / alemtuz / lenalid / allograft / nothing!

Relapse disease. Blood in press – FCR at relapse. Median PFS 21 months. 3rd line much less with ORR = 17%. Probably supports FCR as 2nd line but no further (need to see this paper). Need much more attention to anti-microbial prophylaxis at relapse.

Allografting – range of published protocols. Most indications are 2nd remission apart from 17p del / mutation.

2nd maliganancies – tMN post F/FC/FCR (MDACC 2.8%, Australian 6%, Intergroup 4.7%). Second cancer risk RR=2.2

Prognostic markers – 38 abstracts at ASH. Of course the dominant ones are response to therapy, as MRD negative post 1st line therapy appear to dominate other prognostic markers. However, if alternative treatment options are available from the beginning, need an assessment panel pre-treatment. Much debate about the usual ones. Not much to change standard practice yet.

1. Pete Hillmen presented the UK ritux-CBL Phase II. Well tolerated. ORR 80% with CR 12%. No marrow MRD neg. Note, no CR in 11q. Median PFS = 24 months vs 18 months from historical control CLL4.

2. German relapsed CLL F vs F-campath. 335 patients, but only 15% prior fludarabine, so this is similar to REACH trial. Overall F-campath better on all measures, esp Rai ¾. Toxicity OK and not really different, but I don't think there is a place for this data in today's algorithm

3. German CLL 2O for refractory CLL / 17p deleted 1st line or relapse. Good trial. 101 patients. All s/c campath as per UK. Use dex 40mg OD days 1-4 and 15-18. Standard prophylaxis. Restage every 4 weeks up to 3 blocks. If PR / CR can either allo or maint campath 1 dose / 14 days (physician / patient choice). Very poor patients. 85% F refract post F/R. ½ of F-refractory were 17 deleted (i.e. over 80% of the whole trial). Overall CR / PR rates look v. Good compared with REACH 17p del or CLL8 17p del. OS of F-refrac = 6 months. 17p first line much better. 23 patients → maintenance (4 – 82 weeks). Only 4 SAE on maint (i.e. they happen in first 12 weeks). 9/23 PD → 5 deaths (4/5 after attempted allo in relapse).

4. Ofatumumab in relapse (FA refract / Frefrac + bulky). Overall little new data here. Very difficult patients. OS 17 months (BF) vs 14 months (FA refract)

5. UK campath trial in F-refractory →s/c campath up to max respone (1.6 -24 weeks). Median = 18 weeks. 50% ORR (24/49). Now > 5 years median f=up. PFS around 13 months, median OS = 20 months with 5 year OS = 22%. Not too bad compared with other datasets. Key predictor of long term OS is remission status CR MRDneg > CR> PR etc. CR = median 63 months OS.

6. MDACC OFAR1/2 for relapsed CLL and Richters. I thought this was a poor presentation with big conclusions from small patient numbers. One interesting observation was that IF get PR / CR AND fit enough for allo, then 14/14 alive with median f-up 13 months. If allo in refractory disease, 5/8 died.

7. Long term f-up of US Intergroup trial F vs FC for tMN. Overall, 13 cases. Median 5 years (0.7 – 8 years). 10/12 analysed had v. Typical cytogenetics for tMN. To correct for death, they calculated cumulative incidence at 7 years = 8.2% (FC) vs 4.6% (F). NOT statistically significant difference – roughly in line with other data sets, probably around 5-7% by 7 years.

POSTERS

1. Barcelona AIHA – records of 960 CLL pt. 7% AIHA (correl with higher wcc, shorter LDT etc.) No clear association with survival (cf some other data). Not apparently assoc. With any spec. Therapy. OS C immune = 7.4 years, OS C (infiltration) = 3.7 years.

2. Italian stage 0 CLL looked IgH chain usage - V1-69 = most (90% unmutated) and 1/3 of all unmutated are Vh1-69. Looking at HCDR – identify benign patterns

3. Lenalidomide in CLL. Pan Europena phase I. Started at 2.5mg increasing to 25mg. (mix of relapse patients). 5/50 flare reaction. 2/50 laboratory TLS. ORR LOW (PR 12%) - ? reflect dose?

4. MDACC ritux + lenalidomide at relapse. N=59. ORR 64%, but 9% CR. 60% neutropenia and 1/3 gd ¾ infection.

5. Italian phI relapsed CLL: FC + lenalidomide 2.5mg. Well tolerated (small numbers), but 6/9 responses and 3/9 = CR

6. Remission Lenalidomide as maintenance. Mayo clinic 44 pt. 5mg / day then escalate. Median f-up 16 months. Only 34 analysable – 4/34 improved, 3/34 PD. All very early.

7. Austrian FCR x3 →FR x 3→ if PR / CR → R maint. Data looks reasonable. ORR 87%, with CR / Cru = 67%. 80% completed 6 cycles. If get CR, 91% PFS at 3 years. All that started maint, PFS 77% at 3 years.

8. Flavoperidol. Note median PFS in difficult population 8 months.

9. Dana Farba looking at ritux + campath. LN not respond, but ½ cleared BM. 10/28 →allo

10. Spanish FCMR + R maint. 45% MRD negative B4 R-maint. 5/24 that were + → MRD –ve after rituximab. Another separate poster showed similar results: After FCMR, 37 completed 1st year of maint. 24/37 = MRD neg pre and post. 1/37 mrd neg became pos. After R maint. Another 8 started CT neg, MRD +, and 3 / 8 became MRD negative after 1 year rituximab. Conclusion is R-maint might keep CLL in remission, and convert a small % of MRD+ to MRD- over time.

11. NIH Bethesda. Relapsed CLL. 31pt with lenalidomide. 5 / 31 = PR (4/5 = 17p del). 18/31 = SD. PFS SD patients = 6 months. PFS of the responders = 16months, but TTNT = 17 months. As soon as stopped – relapsed.

12. Italian FC + campath at relapse. Poor risk group, but ORR 67%. 13/43 = CR and 6/43 = MRD negative. Of responders, 8/29 died mostly of PD soon after stopping.

13. REACH – MRD data – very similar to CLL8. Data incomplete, but MRD neg correl with much longer PFS. Mostly blood and BM concordant.

14. CBL + GA101 – 1st 6 patients on run in trial. Very rapid clearance of CLL cells from PB. Note neutropenia in 3/6 caused delays to next cycles.

15. Forodesine – novel nucleoside analogue that is not phosphorylated – not incorporated into DNA. Accumulates deoxyGTP → toxic. Oral. Well tolerated. 3/20 =PR

16. Monocolonal FLC → amount is prognostic for TTfirst treatment. Italian study said the same with total (polyclonal).

17. Richters – Italian. Of 18 cases, 7/18 not clonally related. 11/18 – can track evolution within the clone. Pick up other chromosomal abnormalities.

18. Looking at OS of different patients in CLL8. 11% of patients in the trial relapsed within 6 months of therapy (or primary refractory) (median OS = 22 months from study entry). 6% relapsed 6-12 months (median OS – 21 (?this figure) months). 14% relapsed 12 – 24 months post (OS = 48 months). Relapse >24 months median OS not reached. i.e. true overall survival strongly correlates with PFS in this study.

19. Family with medelian inheritance of CLL. Found amplification of 6p (IRF4)

20. Long term follow-up of Benda vs CBL. Looks encouraging, with lines staying separated. No diffs in OS yet.

21. IgH translocations in CLL – up to 26% of patients (I'm sure Peter Campbell didn't find this many!). ? correl with worse OS in 13q deleted group?

22. Plerixiflor + rituximab in CLL – aim to separate from nurse like cells that nurture CLL!

23. French AIHA – use RCD protocol. Given every 2 weeks. Or altered doses every 4 weeks. Aim 3-6 cycles and claim CRs 80+% for AIHA and ITP in CLL patients.

24. ABT 263 – now have oral preparation, combining with FCR or BR on a rather complex schedule. All relapsed patients. Data looks good. BR=12. 3/12 = PR, 4/12 = CR. 3 →allo. 2patients on FCR – both off study (no details)

25. Czech FCR light. Data looks OK. N-102. CR = 35% ORR 70%.

26. Elderly CLL in Italian study. CBL + ritux. Dosing different from UK, but overall results look fairly similar.

27. 13q deletion- size important – if delete RB1= worse. Also worse with higher % cells deleted. Also appears worse if 13q combined with other FISH abnormalities.

28. Study of seroconversion rates after influenza vaccine. Untreated stage A0 CLL, approx 50% seroconvert (normal population 88%). Overall rate and quality is lower. ? support the practice of double immunisation (no data given)

29. Richters – 59 cases. Italian study looking at clonally related and unrelated. Unrelated (n=10, 1 allo) median OS = 62 months vs 14 months if clonally related (n=49 with 8 allogr). (TP53 status within the RS also a clear RF for early death).

NOVEL THERAPIES

1. Anti CD200 – some responses

2. CAL-101. Looks very interesting. ORAL. Inhibits PI3K pathway.Monotherapy but also combining bendamustine or rituximab. Both see decrease in LN size in ALL patients.

3. (other PI3K p-way inhibitor = tensorolimus / evorolimus. Some responses at higher doses. Note Waldenstroms – 70% ORR. NOTE – look out for pneumonitis.

4. BCR pathway –
    a. syk kinase inhibitor. Oral. Fostimatinib. ORR 50% in SLL (less in others)
    b. Bruton kinase inhibitor. Induces apoptosis. ORR 50+% in CLL / SLL
5. Anti-CD37 SMIP – very small – can penetrate tumour mass better?
6. Anti-apotosis p-way ABT263 now oral. Early dat with bendamustine in relapse looks very encouraging.
7. New anti CD20 antibodies
    a. Ofatumumab – update on phase II relapsed data. Nothing new.
    b. GA101 – trial started in CLL in combination (low grade relapse data looks good)
    c. Veltuzumab –smaller vols – sub/cut
    d. New conjugates – see indolent lymphoma section

Hodgkin Lymphoma

Education session (Nancy Bartlett).

Big debate in HL is the survivorship question. How to manage early stage unfavourable? Many leaning towards 6 x ABVD and no RT. With this approach from published data 5 year PFS 81-94%. Does appear consistently less than chemo +RT group. Current approach is to see whether PET can identify the best patients and save them from RT without compromising their outcome. BUT EORTC HD 10 has closed the chemo only arms in early favourable and unfavourable groups in July 2010 (1100 pt in the trial). Not formally told why, but conclusion is PFS is not as good in chemo only.

BUT long term effects of RT JCO 2007 – 19000 long term HL survivors. Increasing second cancers by decade. Females much earlier (breast). 20 years post = 10% and 25% (female). By 40 years, male = 27% and female = 28% compared with population matched control of 17% vs 15%. Also looked at RR of fatal MI – 2.5 fold higher with RT to neck / mediastinum.

? can reducing RT have benefit? Not very much data here, but childhood cancer survivors registry dose suggest linear relationship between dose and RR cancer. ? size of field? 2 studies in breast cancer showing Mantle 2.7RR> mediastinal, and EFRT 3.5RR> IFRT.

Does RT really reduce the risk of relapse? Really need the prospective studies that are currently underway. EORTC and current German early stage both have arms where PET in done and result ignored (i.e. get chemo + RT whatever the PET result). In the Gallamini study, 70 /260 patients were IIA unfavourable. Of these 70, 7 were PET + at PET2, and 2 / 7 relapsed. Most had RT. Clearly we need the prospective trials to answer this, but in HL, many clinicians are making the choice to avoid a therapy that probably DOES improve PFS. (She gave a case study of IIA young student with a radiation oncologist as a parent! In the end she opted for 6 x ABVD and no RT)

Advanced HL. Of the larger international trials, the RATHL, Intergroup and Italian are looking at escalation based on PET. The Germans are looking at primarily de-escalation based on PET. Can you get any further in decision making before you start treatment if not on trial? CD68+ macrophages appear very predictive of poor outcome (Steidl NEJM), but concerns with any immunohistochemistry technique are reproducibility. IPS score. BC group did large look at 'recent period' IPS data in ABVD treated and showed 0,1,2 all group fairly closely in advanced with OS 80+% (note this is lower than HD9). IPS 3 + still have worse OS (as low as 65% for worst group). Does this support starting these patients on more intensive therapy (or experimental therapy) from the outset. Bartlett has clearly shifted a little towards a German mindset! - "escalated BEACOPP is a reasonable therapeutic strategy for higher risk HL". Note also the phase 1 ABVD + SGN-35 first line therapy ? at the MDACC?

Other novel agents. Pabinostat. Monotherapy data not very convincing, but ? in combination? Lenalidomide – combination of 3 studies, ORR round 17%, BUT 'cytostatic repsonse' means an SD that lasts for 6+months in a decent number.

1. SGN35. Conjugate antibody anti-CD30-MMAE (microtubular toxin). CD30 internalises and link degraded within lysosyme. Relapsed HL. Phase II 103 patients. All prior autograft – 71% primary refractory (i.e. tough group). Median last duration of previous response = 18 weeks. Given iv every 3 weeks restage every 2 cycles. Max 16 cycles. ORR 74% with 94 % patients seeing some reduction in tumour bulk. No clear difference between primary refract and relapse. CR=34%. Median = 9 cycles. Median duration = 47 weeks (29 weeks IRB). Response duration CR>PR>SD. 1/2 patients sensory neuropathy (8% gd 3, 0 gd 4). 2/3 improved within 2 months. 3 patients so far → allograft. No problems reported. Now recruiting to phase I ABVD+SGN35 upfront!!

2. Andreas Engert updated on HD15. 2,100 patients. 3 arms (6 x escB, 8 x esc B and 6 x B-14). 701 patients had end of treatment PET and f-up for > 1 year. Median f-up 3+ years. If PET neg at end, NO RT. If + → IFRT. 540 pt PET neg → 96% no event. 188 pt PET positive → RT 89% no event. 8 pt had RT by mistake. Curves v flat. At 3 years EFS 92% vs 87% for pet neg and pos. Overlap HD9, HD12, HD15, see absolutely same PFS with 59% of patients saved RT. Therefore, IF treating advanced HL with escB, can safely NOT use RT if PET negative. HD18 is currently recruiting (over predicted!) with 900 patients so far! (2 x escB→PET and plan arm depending on result. In that trial, only end of treatment PET POS will get RT.

   BEWARE. Much debate from the floor about the value of PET in different treatment contexts. i.e. the German data must be interpreted in the context of escB. The EORTC HD10 trial of ABVD in early favourable and unfavourable has just had chemo only arms CLOSED by the safety monitoring committee. It is assumed this was due to worse PFS in non-RT arm but can't be sure. Also debate from the floor about a Dutch advanced HL trial with ABVD and no RT (I didn't catch this).

3. HD14. Early stage unfavourable. Standard German criteria. 4 x ABVD + 30Gy vs 2 escB +2 ABVD + 30Gy. 1655pt. Safety committee stopped ABVD arm because of inferiority. Toxicity as expected short term but tMN 0 vs 0.5 % (3 cases). NHL (ALL fatal) 10 in ABVD arm vs 5 in escB. 4 early toxic deaths in escB vs 1 BUT 6 ABVD patients died in salvage vs 1. More

autografts in ABVD arm (10% vs 4%). PFS 89% vs 95% at 5 years. Infertiliy: Amenorrhoea 12.5% vs 16%. BUT 11% ABVD had babies vs 18% escB.

4. ECOG 812 pt ABVD + RT vs St. V +RT. OS is 85% at 5 years both arms overlapping. This trial included full range of patients from early intermediate risk to advanced. ¼ patients had bulky mediastinal mass. Again no diff in OS.

5. German elderly don't give esc B (TRM>20% if >60!). 5 year PFS 70% in >60 with much more toxicity than younger.

6. Pabinostat (Anna's paper!)– use post auto. Only 5/129 = CR, BUT ? induce period of stability for 6 months (note low platelets)

POSTERS

1. Zinzani – Long term follow-up of interim PET cohort of 147 early stage and 157 advanced stage. All treated from 1997 to 2009 with ABVD-based therapies (not clear how much RT). All patients had pet pre, post 2 and post completion. PET2 negative. Early –pet2 neg = 97% in long term CR. Of advanced stage, 123/157 = interim PET2 neg → 109/123 = 88% stay in CR. In both early and advanced, interim pet+ → much higher relapse.

2. Another Italian study looked at PET2 in 250 EARLY stage HL. Again, negative = very strongly predictive (1/153 relapsed) (? All but 15 patient had ABVD + RT). 32 patients had PET2 +. Of these, 17 non-bulky, 10/17 progressed. Of the bulky, 6/15 Pet+ progressed / relapsed. i.e. interimPET2 is strongly predictive, but as always at interim, NPV of a negative scan is much higher than PPV of a positive scan.

3. Concordance study of PET analysis in Italian equivalent of RATHL (236 pt already recruited) shows very high concordance using the Beauville scoring system.

4. HL and HIV (French / Italian / Spannish) → id 596 patients. RF for long term OS → CD4 count <200, performance score >2. Score 0,1,2 → very strong sep of patients TTF and OS

5. BC data using ABVD in NLP HD. Found 89 cases of NLPHL treated in different eras (EFRT, ABVD x 2 + IFRT (1993 onwards), ABVD alone. 1/56 patients that received ABVD have relapsed (5 years post → given RT) none transformed. Of 33 patients treated only with RT there have been 5 / 33 transformation to high grade lymphoma and 6 relapses. (longer f-up)

6. A SMALL German HL trial of BACOPP-D (remove etoposide and add dacarbazine). Hard to make conclusions on small numbers. Appears efficacious with no 2. tMN as yet.

7. Long term risk of stomach cancer in HL. 17000 survivors (>5 years) followed. Risk of stomach cancer 0.4% RF = RT and alkylator therapy.

8. tMN risk with escBEACOPP. Pooled trials and study incidence of tMN in 12,000 HL patients. 4+ escB → risk = 1.5% vs 0.5% for all other groups.

9. Cellular background of NLPHL – if T cells, ? higher risk of high grade NHL transformation?

10. Microenvironment of HRS – CD45+RO+ and LOW FoxP3+ = worse (note CD68+ story in addition)
11. HIV HL. Vinblastine + ritonavir 55% neurotoxicity. Can be irreversible. ALERT TO THIS
12. MDACC treating NLPHL with R-CHOP. 15 cases. 90% CR. 100% ORR. No relapses with median f-up 42 months