AML

AML MOLECULAR BIOLOGY

L Bullinger et al, Stanford and Ulm (NEJM 2004;350:1605-16). Gene expression profiling with DNA microarrays with 133 genes identifies two groups of pts, better prognosis versus worst prognosis OR 8.8. Good prognosis associated with forkhead box O1A gene (FKHR or FOX0'1A). Poor prognosis associated with overexpression of Homeobox gene disregulation (HOXA, B, etc) and FLT3.

P Valk et al Netherlands (NEJM 2004;350:1617-28). Gene expression profiling with Affimetrix U133A gene chips (13.000 genes) identified 16 groups of pts with AML. Good clustering driven by chromosomal lesions t(8;21), t(15;17) and inv(16), as well by genetic mutations CEBPA, EVI1, 11q23 etc…

D Grimwade and T Haferlach (NEJM 2004;350:1676) Editorial. Pts with favourable prognosis in groups with chromosomal alterations do not benefit from allotransplant after CR. Otherwise, in pts with adverse features (-5,-7, abnormal 3q, t9;22 and complex karyotype, allotransplant is the treatment of choice…

M Smith et al (NEJM 2004;351:2403-7). Familiy inherited CEBPA mutation and AML: all good remission and NED.

L Tourneur et al (Ca Res 2004;64:8101-8). FADD low/absence is related to refractoriness to chemotherapy and poor survival time.

W Blum et al CALGB (Cancer 2004;101:1420-7). Reviewed CALGB experience with t(6;11)(q27;q23), and found 16 pts (0.6%) in CALGB series and 33 in the literature search. 81% were FAB M4-M5. Gingival presentation common 31%. CR 69% but duration of CR med 9 mo. 2yOS 13-15%. Consider early transplant…

RF Schlenk et al German AML Group (JCO 2004;22:3741-50). Reviewed all pts with CBF AML (t8;21 and inv16) looking for prognostic factors. In t(8;21)(q22;q22) where RUNX1 is fused to CBFA2T1, is associated to FAB M2, Auer rods, elevated CD19 expression, extramedullary leukaemia (granulocytic sarcoma), loss or del 9q, high rate of CR and good activity for HD-AraC postremission, while poor results associated with high WBC, extramedullary presentation, expression of CD56 or del 9q. The prognostic variables for survival identified were lower WBC, higher platelet count, and loss of Y chromosome. In inv(16) t(16;16)(q22;p13), were CBFB fused to MYH11, associated with FAB M4eo, extramedullary involvement, association with trisomy of 8, 21 and 22, found high CR and favourable outcome and the factors which correlated with prognosis were good RFS in trisomy of 22.

*AML: Mutated ras related to CR after AraC (CALGB study). Relapse rate at 10 y was 45% vs 71-100% for non mutatwed ras and low dose AraC, while it was 11% for mutated ras (Abst 6514 Proc ASCO, 2005; 23)

G Marcucci et al (Clara Bloomfield). (JCO 2005;23:9234-42). ERG expression in normal karyotypic AML, characterized for BAAL, FLT3-ITD, MLL). M F-up 5.7 y. N=84. High ERG and MLL expression predicted relapse and por survival in patients with low BAALC.
C Baldus et al (Clara Bloomfield) (JCO 2006;24:790-7). Studied prognostic factors in patients without chromosomal aberrations, situation occurring in half of the adults with AML. About 40% of these are long term survivors. Increased expression of BAAL C (Bra and acute leukemia cytoplasmic) (above 50% cut off line) and FLT3-ITD (Internal Tandem Duplication) had prognostic impact: Increased BAAL correlated with primary chemotherapy resistance in 16% (vs 6% in low expression). Combined with FLT3, both independent factors correlated with high relapse and poor survival.

***SJ Schonfeld et al (JNCI 2006;98:215-8). Review secondary AML after HD (N=35.511 from Nordic Registries & USA). Excess absolute risk (EAR) = 6.7 (217 cases observed & 11 expected). Risk was reduced from cohort 1970-84 to cohort 85-2001(Older 16.4 and <35 EAR 7 vs EAR 9.9 and 4.2 respectively)**

AML THERAPY

A Tsimberidou et al MDACC (Cancer 2003;97:1481-7) New program MFAC: Gemtuzumab (Mylotarg) 6 mg/m2 iv d 1 + Fludara 15 mg/m2 bid d 2-6 + AraC 0.5 g/m2 bid d 2-6 * CsA 6 mg/kg loading, then 16 mg/kg civi d1 & 2 (before Gemtuzumab). Treated 59 pts (66% AML & 34 MDS with transformation) m age 57 yo, CR 46% + CRp 2%. MST 8 mo, 1 yOS 38%, VOD 7% and liver toxicity 7%. Good results, probably not better than IDA-AraC (CR 51%)…

J Kolitz et al CALGB (JCO 2004;22:4290-301). Escalated dose of DOX up to 90 mg/m2 x 3 and of VP up to 100 mg/m2 x 3 in Ara C combination 100 mg/m2 civi qd x7, improving somewhat the RC to 78% and 3 yDFS 38% in CBF AML. Then Phase II of same combination with PSC833 (2.8 mg/kg loading 2 h iv then 10 mg/kg/d civi x 7d) and had to reduce DOX to 40 mg/m2 x 3 and VP 40 mg/m2 x 3 but found a 3YDFS 59% in CBF AML, while the CR and OS were unchanged. Now proceeding to a randomised trial…

S Faderl et al (Cancer 2005; 103:1985-95). Review results of Clofarabine (nucleoside analog with properties of cladribine and fludarabine) with extraordinary biological synergism with AraC). Phase II in adults OR 40% AML, 25% MDS, 8% ALL, 35% CML-BP. Phase II children ALL: CR 12%, CRp 8%, PR 11%, obtaining FDA approval for second line therapy in pediatric ALL…

JE Karp et al (Clin Ca Res 2004;10:3577-85). Trial of AraC 2 g/m2 72 h d1 + MTZ 40 mg/m2 d 4 associated to Bevacizumab 10 mg/kg d 8, in 48 pts with relapsed or refractory AML. CR 33%+ PR 15%. Wonderful results for same drugs in relapse…Clearance of residual BM AML after the 8 day can be attributed to BV… Keep an eye on this study.

J Cortes (Clin Ca Res 2004;10:3371-6) Bortezomib phase I MRD 1.25 mg/m2 biw x 4 q 6 , with only signs of haematological improvement in 5/15 pts.

J Karp et al (Clin Ca Res 2005;11:8403-12). Phase I, N=34 adults with AML & ALL refractory/relapsed. Flavopiridol MTD 50 mg/m2 qd x 3 (1 h iv) + Ara C 2 g/m2 72 h civi d 6 + MTZ 40 mg/m2 d 9. Response: OR 47%, tumor lysis 26%, TD 12%. AML: OR 31%, ALL OR 12.5%. Continue development…

D Breems et al (JCO 2005;23:1969-78). Prognostic index for pts in first AML relapse. Factors were: RF interval after CR >18, 7-18 and <7 mo (points 0,3 & 5); Cytogenetics at diagnosis inv16, t8;21 and others (points 0, 3 & 5); Age at relapse <35, 36-45, &>45 (points 0, 1 & 2); and prior stem cell transplant no or yes (points 0 & 2). Score good (1-6) 5yOS 46%, intermediate (7-9) 5yOS 18%, Poor (>10-14) 5yOS 4%. Second response related to score as well (85%, 60% and 34% respectively).

*RA Larson (Cancer 2005;104:1442-52). Phase II Mylotarg study in CD33+ relapsed AML . Mylotarg 9 mg/m2 2 h iv x 2 d q 2 wk. N=277, median age 61 yo. OR 26%: 13% CR and 13% CRp (without platelet recovery). MRFS 6.4 mo CR and 4.5 mo CRp. Acceptable toxic profile.

E Feldman et al (JCO 2005;23:4110-6). Lintuzumab (Hu M195, MoAb against CD33) 12 mg/m2/d x 4d and repeat 10-12 d after first cycle) + (MTZ 8 mg/m2+VP 80 mg/m2+AraC 1 g/m2) /d x6 randomized Phase III to same chemotherapy alone. N=191 relapsed or resistant primary AML. Results: CR/CRp 36% and 28%; NMST 156 d and 156 d. No improvement in OR or survival.

*C Berg et al (Cancer 2005;104:2717-25) Valproic acid (Histone deacetylase inhibitor, induce in vitro AML differentiation) 5-10 mg/kg starting po dose + ATRA 45 mg/m2 po +/- Ara C or HOUrea low doses. Results: 19/26 completed 4 wks therapy, 7 withdraw prematurely and15 required cytoreductive chemotherapy. OR: 2 PR + 1 mR. No differentiation of blasts (CD34 cytogenetic analysis).

AML: VNP40-101M sulfonylhydrazine alkylating agent active in AML/MDS refractory: OR 27%. N&V, diarrhea, hematological toxicity (Abst 6541 Proc ASCO, 2005; 23)

*AML: TOPO 1.5 mg/m2 d 3-7 + MTZ 12 mg/m2 d 1&2 + AraC 1 g/m2 2 h infusion d 3-7.Refractory AML had CR 45/81 (56%) in 1st relapse and 4/10 refractory. (72% had prior IVA). 2 yOS 41% alloSCT and 11% without alloSCT. (Abst 6613 Proc ASCO, 2005; 23)

A Kuendgen et al (Cancer 2006;106:112-9). Valproic acid 50-100 ug/mL serum concentration N=58; OR 5% AML and 16% MDS. Addition of ATRA. N=27, not better. Recommend combination with chemotherapy or demethylating agents.

*F Giles (H Kantarjian) (Clin Ca Res 2005;11:7817-24) Phase I Chloretazine (alkylating agent, sulfonylhydrazine), MTD 600 mg/m2 + AraC 1.5 g/m2/civi x 4 d. N=40 refractory AML. Results: CR 27%. O6 alkyl guanine alkyltransferase (AGT) was lower in patients who responded to treatment.

**H Kantarjian et al (Cancer 2006;106:1090-8). Reviewed 998 pts >64 yo with AML/MDS to construct a predictive model for aggressive chemotherapy results. Factors were: Age >74 yo, unfavorable karyotype, treatment outside laminar flow room, antecedent hematologic disorder >1 y, PS ECOG >2, LDH >600 u/L and Cr > 1.3 mg/dL. Score 0 factors, 1-2 factors and >2 factors had incidence 121, 568 and 301 respectively; 1 y OS 63%, 33% and 9%; 2 y OS 35%, 19% and 3%; CR rate 72%, 51% and 17% and 8 wk mortality 10%, 26% and 57% respectively.

*****J Büchner et al (JCO 2006;24:2480-89). N=1770 AML and high risk MDS primary or secondary leukemia; 53%>60 yo. Randomized conevtional vs intense chemotherapy induction and also maintenance chemotherapy vs stem cell transplant. First randomization was: TAD-HAM (TAD: 6TG 100 mg/m2 po q 12h d 3-9 + AraC 100 mg/m2/d civi x 2 days & then in 30 min iv q 12 h d 3-8 + Dauno 60 mg/m2 iv 1 h d 3, 4 & 5) (HAM: AraC 1 g in >60yo or 3 g in <60 yo/m2 in 3 h iv q 12 h x 6 d 1-3 + MITX 10 mg/m2 1 h iv d 3-5) versus HAM-HAM (more intensive arm). In <60 yo or >5% blasts, double induction. All patients in CR were given TAD reinduction. Second randomization was Maintenance (AraC 100 mg/m2 q 12h d 1-5 + Dauno 45 mg/m2 1 h iv d 3-4 or TG 100 mg/m2 q 12h d 1-5 or CPA 1 g/m2 d 3 rotating in each cycle x 3 years with dose reduction according to N<500/uL or Plataelets< 20.000/uL) versus Autologous Stem Cell Transplant (2x10e6/kg CD34+ cells collected after GCSF/2nd HAM after TAD reinduction, with conditioning based in BUS 41 mg/kg qd x 4 po d-7 to –4 + CPA 60 mg/kg/d iv d –3 & -2). Results: >60 yo CR 70% , 3 y RFS 40%, ongoing remission 48% and 3 y OS 42%; >60 yo CR 53%, 3 y RFS 19%, on going remission 22% and 3 y OS 19%. No differences observed in the induction programs TAD-HAM vs HAM-HAM and no differences between postremission ASCT or 3 y maintenance. No differences in AML/MDS secondarism, cytogenetics, WBC conut, LDH or early blast clearance...**

AML BMT

NEJM 2004;351. V Rocha et al Eurocord Registry and M Laughlin et al American experience. Presentation of results with cord blood transplant, unrelated. Found acceptable procedure in terms of Mortality and relapse rate when only one HLA mismatch identified…

ANLL CHILDREN

E Roman et al (Clin Ca Res 2005; 11:7164-70). Gentuzumab ozogamycin after mini Allo transplant in children with AML CD33+. N=8. Pretransplant Fludara 30 mg/m2 x 6 + BUS 3.2 mg/kg x 2 d (or 4 mg/kg/d if < 4 yo) + Mylotarg d 60+ to d 180+ and a second dose 1 y after transplant. Day 60 chimerism 94%. No toxicity. Aplasia 2/11 treatment courses (Neutropenia occurred in all patients and recovery observed on d 13+).

H Lapillone et al (JCO 2006;24:1507-15). High WT-1 expression found in 78% pediatric AML. Elevated expression >50 after chemotherapy induction correlated with relapse and death.

APL

APL TREATMENT

S de Botton et al. Eurp APL Group (JCO2005;23:120-6). Review 3 protocols and the additive series of 122 pts who failed to initial therapy and had a second CR with ATRA+Chemotherapy which was then consolidated with AuyologousSCT (7yRFS 79%, 7 yOS 59% and mortality 6%), allogeneic (7yRFS 92%, 7yOS 51% and mortality 39%). Very good results in pts with molecular response (only 10% relapses).

S de Botton et al Europ APL Group (JCO 2005;23:120-6). Review results with SCT in APL with failure to ATRA, with a second CR with ATRA+Chemotherapy, used as consolidation therapy 7yRFS were 79% autologous, 92% allogeneic and 38% other RX, with mortality 6% autologous and 39% allogeneic. Cases with a molecular OR had only 10% relapses. As2O3 was not given to these patients…

ALL

ALL CHILDREN
BFM protocol JCO 1997;15:2222-30
MSKCC NEW YORK-II protocol Cancer 1993;72:3120-30
St Jude's TOTAL THERAPY XIIIB-ALL Blood 2004;104:2690-6

D Hawkins (Clin Ca Res 2004;10:5335-41) PEG-Asp 2500 IU/m2 im d 2, 9, 16, 23 in induction therapy and 2500 IU/m2 d 7 in intensification. Activity was >0.1 iu/ml in 91-100% pts during induction and same level in 80-94% pts during intensification. Levels are good and should get into future use to examine tolerance and side effects…

**J Roman-Gomez et al (JCO 2005;23:7043-9). Methylator phenotype (CpG island) >2 present in 76% T-ALL define a group with 12 y DFS 20% (vs 100% for non methylated group) and 13 y OS 17% (vs 91% in the non methylator group). New parameter for treatment?.

*NELARABINE, prodrug of 9Beta-D arabinofuranosylguanine (AraG) approved by FDA in T-ALL and T lymphoblastic lymphoma. Children 650 mg 1 h iv qd x 5 q 3 w, OR: CR 48% as a first line therapy and 23% second line. Adults 1500 mg 2 h iv d 1, 3 & 5 q 3 w. OR: 27% CR first line and 21% second line. DLT neurologic 22% grade 3-4, headache, somnolence.

**P Cole et al (Clin Ca Res 2005;11:8089-95). Aminopterin was discarded too early probably due to folate contamination that made toxicity unpredictable. Recent comparative studies showed better activity, increased bioavailability and greater cell accumulation than MTX as well as tolerable toxicity. 6/22 children with ALL had OR, no mucosal toxicity. Deserve a new trial with current standards.

S Verstovsek et al (Cancer 2005;104:1230-6). AMN-107, aminopyrimidine inhibitor of p190 bcs-abl better than imatinib in cell lines.

S Jeha et al (JCO 2006;24:1917-23). N=61, refractory ALL, median age 12 yo, median prior therapies 3. Clofarabine 52 mg/m2 iv 2 h infusion qd x 5 every 2-6 wks. OR 30% (7 CR + % CR plat + 6 PR). Patients received transplant after. Non transplanted patients had a MDR 6 wk. Combination therapy on going.

ALL CHILDREN- HEMATOPOIETIC STEM CELL TRANSPLANT

C Peters (BMT 2005;35:9-11) Consensus of BFM, IBFM and EBMT for allotransplant in ALL is as follows: First CR: In poor prednisone responders good matches in all cases except for t(9;22) where a mismatch is acceptable. After relapse/second response All matches for Tcell, no remission in 30 days or Bcell precursor, as well as MRD >10e-3. After 3rd relapse mortality is very high and no consensus reached. Best conditioning is VP+TBI. GVH prophylaxis with MTX+ATG.

ALL ADULTS

H Kantarjian et al MDACC (Cancer 2004; 101:2788-801) Review updated results with HyperCVAD, N=288 pts. CR 92%, induction mortality 5% (15% with ages >60 yo), MF-up 63 mo, 5yOS 38%, 5yCR duration rate 38%. Best results ever published.
Program: CPA 300 mg/m2 iv q 12 h x 6 d 1-3 + Mesna (equal dose of CPA civi until 6 h after CPA) + VCR 2 mg iv d 4 & 11 + DOX 50 mg/m2 d 4 + DXMTS 40 mg qd d 1-4 & 11-14. Alternating with HD MTX 200 mg/m2 2 h iv followed by 800 mg/m2 in 24 h civi + CF 24 h later 15 mg q 6 x 8 d1 + AraC 3 g/m2 2 h iv q 12h x 4 d 2 & 3 + PRDNS 50 mg iv bid x 3d, repeat x 4 cycles each and followed (exclude Burkitts & Ph+ that should go to transplant) by POMP: 6 MP 1 g/m2 iv x 5 q mo + MTX 10 mg/m2 iv x 5 q mo + VCR-PRDNS

*ALL Adult: Randomized study comparing ALL2 (induction with AraC 3 g/m2/d x 5 + MTZ 10 mg/m2 qd x5) or L20 (classical 4 drug PRDN+VCR+CPA+DOX): Similar mortality 9%, 5yDFS 26% vs 16%,

CR 85% vs 47%, 4yOS 40% vs 22%. Better ouitcome and new standard. (Abst 6516 Proc ASCO, 2005; 23)

D Thomas et al MDACC (Cancer 2006; 106:1569-80). HyperCVAD + RITX in 31 pts with adult B-ALL and Burkitt ly. Results: CR 24/28 (86%) + PR 3 + PD 1. 3 yOS 89%, 3yEFS 80% and 3 y DFS 88%.

ALL ADULTS- HEMATOPOIETIC STEM CELL TRANSPLANT

M Kiehl et al German Group (JCO 2004;22:2816-25). Allotransplant better after first CR than second CR (40% survivors as compared to 29% survivors). BMT not better than SCT. TBI better than Busulfan. Largest series published (N0264 pts), 5 y DFS 28%. Better results in B cell than T cell and no differences found for Ph+ALL.

MYELODYSPLASTIC SYNDROMES

S Faderl & H Kantarjian (Cancer 2004;101:226-41). Novel therapies: PDGFRBeta (5q33) treated with Imatinib, no responses. FTI: Tipifarnib (R115777) some benefit in 6/20 pts, Lonafarnib (5CH66336) also obtained some benefit in 12/42 pts. Angio inhibitors: Thalidomide 400 mg/d benefit in 20% pts, poor tolerance. Revimid (CC5013) more frequent benefit, 60%. VEGF-RTK inhibitors No responses found (PTK787, SU5416, SU11248. As2O3, 0,25 mg/kg qd x5 each wk x 2 q 4, benefit found in 7/28 pts. Epigenetic therapy: Benefit and extended survival 9 mo in randomised trial comparing Vidaza and supportive care (transfusion). Vidaza 45-50 mg/m2 qd x 3 q 6 wks. MDR 10 mo.

E Kaminskas et al FDA (Clin Ca Res 2005;11:3604-8) Approval of Vidaza (Azacytidine) in MDS in May 2004.

A List et al (NEJM 2005;352:549-57) Lenalidomide (analog of Thalidomide), 10 mg/d x 21 q 4 wks. In 43 pts, 58% had reduction of the dose due to decreased WBC and platelets. Response observed in 56% (independence of transfusion), MDR > 2years. Response was better in del5q31.1 (83%) as compared to other types (12%). Complete cytogenetic response in 50% in 20 pts with karyotypic alterations.

*C Rosenfeld (Sem Oncol 2005;32:465-72). Decitabine Phase I: 5-20 mg/,2 iv 1 h qd x 5 wkly x 2. Most active schedule was 15 mg/m2 x 10 d (OR 65%, 11/17). Results: OR 50%, CR 24% and increase in platelet count in 83% thrombopenic patients. MDR 9 mo, MST 15 mo, TD 6% due to cytopenia. Retreatment after progressive disease reinduced a response in 45% but MDR was shorter. When p15 was confirmed demethylated cytogenetic response was demonstrated in 31%. Combination to DOXO and Valproic acid improved OR rates…(AML)

***MDS with 5q31del treated with lonalidomide: 64% became independent of blood transfusion, median increase in Hb 3.9g, cytogenetic response 76% (CR 55%), pathologic CR 29%. Highly effective... (Abst 5, Plenary Proc ASCO, 2005; 23)

MDS: Decitabine, 15 mg/m2 iv qd x10 + Valproic acid (histone deacetylase inhibitor) 50 mg/kg po x 10, are synergistic. N=51 pts with MDS/AML CR 8 + PR 1 (OR25%). Above expectations. (Abst 6544 Proc ASCO, 2005; 23)

MDS: Better schedule for DAC (Decitabine) 20 mg/m2 iv in 1 hr qd x 5 (OR 48%), better than 10 d treatment (Abst 6545 Proc ASCO, 2005; 23)

Decitabine 2.5-20 mg/m2/d, x5 qwk x 2 wk demonstrated very active demethylation at low doses in peripheral blood mononuclear cells. Some OR... (Abst 3110 Proc ASCO, 2005; 23)

H Kantarjian et al (Cancer 2006;106:1099-109). TOPO 1.25 mg/m2/d civi + AraC 1 g/m2/d x 5. N=510 with high risk MDS (82% intermed-high risk, 32% secondary MDS, 40% chromosome 5/7 abnormalities), median age 63 yo. OR 55%, induction mortality 17%, 5 y OS 8%. Less toxic than combination with IDA, Fludara or CPA…

M Arai et al (Cancer 2006;106:1744-50). 5 Aza 2 Deoxycytidine 1uM in cell culture assay to monitor the changes in gene expression due to therapy. Microarray with 4608 combinational DNA. Found that cytoskeleton/extracellular matrix genes were upregulated while metabolism genes were downregulated.

***B Rüter et al (Cancer 2006;106:1744-50). N=108 MDS treated with DAC 15 mg/m2 in 4 h iv tid x 3 q 6 wk x 6-8 cycles. OR 60%, MDR 10 mo. Among responsive patients 33/65 received supportive care and then 10 patients went on onduction chemotherapy at recurrence (MOS 18 mo). Another 22/65 had DAC (same schedule x 3 cycles)retreatment at time of progression (MTT retreatment 11 mo) and had OR 45%, MDR 4 mo (12 no response and 13 AML), for a total MOS 27.5 mo. These results suggest that prolongation of therapy up to 10 cycles with low dose DAC, maintenance or retreatment is associated to better survival...**

H Kantarjian et al (Cancer 2006;106:1794-80). N=170. Randomized study of DAC (15 mg/m2 3 h iv q 8 h x 3 d up yo a total dose 135 mg/m2, q 6 wk) with OR 17%, CR 9%, Improvement 13%, MDR 10.3 mo, MTT leukemia or death 12.1 mo vs best supportive care with OR 0, Improvement 0, MTT leukemia or death 7.8 mo.

N Vey et al (JCO 2006;24:2465-71). As2O3 Phase I 0.3 mg/kg loading and then 0.25 mg/kg biwk x 15 wk maintenance. N=115. OR 24 (19%), 26% in low risk and 17% in high risk. MDR 3.4 mo.

*S Nimer (JCO 2006;24:2576-82). Review MDS with del 5q. Often anemia requires blood transfusion and iron chelator therapy. EPO, Darbepo and hypomethylating drugs improve hemtopoiesis and anemia. Lenalidomide very active (83% sustained trnasfucion independence) leading to complete cytogenetic responses in 75% (9/12 patients).

G Schiller et al (JCO2006;24:2456-64). As2O3 0.25 mg/kg/d x 5 q wk x 2 wk and 2 wk rest. Hematological improvement: In low-intermediate 1 risk 34-39%, and in intemediate 2 and high risk 6-9%. Responses observed in erythroid and platelet lineages. Recommend its use in combination therapy.

CLASSICAL CHRONIC MYELOPROLIFERATIVE DISORDERS (ESSENTIAL THROMBOCYTOPENIA, POLYCYTHEMIA RUBRA VERA, MYELOFIBROSIS WITH MYELOID METAPLASIA, CHRONIC NEUTROPHILIC LEUKEMIA, CHRONIC EOSINOPHILIC LEUKEMIA, CHRONIC IDIOPATHIC MYELOFIBROSIS WITH EXTRAMEDULLARY HEMATOPOIESIS)

*Response to Gleevec observed in Essential Thrombocythemia (-), Polycythemia vera (+/-), Myelofibrosis with myeloid metaplasia (+/-), Hyepreosinophilic syndrome FIP-1L/PDGFRA (+), PDGFRB rearrangements (+), Chronic myelomocnocytic leukemia with t(5;12)(q31-33;p13) fusion of TEL-PDGFRB (+), Systemic mastocytosis with KIT mutation (+), chronic eosinophilic leukemia (+).

****Mutation in $JAK2^{v617f}$ leading to constitutive activation (phosphorylation) in 90% PV, 50% ET and 40% CIMF (Baxter et al, Lancet 365:1054-61, 2005; James C et al, Nature 434:1144-8; 2005; Levine R et al, Cancer Cell 7:387-97;2005; and Kralovics R et al, NEJM 352:1779-90;2005).

***R Kralovics et al (NEJM 2005;352:1779-90). 9pLOH JAK2 mutation V617F (phenylalanine substituted for valine) give a survival advantage and caused disease in Polycythemia vera 83/128 (65%), Idiopathic myelofibrosis 13/23 (57%), Essential thrmbocytopenia 21/93 (23%).

POLYCYTHEMIA RUBRA VERA

J Spivak (Blood 2002;100:4272-90). Result of myeloaccumulation not myeloproliferation due to a decrease in apoptosis with overexpression of Bcl-xL and elevation of growth factor mpl. Diagnosis triad, based in erythrocytosis, cianosis, splenomegaly (Osler 1903) actually is based in 3 major criteria: elevated red cell mass, normal pO2 saturation and major splenomegaly or in case of no splenonegaly 2 mionor criteria (leukocytosis >20.000, thrombocytosis > 400.000, Phase alkal >100, Vit B12 serum >900 pg/mL & Vit B12 binding capacity >2200 pg/mL (Waserman 1971). Measurement of red cell mass ($Chromium^{51}$) and plasma volume (Albumin-I^{125}) taking 2 standar deviations (25%) above the mean is very important to rule out contraction of plasma volume. Therapy: Antiaggregants or low dose ASA to avoid thrombosis and hemorrhage in the CNS (20% and 10% respectively), P^{32}, Correct iron defficiency due to phlebotomies.

L Solberg (Sem Oncol 2002;29:10-15). Clonal disease not related to IL6, affecting in 6^{th} decade, with thrombocytosis, migraine, erythromelalgia, thrombosis and pulmonary embolism, splenomegaly. Therapy indicated when platelets >600.000 with/out thrombosis. Treatment: HOUrea 1000-1500 mg qd, risk of leukemia in 15 y. ANAGRELIDE (therapy of choice) 0.5 mg qid. IFN alfa 5 MU sq qd and then maintain with 3 MU tiwk (better option in pregnancy). Low dose ASA in patients with lower risk. Phlebotomy if Hct >42% in women and Hct >45% in men. BUS 4 mg qd x 7 then 2 mg qd x 21 and then 2 mg qod x 3 mo, then stop. P^{32} 2.7-2.9 mCi (total <5 mCi) q 3-6 mo.

PRIMARY THROMBOCYTHEMIA (ESSENTIAL THROMBOCYTOSIS)

J Samuelsson et al (Cancer 2006;106:2397-405). Phase II with PEG-Intron alfa2b, 0.5 ug/kg, in PV (N=21) and ET (N=21). CR 29/42 (69%), 19 completed 2 y treatment in CR. Neutrophil polycythemia rubra vera-1 (PRV-1) messenger RNA normalized in 5/14 (36%) initially positive patients. Therapy was discontinued due to intolerance in 16/23 patients.

***Harrison et al (NEJM 2005;353:33-45). N=809 high risk ET, M F up 39 mo. Randomized Hydroxyurea + low dose ASA (Sandard therapy) vs Anagrelide + Low dose A>SA. Found unexpected increased risk of blieding and excess transformation to myelofibrosis in the anagrelida group.**

***R Saba et al (Cancer 2005;103:2551-7). IFN alfa in ET. N=23 with amedian platelet count of 1.350x10e9/L, M F up 174 mo (14.5 y). OR 15/20, 14 CR, MTTR 6 mo, MDR 48 mo. 7 patients maintained CR > 3 y after discontinuation of therapy. 78% recurred (7/14) and 2/5 had a second OR.**

***N Gangat et al (Cancer 2006;106:2406-11). Reviewed risk of thrombosis associated with ET receivimng estrogens. Risk was elevated in > 60 yo and plataelt count >1.500x 10e9/L. Major thrombosis found in 19% of patients (similar to 26% in patients without estrogens). Oral contraceptives increase risk of venous thrombosis.**

EOSINOPHILIC SYNDROMES ASSOCIATED TO CMPD

SG Plotz et al (NEJM 2003;349:2334-9). Hypereosinophilic syndrome with FIP-1L fused to PDGFRA respond to Gleevec. Hyepreosinophilic syndrome associated with clonal T cell skin lesions respond to anti IL5 MoAB MEPOLIZUMAB, 750 mg q 1-2 wk and then monthly (very active in 24 h).

PRIMARY MYELOFIBROSIS

J Thiele and H Kvasnicka (Sem Oncol 2005;32:359-64). Prefibrotic stage (CIM-0, chronic idiopathic myelofibrosis) presents initially with granulocytic and megakaryocytic myeloproliferation with dysplastic signs, focal lymphoid nodules (30%), and mild anemia. About 65% progress to CIM 3-4. This is the fibrotic stage with collagen bundles, dense reticulin, osteosclerosis, with patchy BM cellularity, atypical megakaryocytes, myelodysplastic changes, 10% blasts in peripheral blood, splenomegaly, decrease in apoptotic pathways and increased angiogenesis, loss of CD34+ cells (<12 cut off point). HOUrea, IFN alfa and BUS help to stabilize progression to high grade CIMF (50% at 3 y. MST is 3.5-5.5y when MF+MM. Prognostic factors are: Age >70 yo, Hb< 10 g/dL, platelet <300.000/L, WBC >20.000/L, or myeloblasts >2% and erythroblasts >2%. Scores <2 factors have 10 y OS 80%, while 2-4 factors 60% and >4 factors 30% for CIMF. Therapy consist in splenectomy (mortality 10% and MST 2 y), resulting in late complications such as hepatomegaly 20% and leukemia transformation 15%, also thombocytosis. Alternatively spleen RT 30 Gy (7-10 F), and RT to liver, lung (pulmonary hypertension), abdomen, paraspinal. Danazol (androgen), Erythropoietin, Chemotherapy (HOUrea, 6TG, BUS, LPAM, 2 CdA, Anagrelide, IFN alfa (PEG OR 48% splenomegaly), IFN gamma. Recently: Thalidomide (OR 40-40%, combined to PRDN 60%), Gleevec (OR <10%), ZARNESTRA (FTI, R115777, 600 mg bid x 4 wk q 6 wk, OR 4/8), Decitabine, Ethanercept (benefit 40% symptomatic, OR 20%). ASCT 2 yOS 61% and Allo 2 y OS 50%, miniAllo despite short series is promising.

MYELOFIBROSIS WITH MYELOID METAPLASIA

M Marchetti et al (JCO 2004;22:424-31). Low dose Thalidomide 50-400 mg/d (mostlñy receiving 100 mg/d) in N=63 with MF with myeloid metaplasia. Results: Anemia improved in 22%, 39% out of transfusion, platelet improved in 23% and splenomegaly decreased in 19%.

A Tefferi et al (Cancer 2006;106:1739-43). Relationship between cytogenetics and JAK2^{V617F} mutation in MMM. N=105. Cytogenetic abnormalities 45% (13q-, 20q- favorable cases had JAK2 mutation 90% and all unfavorable had KAK2 mutated only 23%). JAK2 mutation 50%. Response to EPO occurred more in favorable cytogenetics and less in JAK2 mutation.

DA Thomas et al. Thalidomide 200 mgqd upto 800 mg to reach the higher tolereble dose. 17/41 OR: CR 10%, PR 19%, Hematological improvement 21%. Anemia improved in 21%, Platelet improved in 20% and 21% became transfusion independent. Adequete for combination therapy trial.

CHRONIC MYELOID LEUKEMIA

CML- MOLECULAR BIOLOGY

N Shah et al (Science 2004;305:399-401). BMS-354825 binds abl with less stringent criteria than Gleevec. Orally available. Potency x 2 relative to Imatinib. Active in 14/15 resistant Bcr-Abl mutant cell lines.

B Calabretta & D Perroti (Blood 2004;103:4010-22). Review blast crisis: Genetic and molecular changes: Double Ph chromosome (38%), trisomy Chrom 8 (38%), I(17q) (20%), trisomy Chrom 19 (13%), t(3;21) (2%) and t(7;11) (<1%); p53 mutation 30% (myeloid blast crisis), p16/ARF mutation 50% (lymphoid blast crisis), Rb mutation/deletion 18% (lymphoid blast crisis) and rarely Ras mutation.

F Michor et al (Nature 2005;431:1267-70). Model of CML to fit Imatinib response indicate the presence of several cell compartments: Compartment of tumor stem cells no sensitive to Imatinib. Compartment of Progenitor cells which present a delayed response after the initial prompt response of the differentiated cells to Imatinib. Differentiated and terminally differentiated cells which present an early response. According to this model a cure requires stem cell death…

C Cameron Yin et al (cancer 2006;106:1730-8). Review t(3;21)(q26;q22), occurring in 24/26 after chemotherapy (Hydroxyurea /antimetabolites in 14 CML patinets and in another 10 after other tumors or myeloproliferative disorders treated similarly. This translocation activate fusion of AML1 to MOS1 and EVI1 (AME).

A Morotti et al (Cancer 2006;106:1188-96). Valproate 5 uM 48 h + Imatinib 0.5 uM enhanced cytotoxicity

CML- THERAPY

H Kantarjian et al MDACC (Blood 2004;103:2873-8). Imatinib 400 mg bid in 114 pts. Major cytogenetic response (less than 35% Ph + cells), 96% and complete response (Ph 0%), 90. With Med follow-up 15 mo no progression to BP of accelerated phase. 2 y OS 94%. Quantitative PCR Bcr-Abl/Abl ratio 63% < 0.005 and 28% undetectable. More toxic.

D Marin et al Imperial College of London and Hammersmith Hosp (Cancer 2005;103:1850-5). Addition of Homoharringtonine to Imatinib when >35% Ph+ cells (cytogenetic response). Recommended dose 1.5 mg/m2 bid x 3-4 doses (test tolerance). In 10 pts there was a decline in Bcr-Abl in 7. Asthenia and cytopenias…

*M Bocchia et al. Dept Hematology Siena University, Viale Bracci 1, Siena, 53100 Italy (Bocchia°unisi.it) (Lancet 2005;365:657-62). P210 peptide vaccine associated to Gleevec or IFN alfa therapy in pts with residual disease . All pts had CML with b3a2 fusion point at p210, at least 12 mo treatment with IFN or Gleevec and stable residual disease not progressing for at least 6 months. Vaccine designed as CMLVAx100 consisted in peptide 210+GM-CSF+QS21 adjuvant, and was given x 6. Among 10 pts with Gleevec all improved and 5 reached complete cytogenetic response, 3 undetectable PCR transcripts. Among 6 pts with IFN alfa, 5 improved and 2 reached complete cytogenetic response. Hypersensitivity skin reaction to peptide occurred in 11/16, CD4 proliferation in 13/14 assessed pts and IFN gamma release in 5/5. Very impressive results…waiting for confirmation.
CML: High dose Gleevec 800 mg/m2 better results in untreated CML. Molecular CR (BCR-ABL/ABL ratio<0.05% at 3 mo) in majority of pts, and in 41% undetectable by Q-PCR (Abst 6518 Proc ASCO, 2005; 23)

**CML: BMS354825 dual KI with a >300x Gleevec potency & active in mutant/resistant cell lines, given 15-180 mg/d. N=36. CR 86%, 13 cytogenetic improvement (5CR+4PR=9 major cytogenetic response. MDR >33mo. OK (Abst 6519 Proc ASCO, 2005; 23)

**CML: BMS354825, 35-90 mg bid, active in accelerated (OR 75%), blastic Phase (76%) CML and Ph+ALL (2/2 OR). Major cytogenetic response in blastic Phase was 53%. OR documented in Gleevec resistance due to mutation (Abst 6520 Proc ASCO, 2005; 23)

**CML: The only mutation cross resistant to BMS354825 is T3151 (Abst 6521 Proc ASCO, 2005; 23)

JP Issa et al MDACC (JCO 2005;23:3948-56) Decitabine 15 mg/m2 iv 1 h infusion x 5 q wk x 2. N=35 Imatinib refractory/ intolerant CML: CHR 34%, PHR 20%, MCR 17% (minor CR 29%). MDR 3.5 mo. OR were observed in Chronic Phase 83%, accelerated phase 41% and blastic crisis 34%.

CML:AMN107 (aminopyrimidine ATP inhibition of Bcr-Abl in Gleevec resistant pts demonstrated 58% OR. Effect observed at 400 mg qd but dose can be increased further up to 800-1200 mg qd. Hematological and hepatic toxicity. (Abst 3014, Proc ASCO, 2005; 23)

*** M Deninger, E Buchdunger and BJ Druker (Blood 2005;105:2640-53). Final results of Imatinib in CML: Complete haematological response, Majot cytogenetic response, Complete cytogenetic response and MST were 15%, 16%, 7% and 6.8 mo for Blast crisis; 22%, none, none and 4.9 mo for Ph+ ALL; 53%, 24%, 17% and not reached for Accelerated Phase CML; and 95%, 73%, 56% and not reached for Chronic phase CML. Corresponding results for IFN alfa + AraC were 55%, 22%, 8.5%. Resistnace to Imatinib due to increased expression of Bcr-Abl requiring dose escaltion up to 800 mg/d, mutation of Bcr-Abl (present in 50.90% of cases) requiring alternative inhibitors. Frequent mutations are P-loop mutation, mutation of t315, mutation m351, A-loop mutations and other. BMS354825 analog (2 aminothiazole 5 carboxamide) active at very good IC_{50} nM concentration against wt Bcr-Abl and mutations E255K, M351T, H396P but not T351I. None of the currently developed analogues is active against the later. Also active inhibitor of src phosphorylation.

I Iacobucci et al (JCO 2006;24:454-9). No differences in 4 y PFS (88% vs 100%) for time to complete cytogenetic response <1 y or >1y in CML.

M Talpaz et al MDACC (Clin Ca Res 2005;11:6247-55). Pegasys (PEG IFN different from PEG-INTRON) single agent >630 ug/wk or combined to AraC at MTD 540 ug/wk. OR alone 52% complete hematological remission and 11% cytogenetic response; combination to AraC 69% hematological remission and 13% cytogenetic remission. Interest in combining it to Imatinib.

****Talpaz M et al (NEJM 2006;354:2531-41). Dasatinib (BMS drug) developed from src inhibitors completely different of Gleevec, selected after cristalographic studies, at doses 15-240 mg qd (once or twice divided dose) tested in CML or Ph+ ALL resistant/intolerant to Gleevec. CML hematologic response 37/40, major cytogenetic response 45%, maintained response 95% and in accelerated phase CML/Blast crisis/ALL hematological response 31/44, major cytogenetic response 25% and maintained response 82%. No responses observed in T315I mutation fp Bcr-Abl genotype. Side effects pleural effusion and mild myelotoxicity.**

****H Kantarjian et al (NEJM 2006;354:2442-51). Nilotinib (Novartis drug) based on crystallographic studies, higher affinity binding to Bcr-Abl, TKI potency x20-50. Dose ranged 50-1.200 mg qd or 400-600 mg bid. Results: Blastic phase 33: 14 hematological response (39%), 9 cytogenetic response (27%); Accelerated Phase 43: 33 hematological response (75%) 22 cytognetic response (55%); Chronic Phase 12: 11 complete hematological response (92%) and complete cytogenetic response (35%). Liver toxicity. The T315I mutation genotypes were resistant.**

CML ALLOGENIC TRANSPLANT

**G Hess et al (JCO 2005;23:7583-93) Minimal residual disease after allogeneic transplant treated with Imatinib 400-800 mg/d. N=44. Results: 70% achieved complete molecular response (3 negative in nested PCR for Bcr-Abl) and lasting >1y without therapy in 4/10 who stopped Imatinib. Propose to combine with DLI or use alone after Allogenic transplant.

NON HODGKIN´S LYMPHOMA

NHL- MOLECULAR BIOLOGY

I Lossos et al (R Levy) (NEJM 2004; 350:1828-37). Studied 36 genes to predict survival in DLBCL and selected 3 for long-term survival (LMO2, BCL6, FN1) and 3 for short survival (CCND2, SCYA3 and BCL2). These genes carried significance independently of IPI!…

D Thorley-Lawson (NEJM 2004; 350:1328-37). EBV infects in vitro resting B cells and transforms them into proliferating blasts leading to a policlonal expansion. Their growth program is developed under EBNA2 transcription viral factors and all its genes. In vivo EBV infect germinal centre cells and express the default program with only EBNA1, LMP1 and LMP2A genes which cause cell differentiation of activated B cells into memory resting cells which are not rejected because do not express viral proteins, allowing their survival. When this memory cell divides EBNA1 allows viral DNA in latency to divide. Both HD and Burkitts express the default program EBV genes. It is not well understood how it became active and malignant transformation do occur.

B Strenbel et al (NEJM 2004;351:250-9). Microvascular endothelial cells in B cell Follicular lymphoma have and demonstrate the same genetic alterations (Fusion proteins due to translocations) as the tumor cells indicating a close relationship. Mechanism unknown.

I Lossos et al (JCO 2005;23:6351-7). Molecular pathogenesis of DLBCL: 20% p53 mutated, 20% amplification of rel, myc, bcl2, 6% t(8;14), 17-10% t(14;18), 30-40% substituted bcl6 promoter, 50% somatic mutation Bcl6, myc, pim-1, pax5, RhoA/TTF. GC-like: genes characteristic of GC Bcell (Bcl2, Rel) carry favorable prognosis with a 60% 5y OS and Non GC like made of activated B cells with genes like plasma cells, NFkB, and carry poor prognosis with a 35% 5 y OS.

JM Pagel et al (Oliver Press). (Clin Ca Res 2005;11:4857-66). Preclinical study of Anti CD20 MoAb associated to LPAAT-Beta (Lysophosphatidic acid acyltransferase Beta) that pays a role in raf, Akt/mTOR mediated signal transduction promoting apoptosis) in animal xenografts induced marked pro-apoptotic effect.

NHL AGGRESSIVE: CHEMOTHERAPY

F Reyes et al GELA (NEJM 2005;352:1197-205). Over 600 pts, compared CHOP+IF RT with intensive therapy in Stage I-II DLBCL. Final results better for intensive therapy arm: DOX 75 mg/m2 + CPA 1200 mg/m2 * VDS 1.2 mg/m2 + Bleo 10 mg d 1 & 5 + PRDNS 60 mg x 5 d x 4 followed by HDMTX 3 g/m2 + AF x 2 and consolidation with VP 300 mg/m2 + IFX 1500 mg/m2 x 4 and AraC 100 mg/m2 sq x4 q 2 wks x 2. What about RITX addition to it. Very clear results, finally…

M Crump et al, NCI Canada (Cancer 2004;101:1835-42). GEM 1000mg/m2 d 1 & 8 + CDDP 75 mg/m2 + Dexa 40 mg po d 1-4 q 3 wks, in 51 pts, most DLBCL, obtained 11 CR + 16 PR (OR 53%) (63% went on to ASCT). Add RITX?

A Goy et al (JCO 2005;23;667-75) Bortezomib 1.5 mg/m2 d 1,4, 8 &11 q 3 wk x 6. In Mantle cell ly 6 CR +6 PR (OR 41%) out of 29 assessable pts, while 2 CR + 2 PR (OR 19%) out of other pathologies 21 assessable pts.

*Aggressive NHL: BV OR 50% (Abst 6592 Proc ASCO, 2005; 23)

NHL AGGRESSIVE- BIOLOGICAL THERAPY

**NH Dang et al Ligand Pharmaceuticals and MDACC (JCO 2004;22:4095-102). Denileukin Diftitox (Fusion of Diphtheria toxin and IL2) to target IL2R (CD25, CD122, CD132) 18 ug/kg iv in 45-60 min x 5 q 3 wk x 8. N=45 pts all with prior ChX and RITX, all refractory B cell. Obtained 6.7% CR (3) + 17.8% PR$ + 20% NC, MTTP 7 mo, MPFS at 2 y 24%, Toxicity mild transient, haematological. OR not related

to presence of CD25 so the target might be CD122. T cell lymphomas had demonstrated response in prior trials. Very interesting data. Ready for combination studies?

A Younes et al MDACC (Clin Ca Res 2004;10:5432-8). Phase II study of IL12, at 250 mg/kg qd x 5 q 3 wk iv or 500 mg/kg sq biw, in N=42 (16 prior ABMT) and found 6/29 assessable with OR (21%) in NHL and =/10 in HD, increase in T8 (from 423/ul to 576/ul), decrease in VEGF and BFGF (37%). Deserve further study.

NHL-AIDS ASSOCIATED LYMPHOMA

N Mounier et al (Blood 2006;107:3832-40). Review series of AIDS treated patients with different chemotherapy intensity adapted protocols including ACVBP, CHOP, low dose CHOP and others) according to HIV score (PS, prior AIDS, CD4+ count <0.1x10e9/L, as well as IPI or HAART therapy. Dose intensity did not affect OS but HIV score IPI and HAART did.

NHL – CNS PRIMARY

A Ferreri et al International Consensus Statement Lugano 2002 (JCO 2003;21:2407-14). HDMTX >1 g/m2 OR 50-80%; WBRT 45 Gy OR 30%, Combined 3 y OS >50%, HDChX+PBSCT 3 y OS >60%. Leptomeningeal lymphoma: Depocyte q 14 d. Ocular lymphoma: HDMTX >8 g/m2 reaches micromolar concentrations of MTX in vitreous and aqueous humor.

H Pels et al (JCO 2003;21:4489-95) N=65, Mf Up 26 mo. No RT given ChX: HDMTX 5 g/m2 cycles 1, 2 , 4 & 5. AraC 3 g/m2 x 2 cycles 3 & 6. DXMT+VDS+IFX+CPA, Intrathecal MTX 3 mg x 4 + PDRNS 2.5 x 4 + AraC 30 mg x 1. Results: CR 61%+PR10%, TD 9%. MTTF 21 mo, MOS 50 mo.

P Portmans et al (JCO 2003;21:4483-8). N=52, M F Up 27 mo. MTX 3 g /m2 d 1 &15 + VM26 100 mg/m2 d 2 & 3 + BCNU 100 mg/m2 d 4 + PDRNS 60 mg/m2 d 1-5 + intrathecal MTX 15 mg-AraC 40 – HOCostisone 25, then RT 40 Gy. Toxicity 3-4: 78%, OR 81% (all but 2 patients had a CR). MOS 46 mo.

S Plotkin et al (Clin Ca Res 2004;10:5643-6). HD MTX (>3 g/m2) single most active agent in CNS-NHL. Most of CR relapse. N=22, median age 58 yo. OR 91% first salvage (MST 61 mo) and 100% second salvage (MST 92 mo).

NHL- BONE NHL

K Beal MSKCC (cancer 2006;106:2652-6). Review series of 101 patients, median age 48 yo, M F up 67 mo. Results: 80% DLBCL, 81% stage I-ii. Treatment 57% combined RT/ChX; 30% ChX alone and 14% RT alone. 5yOS 88% and 5 y FFTF 81%. 5y OS combined modality 95% vs 78% for single modalities.

NHL- CUTANEOUS B-CELL LYMPHOMA

B Smith et al (JCO 2004;22:634-9). N=34. Follicular center cell 53%, marginal cell 13% and LBCL leg 9%. 5yRFS all sites 62-73% except leg 33%; 5 yOS 100% all sites and leg 67%. Recommend RT, most are indolent.

PL Zinzani et al (JCO 2006;24:1376-82). N=467 from 11 Italian Centers, 24 y observation period. Results: FCL 56.7%, MZBCL 31% nad DLBCL leg type 10.9%. RT first modality 52.5% and ChX first line therapy 24.8%. CR 91.9%; Relapse rate 46.7%. 5yOS 94%; 10y OS 85%. Leg type less CR and multiple cutaneous relapses.

NHL- DLBCL

B Coiffier et al (JCO 2005;23:6387-93). Advances in 1995-2005 in the therapy of LBCL are: Addition of RTX into induction and maintenance, dose dense programs (q 2 wks) and BMT displacement to high risk young patients. Radioimmunotherapy ?.

NHL- SMALL NON CLEAVED CELL LYMPHOMA

***** Nancy L Harris and SJ Houring, Editorial (NEJM 2006;354:2495-8), M Hummel et al (NEJM 2006; 354:2419-30) and SS Dave et al (NEJM 2006;354:2431-42). Use of molecular markers (Dave) and microarrays (Hummel) to define BL signature genes was demonstrated. Confusion in BL diagnosis is frequent because BL like features are very common. In both series 17-34% of BL were called DLBCL; 0.4-4% non BL were called BL like; and 3-8% of DLBCL had a BL signature. The message according to N Harris et al is that myc rearrangement is not enough to confirm the histological diagnosis and more markers are needed. Features of BL are: IgG-myc only translocation, the classical immunophenotype CD10+, Bcl6+, Bcl2- and the new CD44-, MUM1-, TCL1+, HLA1-, CD23- and cyclin H-. For the other part features of non BL are: Non IgG-myc trasnlocation or myc negative (other myc rearrangements allowed), and other Bcl2/ Bcl6 translocations, the classical immunophenotype CD10-, Bcl6-, Bcl2+ and the new markers CD44+, MUM1+, TCL1-, HLA-1+, CD23+, Cyclin H+.**

NHL CHILDREN

S Murray Yule et al (Clin Ca Res 2004;10:455-60). Metabolism of CPA in 36 children. Pts with DFS had a clearance rate of 3.7 liter/hour/m2 (r 2.3-5) as compared with pts with recurrent disease who had a clearance of 2.2 (r 1.5-2.5).

**K Seidemann et al (BFM95) (JCO 2005;23:8414-21). Studied TNFalfa and Lymphotoxin alfa polymorphisms in 488 patients and found $TNF^{308G>A}$ homozygous are low producers and LT $alfa^{252A>G}$ homozygous are also low producers. TNF and LT high producers (N=146) had a 3 y PFS 69% while TNA and LT low producers (N=342) had a 3 y PFR 85%, risk of events x2.34 (probably related to sepsis, complications and dose density/intensity of chemotherapy).

NHL AGGRESSIVE: BONE MARROW TRANSPLANT

N Mielpied et al GOELAMS, France. (NEJM 2004;350:1287-95). Pts 200 with untreated aggressive pathological types, 15-60 yo, MFU 4 y. Randomized CHOP x 4 and CPA 1200 mg/m2 + EPI 100 mg/m2 + VDS 3 mg/m2 + PRDN 80 mg x 5 q 2 x 2, then MTX 3 g/m2 + AraC 100 mg/m2 civi/d x 5 d on d37 and BCNU 300 mg/m2+ Ara C 400 mg/m2/d x 4 d LPAM 140 mg/m2 d 66. 5yEFS 37.5% vs 55.5%. Better outcome for HD therapy.

A Martin et al Salamanca (BMT 2004;33:579-87) Total VP> 750 mg/m2 relates to low CD34+ yield and delayed platelet recovery. CD34+ > 1.2 M/kg assures haematological recovery. Transplant related mortality correlate with high cumulative dose (>16 mg/m2) & RT before ABMT, as well as total VP (>350 mg/m2) and PCBZ use. N=103 pts, TRM 5.4%.

**M Escalon et al MDACC (JCO 2004;22:2419-23). Non-myeloablative allotransplant for recurrent NHL after autologous transplant. N=20. FLUDARA 30 mg/m2 qd x 3 + CPA 750 mg/m2 qd x 3 + RITX x 3 at standard doses or addition of CDDP 25 mg/m2/d civi x 4 d + AraC 100 mg/m2 d x 2. Tacrolimus+ MTX

to prevent GVHD. Results: AGVHD gr 2, 5%. 1 PD at 115 d responded to DLI. Rest of pts are DFS (MFup 25 mo), 3y PFS 95%. Excellent.

G van Imhoff et al Dutch-Belgian Group (JCO 2005;23:3793-801). Report two non randomised trials involving 147 pts, 80% DLBCL. Program 3 CHOP and then sequential HD-1 (CPA 4 g/m2 +DOX 70 mg/m2 + PRDNS 100 mg x 5) followed by HD2 (VP 2 g/m2 + MTZ 30 mg/m2 + PRDNS 100 mg x 5) and then BEAM-ASCT + IFRT . These results were compared with first series treated with same program without the initial 3 CHOP and found that CR was better (51% vs. 45%), 4 yOS also better (50% vs. 21%) and 4 y EFS 49% vs. 15%. Induction is convenient.

**IF Khouri et al MDACC (JCO 2005;23:2240-7). Studied HD RITX associated with BEAM + SCT. Program consisted in RITX d 1 before ChX and repeated d 7 (375 mg/m2) together with GCSF and GMCSF at mobilization and then d 1 & 8 after SCT at 1000 mg/m2. Results in 67 pts were 2 y OS 80% (historical control without RITX 53%) and 2 y DFS 67% (historical control without RITX 43%). MFup 20 mo. No more infections reported. Quite promising.

***J Vose et al U Nebraska (JCO 2005;23:461-7). Treated 23 pts with refractory/relapsed B cell NHL with I-131 Tositumomab + BEAM + ASCT. I-131 Tositumomab Phase I MRD 0.75 Gy TBD. Results showed with a MF up 38 mo, OS 55%, EFS 39%, similar toxicity to BEAM. Double DFS from 20.3% to 39%.

NHL LOW GRADE

NHL LOW GRADE- CHEMOTHERAPY

PL Zinzani et al Italian Cooperative Group (JCO 2004;22:2654-61). N= 150 pts untreated FL. Randomized to FLUDARA + MTZ + RITX if PR or if BCl2+ at the time of CR vs. CHOP + RITX same criteria. CR 68% vs. 42% and final CR PCR negative 71% vs. 51% indicating up front better results for FM although at 19 mo M F up no differences found in PFS or OS.

*A Forero (Blood 2004;104:227-36). Pretarget therapy consisted in injection of a single chain antiCD20 streptavidin fusion protein B9E9FP targeting B cell NHL, 160-320 mg/m2, and 48 h later inject a synthetic clearing agent 45 mg/m2 to remove unbound B9E9FP, and 24 h later administer Y-90-DOTA-biotin (15 mCi/m2)/In-111 (5 mCi) to target B9E9FP bound B cells. Treated 15 pts. Tumor:whole body RT dose 49:1. No haematological toxicity. 2 CR and 1 PR. Currently escalating the dose of Y-90-DOTA-Biotin.

*Indolent NHL: Treanda (Bendamustine), 120 mg/m2 d 1 & 2 q 3 wk x 3 + RITX. N=63 in 2nd or 3rd relapse. OR 90%, CR 60%. On going a Phase III studyu comparing it to CHOP+ RITX (Abst 6564 Proc ASCO, 2005; 23)

*Low grade NHL: BMS 247550 (epothilone analog), 25 mg/m2 wkly x 3 q 4. Phase I: N=11 pts, 6/9 major OR. Remarkable. (Abst 6569 Proc ASCO, 2005; 23)

*Indolent NHL: Bendamustine 90 mg/m2 d 1 & 2 + MTZ 10 mg/m2 d 1 + RITX 375 mg/m2 d 8 q 4 wk x 4. N=46 relapsed/refractory NHL. CR 40% without RITX and 88% with RITX. (Abst 6616 Proc ASCO, 2005; 23)

**J Hainsworth et al (JCO 2005;23:1088-95). N= 114 pts with indolent NHL previously treated with ChX. Randomised to RITX x 4 q 6 mo vs. RITX x 4 then at progression. Found OR 52% (CR 27%) vs. 35% (CR 4%), PFS 31.3 mo vs. 7.4 mo, 3y OS 72% vs. 68% and duration of RITX benefit 31.1 mo vs. 27.4 mo, favouring maintenance RITX, because of more NED and CR rate but no differences in OS. Recommend continuing RITX in maintenance?

**MS Czuczman et al RPCI (JCO 2005;23:694-704). Treated 40 pts, majority with low IPI 0-2. FLUDARA 25 mg/m2 x 5 on d 7 + RITX 375 mg/m2 x 2 (d1 & 4) and then on cycles 2,4, 6 & then x2 4 wks from last ChX. Total therapy duration 26 wks. Used GCSF in second series after found myelotoxicity. OR 90%, CR 80%. Molecular remission t(14;18) 88%, already some are NED>4 y. MDR >40 mo. Decreased number of T and B cells but not NK cells which are spared. 15% herpes zoster. That was better than expected from CHOP RITX (OR 100%, CR 57%). Literature support also FLUDARA>CHOP (OR 65%, CR 37% vs. OR 64% CR 9% respectively). Very good as first line therapy.

**L Gordan (JCO 2005;23:1096-102). Dosing of RITX in maintenance according to PK levels, targeting 25 ug/ml. Treated 312 pts with an OR 59%, CR 27% (FL OR 63% CR 36%). RITX was given 375 mg/m2 wkly x 4 and the maintenance. Median time to first bolus iv single dose was 5 months, to the second next dose 3.5 months and to the third dose 3 months. Single dose maintenance was correct to achieve PK levels. Important data.

S Horning et al (JCO 2005;23:712-9). I-131 Tositumomab (BEXXAR) in pts after progression to RITX. Standard dose 0.65-0.75 Gy TBD according to platelet count, and based on dosimetric calculations. FL OR 86% CR 59% 3y PFS 48%. Very good results.

JW Friedberg et al (Clin Ca Res 2004;10:7789-91). Reviewed radioimmunotherapy: Zevalin (Ibritumomab tiutexan Y-90) was approved by the FDA in Feb 2002. Zevalin was better than RITX in relapsed pts (RITX OR 56% CR 16% and Zevalin OR 80% CR 30%). BEXXAR was approved by the FDA in June 2003, demonstrating to be better than Tositumomab alone (Bexxar OR 55%, CR 33% and Tositumomab OR 17% CR 8%). Problems are related to: Long term toxicity, with appearance of MDS 1.45% yearly similar to ChX; optimal timing preferred for consolidation of first OR (2 y PFS 81%, better

than CHOP-RITX); Role in aggressive NHL; myeloablative radioimmunotherapy + ASCT/AlloSCT; and Retreatment.

**OW Press et al SWOG (Blood 2003;102:1606-12). CHOP and then consolidation with I-131 Tositumomab: OR 90%, CR 67%, 2y PFS 81%. Excellent.

N Di Bella (Cancer 2005;103:978-84). N= 24 pts, untreated stage III-IV, low grade, med age 62 yo. Pentostatin 4 mg/m2 d 1 & 8 + MTZ 10 mg/m2 d 1 + RITX 375 mg/m2 d 1 & 8 q 4 wk x 5. Results were 12 CR + 8 PR. MDR 10 mo. Active and well tolerated.

D O'Connor et al (JCO 2005;23:676-84). Bortezomib Phase II, at 1.5 mg/m2 d 1, 4, 8, & 11. N=26 pts. FL: 10 pts, 2 CR+ 4PR ; SCL &CLL No responses observed; Marginal zone 2/2 PR and Mantle cell: 1 CR + 4 PR + 4 NC. Active in certain types, important for Mantle cell lymphoma.

NHL LOW GRADE- IMMUNETHERAPY

W Weng et al (R Levy) (JCO 2004;22:4665-72). N= 136 pts treated with idiotype vaccination (inducing anti-idiotype immuneresponse). 47% developed responses measured humoral responses (FcgammaRIIIa and FcgammaRIIa). The polymorphisms Fcgamma RIIIa 158V/V had longer PFS than V/F or F/F genotypes (PFS 8.21 y vs 3.38 y). The T cell response was not related to the outcome. Unexpectedly polymorphisms of Fc was related to clinical outcome.

*S Neelapu et al NCI (Clin Ca Res 2004; 10:8309-17). Liposomal Vaccine made with (per mL basis) idiotype protein IgG (isolated by heterohybridoma fusion) 2 mg + 4x10e6 IU IL2 + 160 mg dimyristoyl phosphatidyl choline (generation of liposome). Administered 0.5 mL x 4 sq injections x 5 doses months 0, 1, 2, 3, & 5. Type I cytokine response and antitumor response obtained in 9/10 and 10/10 pts respectively, persisting 18 months the CD4+ and CD8+ cells, and Ab antiId in 4/10. With a MFup of 50 mo 6/10 in CR (first CR). Safe and effective liposomal vaccine.

C Eisabeis et al (Clin Ca Res 2004;10:6101-10). IL2 1 M IU/m2 qd x 4 wk (bolus 3-15 M IU/m2 x 2 at mid term) + RITX 375 mg/m2 wkly x 4. Based on a mouse SCID model with a very good synergism among IL2 and RITX, obtaining cures where none of the drugs alone could obtain it. Monitored NK and cytotoxicity which were both elevated during the treatment. OR 22%. Not remarkable…

G Levy et al (JCO 2004;22:4926-33). Incidence of secondary haematological malignancies at 5 y 3.8% after intensive ChX + ASCT while remain O% after RITX.

NHL LOW GRADE- BMT-SCT

NHL- FOLLICULAR LYMPHOMA

P Solal-Celigny et al (Blood 2004;104:1258-65) Follicular Lymphoma IPI. Factors: >60 yo; Stage III-IV; LDH >2; Hb <12 g/dL; & > 4 nodal areas (cervical R, Cervical L, mediastinum, axillary R, axillary L, epitrochlear R epitrochlear L,, mesenteric, paraaortic, inguinal R, inguinal L, popliteal R & popliteal L). Score : Low 0-1, 36% cases, %yOS 90%, 10 y OS 70%, RR=1; Intermediate 2, 37% cases, 5yOS 77%, 10y OS 50%, RR 2.3 and High 3, 27% cases, 5 yOS 52% and q10 y OS 35%, RR 4.3

***SS Dave et al NCI (NEJM 2004;351:2159-65) Gene expression profiling identified prognostic value for FL the presence of TIL. Analysed 191 pts. Genes of Immune response type 1 (T cells): Death RR

0.15, 5yOS 85% and 10 y OS 55%. Genes of Immune response Type 2 (macrophage and dendritic cells) Death RR 9.35, 5yOS 38% and 10 y OS 30%. Completely unexpected results. Not observed in DLBCL…

FL: 3 CHOP-RITX followed by consolidation with Zevalin: Initial OR 100% with CR 28%, after Zevalin CR 67%. Mfup 20 mo, 2yPFS 77%. Highly active so far (Abst 6577 Proc ASCO, 2005; 23)

AZS Rohatiner et al (JCO 2005;23:2215-23). Meta-analysis of IFN alfa2, 10 Phase II studies with 1922 pts, showed: Addition of IFNalfa2 to primary ChX do not influence OR; meta-analysis of OS showed some benefit with controversial results, improving the results a relative intense initial ChX, at >5 MU doses, at cumulative doses > 36 MU per month and together with associated ChX as a maintenance therapy; finally remission duration better for IFNalfa2.

****M Kamisnki et al (NEJM 2005;352:441-9). I-131 tositumomab as initial therapy for FL. Series of 26 pts, selected age, <25% BM involvement and < 500 g of tumor total burden, stages III-IV. BEXXAR classical therapy with 75 cGy TBD in < 4 wks time administration. OR 95%, CR 75%, complete molecular response (80% of CR by PCR analysis of bcl2). MF-up 5.1 y, 5yPFS 59%, MPFS 6.1 y. After 3 y the yearly recurrence is of 4.4% each year. Out of the 57 CR response pts, 40 remain NED 4.3+ to 7.7+ years. No myelodysplastic syndrome. It appears as an attractive option even without randomisation… What about a consolidation with RITX?.

M Kaminski et al (JCO 2005;23:7985-93). Retreatment with Bexxar after a prior OR >3 moin N=32. OR 56% (CR 25%), MDR 35 mo (1.8 to 5.7+ y) No differences in the quality of the response. Similar toxicity 43-55% WBC/platelet.

**Valproic acid inhibits histone deacetylase and potentiates topoisomerase II inhibitors. Study of Valproic acid loading (Depakine 15-60 mg/kg followed by EPI 75 mg/m2 in pts resistant to anthracyclines demonstrated OR in 4/13, NC 3/13 and PD 6/13. Need to confirm these good results. (Abst 3084 Proc ASCO, 2005; 23)

*J Leonard et al (JCO 2005;24:5696-704). N=35. Induction with Fludara x 3 cycles (OR 89% and CR 9%) followed by Bexxar (OR 100% and CR 86%). M F up 58 mo: MPFS > 48 mo & 5 yPFS >60%. Bcl2- in 77%. Developed HAMA 6%. Highly effective in low-intermediate IPI FL.

SA Jacobs et al (Clin Ca Res 2005;11:7146-50). Full dose Zevalin after BMT was OK.

JP Leonard et al (JCO 2005;23:5044-51). Epratuzumab (anti CD22) 360 mg/m2 wkly x4 +RITX 375 mg/m2 wkly x 4. N=23 recurrent NHL. Results: FL OR 67% and CR 56%; DLBCL OR 67% and CR 42%. MTTP 17.8 mo. Encouraging CR rate.

M Czuczman et al (JCO 2005;23:4390-8). Galiximab (antiCD80) 125.500 mg/m2 wkly x 4 in FL. N=37. Side effects fatigue, nausea, headache, anemia or neutropenia absent (only 1 patient). Half-life 13-24 d. OR 11% and NC 34%.

CLL

CLL- MOLECULAR BIOLOGY

*J Orchard et al (Lancet 2004;363:105-11). ZAP-70 is a TK protein expressed by T and NK cells, co expressed in CLL with a correlation to unmutated IgVH genes, carrying a poor prognosis. ZAP-70 can be detected by cytometry. Studied 167 pts: 108 mutated had ZAP-70 negative and 6 mutated were ZAP-70 positive. Among unmutated 46 were ZAP-70 positive and 7 ZAP-70 negative. ZAP-70 negative MST 24.4 y and ZAP-70 positive MST 9.3 y, equivalent to results of IgVH gene mutational status (unmutated is a pregerminal center malignancy carries a worst prognosis and mutated is a postgerminal memory cell malignancy with a better prognosis).

L Rassenti et al (NEJM 2004;351:893-901). N = 307 pts. ZAP-70 present in 117/164 pts with unmutated IgVH gene (71%) revealing a poor prognosis risk group, while only 24/143 with mutated IgVH gene (17%) had it. It is a predictor of the need of therapy.

*M Albitar et al. (Cancer 2004;101:999-1008). Circulating CD52 in serum binds to Campath and prevents its action on CLL cells. IT should be measured by ELISA. With low circulating levels of CD52 Campath could be given at lower doses…

*J Starczynski et al (JCO 2005;23:1514-21). Polymorphism G(-248)A in the promoter of the Bax gene (occurring in about 15% of the normal population) was found in 26% of CLL (N=203 pts) and associated withy lower bax expression and shorter OS. G/G genotype had a 10 y OS 95% while GA and AA genotype had a 10y OS 60%. It was not related to VH mutation, always worsening survival.

A Krober et al (JCO 2005; 24:969-75). ZAP70 + and VH mutation are highly correlated (concordance 84%) if no other genetic alterations are seen and predict clinical course. When other genetic alterations are present discordance is 39%, that is 92% are ZAP70 – and VH unmutated.

I Del Giudice et al (Cancer 2005;104:2124-32). ZAP70+ (20%) and del 13q confer high risk with time to treatment of 12 mo when both positive, 54 mo for both negative and 26 mo for discordant results.

CLL CHEMOTHERAPY

JF Rossi et al (JCO 2004;22:1260-7). Oral Fludarabine phosphate 40 mg/m2/d x 5 d q 4 wk x 6-8. OR 71.6%, MTTP 841 d. Myelotoxicity. Similar efficacy and safety to iv formulation.

M Keating et al MDACC (JCO 2005;23:4079-88). Initial therapy in 224 pts. FLUDARA 25 mg/m2 d 2-4 cycle 1and d 1-3 cycles 2-6 + CPA 250 mg/m2 d 2-4 cycle 1 and d 1-3 cycles 2-6 + RITX 375 mg/m2 d 1 and 500 mg/m2 d 1 cycles 2-6, cycles repeated every 4 wks. CR 25% + PR nodes 16% + PR 32% (OR73%). 12/37 (32%) molecular bone marrow remission

*CLL: Lenalinomide (Revlimid) immnunomodulatory agent down regulating VEGF/TNFalfa, 25 mg po qd x 21 d q 4 wk. 6/7 OR (1CR+5PR)

CLL: Fludara 30 mg/m2 x 3 d + Campath 30 mg x 3 d q 4 wk x 6 in N=37. OR 83% (11CR+19PR, 47% MRD negative by flow cytometry in peripheral blood/BM. FFTF 12.8 mo (Abst 6558

*CLL: ZAP70+ poor prognosis (IgVH unmutated). Allogeneic BMT overcomes poor prognosis and should be considered earlier. N=25. 2yOS 91%. (Abst 6559 Proc ASCO, 2005; 23)

*JC Byrd CALGB (Clin Ca Res 2005;11:4176-81). Flavopiridol Phase II 50 mg/m2/d civi x 3 d q 2 wk, N=15 pts, No responses observed. Phase II 50 mg/m2 1 h iv qd x 3 q 3 wk, N=36 pts, 4 PR (11%) and 19 NC (53%). Modest schedule dependent activity.

G Del Poeta et al (Cancer 2005;104:2743-52). RITX 375 mg/m2/wk x 4 + Fludara 25 mg/m2 x 5. N=60, ZAP70 stratification, untreated. Results: 78% CR+ 15% PR. 3 y PFS= 68%. In ZAP70+ cases PFS 25% at 3 y vs 100% in ZAP70-.

*T Elter et al (JCO 2005;22:7024-31). Fludara 30 mg/m2 x 3 + Alemtuzumab 30 mg (4 h iv) x 3 q 4 wk (First doses of Alemtuzumab in 3 days: 3 mg-10 mg and 30 mg). N=36, prior chemotherapy lines 2.6, Binet C 28 and several patients were refractory to both drugs as single agents. Results: OR 83%, CR 30%. 2 fungal pneumonia and 1 septic death due to E coli., CMV reactivations. Require Septrin and Valacyclovir preventive therapy. Continue Ganccyclovir 500 mg tid x 2 months after last Alemtuzumab dose.

**WG Wierda, T Kipps and M Keating (JCO 2005;23:6325-32). Review Alemtuzumab, antiCD52. Therapy 30 mg iv tiwk x 12 wk, OR 33%, CR 2%, MTTP 9.5 mo and MOS 16 mo. Very active clearing blood CLL and less so clearing lymph node disease. OR in naïve patients CR 19%, PR 68%. Results with RITX Cr3% and PR 42%, and combination of ALEM + RITX OR 52% and CR 8%. Lumiliximab (antiCD23) OR 50%, no CR, now proceeding to Phase II with doses 500 mg tiw x 4. Apolizumab

(antiMHCII) 3mg/kg tiw x 4. AntiCD40 (CHIR12.12). Fludara + RITX OR 50-97%, CR 35%. Fludara+ ALEM OR 80%, CR 30%. Fludara+CPA+RITX CR 70%, 4y PFS 69% untreated and OR 75%, CR 25% treated. Fludara+CPA+RITX+ALEM OR 55% and CR 23% poor risk. Pentostatin (4 mg/m2 d 1) + CPA+ RITX OR 80% and CR 30%.

A E Frankel et al (Cancer 2006;106:2158-64). Denileukin diftitox 18 ug/kg/d x 5 in 1 h iv infusion q 3 wk x 8. N=22 evaluable/28, 12 PBL response (>80% reduction) and 6 lymph node response (1 CR + 5 PR, 27%) PFI 2-12 mo.

****P Hillman (Sem Oncol 2006;33:S23-8). Review current advances: ZAP70 >30% poor prognosis; IgV_h non mutated (pregerminal) also poor prognosis. According to cytogenetics there are 5 groups: 17p deletion (7%) MST 36 mo; 11q del (17%) MST 60 mo; 12 q trisomy (14%) and normal karyotype (18%) MST 10 y; and 13 q del (sole abnormality) (36%) MST 12 y. Detection of minimal residual siease is improved by selecting B cells by gating CD19 and then differentiate cion of CLL using antibodies to CD5, CD20 and CD79b. CD38 (Ag of normal B cll differentiation) is highly sensitive to differentiate neoplastic CLL cells from normal lymphocytes (MRD<0.05 CLL). Alemtuzumab new strategies include consolidation and MRD therapy. Alemtuzumab consolidation after a CR (30 mg tiwk course x 12) converted 38% to PCR-CR. Autotransplant improved MST (49 mo) in unmutated IgV_H (increasing 10 y OS from 20% to 57%).**

****Eichhorst BF et al , German Trial (Blood 2006;107:885-91) N=250. Randomized study: Fludara 20 mg/m2 d 1-5 + CPA 600 mg/m2 d 1 + GCSF vs Fludara (CR 21 vs 9%, OR 94 vs 85%, TTP 28.2 vs 18.6 mo.**
****Flinn IW et al ECOG (Blood 2004;Abs475, 1399). N=250. Randomized trial: FC vs F: CR 22 vs 6%, OR 70 vs 50% nad RFS 41 vs 18 mo.**

Aloyz R et al (Leukemia 2004;18:409-14) Imatinib sensitizes CLL lymphocytes to Chlorambucil.

Stilgenbauer et al (Blood 2004;104:478 abstr). Alentuuzumab iv first wk and then 30 mg sc. Acute side effects minimized and blood levels equal, with delay to reach target level of Alentuzumab. OR similar to iv route.

**** Montillo F et al (JCO 2006;24:2337-42). N=34, <60 yo, with OR to Fludara induction. Alentuzumab 10 mg sc tiwk x 6 (consolidation strategy and bone marrow purging before ASCT). CR improved from 35% to 79.4% and 59% (19) had MRD negativity. CMV reactivation in 18 patients (oral gancyclovir). PBSC were recovered after AraC + GCSF for autologous transplant. 18 were autograftedand it was feasible (Was it necessary?).**

***N Lamanna et al (JCO 2006;24:1575-81). N=46 treated CLL 32, median age 62 yo and median prior therapies 2. Pentostatin 4 mg/m2 + CPA 600 mg/m2 + RITX 375 mg/m2 q 3 x 6 (plus GCSF, Septrin and Acyclovir). CLL results: 24 OR (75%), 8 (25%) CR. Fludara refractory OR 75%. Quite good results.**

P Ghia et al (Blood 2003;101:1262-9). N=108. CD38- : 57.4%, IgV_H mutation 88%, Progressive disease 12.9% and MST 100% alive at 20 y; CD38 bimodal presentation : 27%, 57.4%, IgV_H mutation 32%, Progressive disease 63.3% and MST 70% alive at 15 y; finally CD38+ : 14.8%, IgV_H mutation 15.4%, Progressive disease 75% and MST 20% alive at 20 y.

CLL BMT-SCT

P Dreger et al (Blood 2004;103:2850-8). Risk matched analysis comparing ASCT in high risk CLL proved favourable even in pts with VH mutated group. This study was done to fund a randomised trial.

E Montserrat (Blood 2006;107:1276-83). Allotransplant (for <50 yo) survival plateau 30-60% using Fludara+LPAM and Alemtuzumab maintenance. Transplant related mortality 18% at 1 y.For patients >50 yo miniallotransplant.

C Moreno et al (E Montserrat) (JCO 2005;23:3433-8). Allogeneic SCT overcome adverse prognostic of unmutated VH gene. N=34: 14 allo (5 y relapse rate 12%) and 20 auto (5 y relapse rate 61%). Unmutated and autotransplant 13/20 recurred, 5 y relapse 66%. Unmutated allotransplant 2/14 recurred and 5 y relapse rate 17%. Allotransplant abrogates VH unmutated prognostic value.

M Sorror et al (JCO 2005;23:3819-29). Non myeloablative allotransplant with conditioning TBI 2 Gy + Fludara, N=64, 61 grafted. Grade III AGVHD 14%, Grade IV AGVHD 2% and CGVHD 50%. OR 67%, all in CR had PCR confirmation but 2 recurred. 2 y EFS 26%, 2 y Relapse non relapse mortalities 18.22%, 2 y OS 6% and 2 y DFS 42%.

MALT LYMPHOMA

A Ferreri et al S Raffaele Milan (JNCI 2004;96:586-94). Association between Clamydia psitacci and ocular adnexal lymphomas: 32/40 samples carried C Psitacci DNA. Treatment with 1 mo doxycycline cleared it and induced an OR in 2/4 pts.

A Woy et al MSKCC (JCO 2005;23:3768-72). N= 24 pts with satge I-IIE gastric MALT treated with IFRT 30 Gy in complete clinical and pathological response assessed by multiple random endoscopic biopsies. M F up 63 mo. 23/34 were in clinical and pathological CR. 14/17 cloned specific pairs showed PCR positivity. It may suggest that monoclonal B cells persist but do not grow because H pylori specific T cells were eradicated by treatment and then B cell lack critical local growth factors…

P Farinha and RD Gascoyne (JCO 2005;23:6370-8). Molecular pathogenesis: Helicobacter pylori associated to gastric MALT Lymphoma, Campylobacter jejunii in the iontestinal, Borrelia brugdorferi in the skin, Chlamydia psitacci ocular and salivary and thyroid unknown germs. All types, independent of the molecular pathways involved have NFkB signalling activation. With Hp-gastric MALT data the molecular classification is as follows: Hp dependent 74% initiate with allelic imbalance, methylator phenotype and trisomies 3, 12 & 18, which is sensitive to antibiotics and might progress Hp independence acquiring other genetic alterations and telomerase transforming into DLBCL. Another group is formed by 5% Hp independent gastric MALT with <1% t(14;18) or <1% t(3;14) or 3% t(1;14) which progress early to DLBCL. Finally is a group of Hp independent 22% t(11;18) which rarely progress to DLBCL and can be multicentric, spreading to other mucosal sites.

*LT Chen et al (Taiwan) (JNCI 2005;97:1345-53). Stages IE and IIE1all treated with 2 wks antiHp therapy, M F Up 5 y in CR: Low grade HP MALT gastric (N=34) with CR Hp 97%, CR Ly 80% and recurrences 13%. High grade DLBCL MALT gastric (N=24), CR Hp 92%, CR Ly 64%, Recurrences 0.

*T Winsdisch et al (JCO 2005;23:8018-24). Stage IE1 gastric MALT followed after Hp eradication. M F Up 75 mo. 5y OS 90%, 80% CR nad 80% of CR had complete histologic remission. 3% relapsed and 17% showed residual disease (all entered a later CR. Patients with t(11;18) had a poor rate of CR and higher relapse rate (15% of all cases).

*A Ferreri et al (JCO 2005;23:5067-73). Regression of ocular adnexal lymphoma after erradication of C Psitacci (present in 80% of cases) with Doxycycline 100 mg bid x 3 wk. N=9. OR: 2 CR + 2 PR + 3 mR. MDR 1+ to31+ mo. Active after multiple relapses.

*****AM Tsimberidou MDACC (Cancer 2006;107:125-35). Maeginal zone lymphoma spleen type is a different category than GI MALT. N=70, median age 64 yo. CD20+ with a median 69x10e3 molecules per cell. OR to RITX 88%, 3 yOS 95% and 3 yRFFS 86%; RITX + ChX OR 83%, 3 y OS 100% and 3 y FFS 100%; and ChX alone OR 55%, 3 yOS 45% and 3yFFS 45%. RITX achieved spleenomegaly disappearance in 92%, Major contribution.**

F Suarez et al (Blood 2006;107:3034-44). Chornic Antigenic stimulation transform lymphoid cells in a different way than EBV, HHV8, HTLV-1 cause lymphoma, through a mechanism of maintenance of a proliferative state: Helicobacter pylori-Gastric lymphoma, Campylobacter jejunii- small intestinal lymphoma, Borrelia burgdorferi- cutaneous lymphoma, Chlamidia psitacci- ocular lymphoma, and Hepatittis C Virus- spleen lymphoma.

HAIRY CELL LEUKEMIA

*B Falini et al (Lancet 2004;363:1869-71). GEP analysis indicated that Annexin A 1 is up regulated in hairy cell leukaemia. Anti ANXA1 MoAb developed showed specificity 100% without false + in hairy cell leukaemia. 500 samples: 62 hairy cell leukaemia, 8 variant type, 20 spleenic lymphoma with villous lymphocytes & others. Interesting because spleenic lymphoma and variant types do not respond to hairy cell leukaemia treatment.

RJ Kreitman et al (I Pastan) (JCO 2005;23:6719-29). BL22 (AntiCD22 Fv fragment fused to truncated Pseudomona exotoxin). MTD 40 ug/kg qod x 3. N=46, 36 with HCL. Results in HCL: 61% CR + 19% PR (25/31), CR after first cycle. At the MRD OR 86%. MDR CR 36 mo.

MANTLE ZONE CELL LYMPHOMA

N Berinstein et al Toronto (Sem Oncol 2004;31:2-6). Review current studies. RITX 30% OR, MDR 14.4 months. ChX + RITX (HyperCVAD) CR 92%, 2y PFS 70% (similar to ASCT?). ChX + RITX (FLUDARA + MTZ + CPA) CR 35%, MPFS 16 mo (better than FMC alone). Probably the best results are that of Gianni (Blood 2003;102:749-55). Sequential CPA 7 g/m2 –then 3 wk interval and AraC 24 g/m2 –then 34 wk interval and LPAM 180 mg/m2 and first ASCT – then 4 wk interval and MitoC 60 mg/m2 + LPAM 180 mg/m2 + second ASCT, together with RITX 375 mg/m2 x 6. Apheresis after each high dose cycle. These results were compared with controls and found 3y EFS 79% 3y OS 89% (controls were 18% and 42% respectively). Another important study is that of Mangel et al (Ann Oncol 2004;15:283-290) treated 20 pts with CHOP and mobilized with GCSF d-5 RITX. Then CBV high doses + ASCT and repeat at 2 & 6 months RITX x 4 as maintenance. 3y PFS 89% and 3 y OS 88% (controls 29% and 65% respectively).

M Rummel et al (JCO 2005;23:3383-9). Bendamustine (Double alkylating agent with a purine structural ring shape) 90 mg/m2 in 30 min iv d 1 & 2 + RITX 375 mg/m2 d 1, q4 wk x 4. FL: 24 pts, OR 96%; MCL 16 pts, OR 75%, CR 50%; CLL 17 OR 100 and MALT 6 pts OR 83%.

MCL: CCI779 (mTOR KI) in relapsed MCL. 25 mg wkly. PR 4/8 + NC 4/8. All pts were t(11;14) and refractory (Abst 6504 Proc ASCO, 2005; 23)

*MCL: Velcade 1.3 mg/m2 id d 1, d4, d8 & d11 q 3 wk x 4. N=48 refractory. OR 40% (Abst 6563 Proc ASCO, 2005; 23)

G Lenz et al German Low Grade Lymphoma Group (JCO 2005;23:1984-92). N= 122. Randomized to CHOP +RITX vs CHOP. OR favored RITX association (94% vs 75%) as well CR (34% vs 7%) and TTF 21 mo vs 4 mo, but had no differences in PFS. RITX appeared very active in this setting.

** JE Romaguera et al (JCO 2005;23:7013-23). HyperCVAD + RITX consisting of Cycles 1, 3, 5 & 7: RITX 375 mg/m2 d 1 + CPA 300 mg/m2 in 3 h iv q 12 h x 6, d 2-4 + DOX 16.6 mg/m2 civi/d 72 h, d 5-7 + VCR 1.4 mg/m2 d 5 and d 12 + DXMTS 40 mg iv/po d 2-5 & 12-15. Cycles 2, 4, 6, & 8: RITX same dose + HD MTX 200 mg iv 2 h loading and 800 mg/m2 civi 22 h (FA rescue), d 2 + ARA C 3 g/m2 iv 2 h q 12 h x 4, d 3-4. Toxicity: Aplasia >60%. OR 97% (CR 87%), 3 y FFS 64%, 3y OS 82%. Recommended in <65 yo because in 75 yo 3 y FFS 73%, 5 toxic deaths and 4 MDS/AML.

*T Witzig (JCO 2005;23:6409-14). Review therapy. R-CHOP OR 95%, CR 37% vs CHOP alone OR 75%, CR 10%. RITX alone OR 30%, CR 3%. R-HyperCVAD OR 100% CR 87% and 3 y FFS 67%. Fludara 35% OR single agent. Fludara+ CPA OR 60%. R-FCM better than FCM in relapse. 2CdA OR 81%. 2Cda+MTZ OR 100% and MDR 2y in relapsed patients. RITX-2Cda OR 54% and CR 21%. Zevalin OR 33% similar to RITX. Consolidation of CR with ASCT vs Ifn alfa better ASCT (MPFS 39 mo vs 17 mo). ASCT combined to Zevalin- CPA-VP OR 100%, 3 y PFS 63%. New agents: Bortezomib 1.5 mg/m2 d 1, 4, 8, and 11 q 3 wk x 6, OR 41%, CR 10%; Thalidomide 200 mg/d up to 400 mg/d + RITX OR 81%; mTOR (CCI779, Temsirolimus) 250 mg qw OR 38%. Current practice <75 yo: R-CHOP then ASCT or HYperCVAD (without ASCT if obtained a CR), both with a risk ofMDS and death. For >75 yo RITX + purine nucleoside analog avoiding anthracyclines.

S Strauss et al (JCO 2006;24:2105-2112). Bortezomib 1.3 mg/m2 d 1, 4, 8 & 11 q 3 wk. Measured TNFalfa and IL6 in plasma. N=24 MCL. OR 29% (1 CR+ 6 PR). TNF alfa reduction was 98.% in 6 responders and 38% ibn 6 non responders.

NHL- T CELL LYMPHOMA

NHL- PERIPHERAL T CELL LYMPHOMA (PTCL)

**NHL: Depsipeptide FK228 (histone deacetylase inhibitor) active in PTCL with 5/19 OR. Some responses occurred after autologous transplant. 2 CR in PTCL and in CD30+ ALCL+ 3 PR. (Abst 3061 Proc ASCO, 2005; 23)

J Kurtzberg et al (JCO 2005;23:3396-403). 506U78 (Neralabine) AraG. Phase II in 93 pts. Adults 40 mg/m2/d 1 h iv x 5 d and children 60 mg/kg/d x 5, q 3-4 wks. OR 31%. In T cell AL, NHL and CLL OR 54%. Neurotoxicity.

S Berg et al (JCO 2005;23:3376-82). Neralabine 650 mg/m2/d x 5 q 3. OR T cell children 55%.

R Go and S Wester (Cancer 2004;101:1404-13). Review panniculitis-like T-cell lymphoma. Literature review with 156 pts. Clinical occurrence in the extremities, ulceration, poor survival and low response rate (30%). HD ChX CR 92%, MDR 14 mo. Hemophagocytic syndrome and Gamma/delta T cell receptors carried poor prognosis. Anthracyclines are active.

***C Dearder (Sem Oncol 2006;33:S44-52). Review interest of Alentuzumab in PTCL: Weidmann E et al (Blood 2004;104:2640 Abstr) DOX+CPA+FLUDARA + Alemtuzumab in 18 relapsed PTCL: OR 61%. Among newly treated patients 7/9 achieved a CR. Gallamini A et al (Ann Oncol 2005;16:321 Abstr) CHOP + Alemtuzumab: 5/9 CR + 1 PR + 1 mR. All alive > 298 d.. Rodriguez J et al Spanish GEL-TAMO (Ann Oncol 2005;16:72 Abstr). Alemtuzumab after ASCT in PTCL 5/14 OR.**

NHL- ADULT T CELL LEUK/LYMPHOMA (HTLV-1+)

**ATL refractory: Single pt treated with Campath 30 mg tiw x 4 achieved a CR > 1 y on going...(Abst 6639 Proc ASCO, 2005; 23)

F Ravandi et al (Cancer 2005;104:1808-18). Present in Japan, Caribbean countries, Southeastern USA and Centrl/South America, caused by HTLV-Type 1 virus (oncogenic retrovirus) was described in 1977. Median age 58 yo. Long latency period of infection to ATLL ranging 10-30 years. Transmision mother to child, sexual and parenteral. Start 57% acute form, 19% chronic, 19% nodal lymphoma subtype and 5% smoldering. Hepatomegaly, anlarged nodes, skin lesions, osteolysis, CNS lesions, hypercalcemia. MST 6-10 mo in acute form. 4 y OS 5% acute, 27% chronic and 63% smoldering. Therapy: AZT + IFN alfa > 58% OR, MOS 12 mo. As2O3 + IFN alfa active. Daclizumab (antiCD25)?. AntiTAC MoAb, OR 7/18 (Y^{90} tagged MoAb?). Chemotherapy not very useful. No reports on antiretroviral therapy?.

NHL-T CELL PROLYMPHOCYTIC LEUKEMIA

F Ravandi et al (Cancer 2005;104:1808-18). Phenotype CD2+, CD5+, CD7+ and CD4/CD8 60%. Cytogenetics: t(14;14)(q11;q32.1), inv(14)(q11;q32.1). Splenomegaly, lymphadenopathy+ skin infiltration and pleural effusion, lymphocyte count > 100.000/L. Small cell variant 20%, cerebriform Sezary like variant 5%. Therapy: Deoxycoformycin 4 mg/m2/wk x 4 , then q 2 wk. OR 32-48%. Alemtuzumab is the treatment of choice, OR 76% (CR 60%) MDFI 7 mo, consolidation with ASCT 3/7 cured. In untreated patients Alemtuzumab CR 100% (4/11 recurred and 4 received ASCT) Combine Deoxycoformycin and Alemtuzumab?

******A Österborg et al (Sem Oncol 2006; 33: S29-35). Alemtuzumab guidelines to improve tolerance and toxicity: First infusion associated to fever and rigors, hypotension, dyspnea 14-20% grade 3-4, due tio cytokine release (IL6, TNFalfa, IFN gamma). Corticosteriods prior to the administration oral and iv, subcutaneous administration had better tolerance (decrease >50% degree and incidence of toxic events nad permits full 30 mg doses be administered , subsequent cycles have better tolerance. No serious hematological toxicity of red cells or platelets, but neutropenia (delayed occur grade 4 in 20% (combination with Fludara makas it worse 30%).**

Transfusion with blood irradiated products, platalet transfusion as required. Neutropenic nadir at 4-6 wk. Use GCSF when ANC<500/uL and stop Alemtuzumab if ANC<259/uL or in case of febrile neutropenia. No dose reductions are recommended. Associated infections are bacterial and fungal. Of greater concern is CMV reactivation (30%)which should be monitored with PCR test, treated with Gancyclovir/foscarnet and stoping Alentuzumab. Associate always Septrin for P Carinii prophylaxis, and Valacyclovir to prevent Herpes virus infection during Alemtuzumab therapy until 2 months after discontinuatuon of treatment. TBC reactivation has been observed.

NHL- LARGE GRANULAR LYMPHOCYTIC LEUKEMIA

F Ravandi et al (Cancer 2005;104:1808-18). This includes neoplastic T cell and NK cells, CD3+, CD8+, CD16+ CD57+. Median age 55-60 yo, recurrent bacterial infections, splenomegaly, hepatomegaly 25%, neutropenia 85%, anemia 50% and thrombopenia 20%. Commonly associated to autoimmune disorders (thrombocytopenia, hemolytic anemia, pure red cell aplasia, rheumatoid arthritis and Felty´syndrome). Serology also present (hypergammaglobulinemia, circulating immunecomplexes, RA+, ANA+, etc.) MST >10 y with occasional spontaneous remissions. Treatment: Low dose MTX, CSA, CPA, PDRN.

NHL-NASAL T CELL LYMPHOMA- H&N ANGIOCENTRIC LYMPHOMA

J Lee et al (Korea) (JCO 2006;24:612-18). Review prognostic signs in N=262, M F Up 51.2 mo. 5 y OS 49.5%. Prognostic factors: B symptoms, Stage, LDH, Regional lymph nodes. Most had low IPI (85%). Scores and results were as follows: Score 1 (o Factors) 27% incidence and 5yOS 80.9%, Score 2 (1 factor) 31% and 64%, Score 3 (2 factors) 20% and 34% , and Score 4 (3-4 factors) 22% and 6% respectively. Validation required…

YX Li et al, Beijing (JCO 2006;24:181-9). RT in Stage IE and IIE. N=105, IE=83, RT alone 31, RT then ChX 34 and ChX then RT 37 patients. Results: 5 y OS 71%, 5y RFS 59%, IE 78 and 63% respectively while IIE 46% and 40% respectively. Initial RT better 83% CR vs 20% CR after ChX. RT alone 5 y OS 66% abd 5 y RFS 61%, RT represents elective therapy.

NHL-CTCL (MYCOSIS FUNGOIDES AND SEZARY SYNDROME)

Current approaches in indolent phases of the disease: IFNalfa2 + PUVA (CR 70%), IFNalfa2 + Bexarotene (300 mg/m2/d, Bexarotene+PUVA, IFNalfa2 + Acetretin 25 mg qd first wk and then 50 mg qd, Denileukion diftitox, 18 ug/Kg/d x 5 q 3 wk (OR 36%), Denileukin diftitox + Bexarotene...

***M Eileen Dolan et al (Clin Ca Res 1999;5:2059-64). O6-Alkyltransferase (AGT) measured by immunehistochemistry in 10 patients with MF showed very low levels of AGT. So far the only human malignancy with low/undetectable levels of AGT. " patients are known to have had a CR to TMZ. These results suggest an indication for TMZ or better BCNU in MF.

AM Tsimberidou et al MDACC (Cancer 2004;100:342-9). Phase II Pentostatin 3.75-5 mg/m2 qd x 3 q 3wk. N= 42. OR 54.8% (Cr 14%). MDR 4.3 mo.

Mycosis fungoides/Sezary: Suberoylanilide hydroxamic acid (SAHA, inhibitor of histone deacetylases class I and II), 400 mg qd. OR 10/37 (Abst 6571 Proc ASCO, 2005; 23)

E Marchi et al (JCO 2005;23:6163-71). GEM front line 1200 mg/m2 d 1, 8, & 15 q 4 wk. N=32, MF26, PTCT 5, Sezary 1. Results: CR 22%, PR 53%, MDR 10 mo. Very active.

LARGE CELL ANAPLASTIC LYMPHOMA (Ki1+)

A Reiter et al BFM trial.(JCO1994;12:899-908). (9 yEFS 81%)

O Linden et al (NEJM2004;351:1466-7). Daclizumab (anti CD25 receptor, IL2R). This is a single case report of a pt with LCA CD30+ cell, ALK protein, t(2;5), treated with all available treatments and BMT. Daclizumab was given 75 mg (1 mg/kg) obtaining a CR lasting > 1 y at the time of report.

NHL T CELL LYMPHOMA HD CHEMOTHERAPY AND SCT

P Corradini et al (NEJM 2004;22:2172-6). N= 17 pts. All resistant to prior ChX. Treated with TTPA+FLUDARA + CPA + Allogeneic transplant (GVH prevention with CsA + MTX). M F up 28 months. 14/17 alive NED, 3 y OS 81%, 3 y PFS 64%. Very good.

HODGKIN´S LYMPHOMA

M Federico et al. EBMT, GISL, GELA, SFGM (JCO2003;21:2320-5). N=163 M F Up 48 mo, with unfavourable HL, increased LDH, large mediastinal mass>33% width, >1 extranodal site, inguinal involvement, low hematocrit. Started with ABVD x 4 and all patients (CR, PR) then were randomized to ABVD x 4 (CR 89%, 5 y FFS 75%, 5y OS 88% and 5 yRFS 88%) or to HD ChX+ASCT (CR 92%, 5 y FFS 82%, 5 y OS 88%, 5y RFS 94%; no significant differences found).

HD early stage: GELA, EORTC, 1591 pts 1^{st} trial and 808 2^{nd} trial. IFRT after a CR comparing 20 Gy vs 36 Gy. Low dose is enough, and omission of RT had more recurrences (30% vs 15%). ABVD is simiklar to BEACOPP and 4 cycles similar to 6 cycles ABVD (Abst 6505

*HD early stage I-II (Diehl trial): 4 vs 2 ABVD nad 20 vs 36 Gy all similar. CR 98% (Abst 6506 Proc ASCO, 2005; 23)

HD: HD ChX better than conventional dose in first relapse HD but not after multiple relapses. Freedom from treatment fasilure was 12% vs 42% in 1^{st} relapse and 32% vs 27% after multiple relapses (Abst 6508 Proc ASCO, 2005; 23)

JM Connors (JCO 2005;23:6400-8) Review. Advanced disease: For 80% patients who present with good risk advanced disease recommended treatment is ABVD considering optimal cure/toxicity rates. For the 20% advanced and high risk disease more aggressive regimes are indicated. Localized disease(I-IIA): Either a short course ABVD x4 alone, or a briefer course ABVD x 2 + IF RT (5 y PFS 87% vs 93% with RT).When B symptoms (or advanced stage) ABVD x 2 after achieving a CR (maximum cycles 8) (DFS 95-98% and OS 93-98%). When bulky disease ABVD x 6 and IRRT. New regimes of chemotherapy: Satanford V (12 wk) + RT 36 Gy (at initially bulky sites > 5 cm) gives 6.9 y M F Up, Act 8y PFS 91% and OS 95%, fertility mantained. BEACOPP (escalated)+ RT, M F Up 6.9 y (N=1185) 5 y PFS 85%, 5y OS 90%, infertility. HD Chemotherapy and ASCT. Long term side effects and complications: infertility, menopause, caries, increase in second tumors, hypothyroidism. (IPI: Male, >45 yo, Stage IV, Hb <10.5, WBC <5000, Ly <600, Alb<4). Follow up q 3 mo x 2 y, q 6 mo x 3 y and then q 1 y.

R Schnell et al (JCO 2005;23:4669-78). Ki4 (MoAb antiCD30-I^{131}. First a tracer dose of Ki4, 5 mg to bind soluble CD30. Then 250-300 MBq I^{131}-labeled Ki4 & scintigram. Finally therapeutic dose on d 8 (for a total body dose of 0.035-0.99 Gy. Results: 1 CR, 5 PR, 3 mR. 7/9 grade 4 hemotological toxicity.

J Kuruvilla et al (Cancer Res 2006;106:353-60). Second line salvage therapy prior to ASCT. M F up after ASC 1.7 y. GEM 1000 mg/m2 30 min iv d 1 & 8 + DXMTS 40 mg po qd divided doses d1-4 + CDDP 75 mg/m2 q 3 wk (OR 62%, apheresis with PBSC>5x10e6 CD34+ 97% and single apheresis 73%, and 15 y PFS 75%, 15 y OS 91%) versus MiniBEAM (BCNU 60 mg/m2 d 1 +AraC 100 mg/m2 bid d 2-5 + LPAM 30 mg/m2 d 5 (max 59 mg) q 3-4 wk (OR 68%, appheresis with >5x10e6 CD34+ 57% -significant p-, single apheresis 36% and 15 y PFS 35%, 15 y OS 82%). Retrospective historical control analysis...

MULTIPLE MYELOMA

MULTIPLE MYELOMA- MOLECULAR BIOLOGY

Classical prognostic factors are B2MG elevation and del 13q14 (absence MST >110 mo, one factor 50 mo and 2 factors 24 mo). Other: t(4;14) very poor and t(11;14) good risk.

PR Greipp et al (JCO 2005;23:3412-20). International Staging System for MM: Stage I: B2MG < 3.5 mg/L + Ser Albumin >3.5 mg/dL (MST 62 mo). Stage II: Intermediate values (MST 44 mo). Stage III: B2MG> 5.5 mg/L (MST 29 mo). Comparison was valid for age >65 yo, 2 standard therapies or BMT, and Durie-Salmon classification system.

B Sirolis and T Powles (Lancet 2004;363:875-87). Pathogenesis: First event primary IgG translocations (75% case 14q32) and second event secondary IgG translocations (c-myc, others), then activating mutations N-ras, K-ras, FGFR3, and finally 13q14 deletions and tp53 mutations. Poor prognosis for –13q, hypodiploidy, t(4;14), t(14;16), p53 alteration. Bone marrow environment: cytokines: IL6 (growth factoer for myeloma), IGF1, VEGF, TNFa, NFkB, IL1 (osteolysis).

MULTIPLE MYELOMA- TREATMENT

**N Bahliset al (Clin Ca Res 2002;8:3658-68). Ascorbic acid 1 g/d (to deplete GSH) + As2O3 0.25 mg/kg/d x 25 d q 7 wk. No DLT identified, no change in PK. 2 OR + 4 NC (targets mitochondria).
*R Gartenhaus et al (Clin Ca Res 2002;8:566-72). As2O3 r5esistant MM lines had complete sensitivity restoration (100%) if given after a prior therapy with buthionine sulfoximine (BSO) to induce GSH depletion. Response is associated to apoptosis mediated through caspases 3,8 &9.

N Takebe et al (Clin Ca Res 2004;10:8301-8). Mycophenolate mofetil (Cellcept) inhibits inosine monophosphate dehydrogenase and induce apoptosis in MM cell lines. N=11. MTD 5 g/d. Grade I fatigue. 1PR+4NC+6PD.

RA Kyle and SV Rajkumar (NEJM 2004;35:1860-73). Review. MST 3 y. Poor prognosis associated to del 13q32, t4;14 or t14;16, and increase in microvessel count. Staging related to B2MG and serum albumin. Diagnosis bases on >19% plasma cells in BM, detectable monoclonal protein in plasma/urine and CRAB end orhan damage (calcium, renal, anemia and bone). Progression of MGUS related to bone resorption, lysis and angiogenesis (prevention?). Smoldering myeloma takes 2-3 y to became aggressive. Treatment: VADx4, then stem cell harvest, one or tandem transplant (auot of miniallo, never allo because of mortality) gives 10% cure rate. Not eligible for BM transplant are treated with LPAM+PRDN or THAL+DXMT or other alternatives. Recent results are as follows: LPAM 8-10 mg po d 1-7 + PRDN 60 mg po d 1-7 (OR 50%); VBMCP (OR 60%); DXMT 40 mg po d 1-4, 9-12 & 17-20 q 4-5 wk (OR 45%). VAD (OR 65%); Thal 200-400 mg po d 1-28 + DXMT 40 mg po d 1-4, 9-12 & 17-21 (OR 65%); Thal + DXMT + LPAM 4 mg po d 1-7 q 4 wk (OR 80%); Bortezomib 1.3 mg /m2 d 1, 4, 8, 11 q 3 wk (OR 35% in relapses); maintenance IFNa not clear effects; Revimid (Lenalidomide, CC5013) 15 mg bid x 21 d q 4 wk, better than Thalidomide; Neovastat; Oblimersen; Farnesyltransferase inhibitors; histone deacetylase inhibitors; As2O3. Treatment of complications: Biphosphonates, anemia, infection (ivIgG), hypercalcemia, renal failura, hyperviscosity syndrome (plasma exchange).

MM: After tandem autograft pts were randomized to Thalidomide vs control . Mfup 35 mo. (N=668).5yEFS 55% vs 40%, CR 62% vs 43%, but 5yOS was similar 68% vs 63%. (Abst 6502 Proc ASCO, 2005; 23)

MM: Velcade better than Dexa in elderly pts (Abst 6533 Proc ASCO, 2005; 23)
*P Richardson et al (NEJM 2005;352;2487-98). N=669 relapsed MM. Bortezomib 1.3 mg/m2 d 1, 4, 8, 11 q 3 wk x 8 and then d 1, 8, 15 & 22 q 5 wk x 3 (OR 38%, CR 6%, MTTP 6.2 mo, 1 y OS 80%) vs HD DXMT 40 mg d 1-4, 9-12, 17-20 q 5 wk x 4 (OR 8%, CR 1%, MTTP 3.4 and 1y OS 66%)

S Jagamath (Cancer Res 2005;103:1195-200). Bortezomib in patients with Cr Cl´ <30 ml/min: OR 3/10. no more toxicity found.

SB Rew et al (Clin Ca Res 2005;11:3377-84). Ag specific T cells generated with protein pulsed dendritic cells, tested by Elispot and CTL assay. (HMI-24 type II glycoprotein expressed on myeloma cells)

SV Rajkumar et al (JCO 2006;24:431-6). N=207. Thalidomide 220 mg po qd + DXMT 40 mg po d 1-4, 9-12 & 17-20 q 4 wk (OR63%) Toxicity 45% vs DXMT same dose (OR 41%) Toxicity 21%.

RM Rifkin et al (Cancer 2006;106:848-58). N= 192 initial therapy. Peg DOX (Caelyx) 40 mg/m2 + VCR 1.4 mg/m2+ DXMT 40 mg d 1-4 (OR 44%) vs DOX 9 mg/m2 civi x 4 + VCR 0.4 mg/m2 civi x 4 + DXMT reduced dose (OR 41%). OD 0.88, less hematological toxicity and less supportive care.

J Berenson et al (JCO 2006;24:937-44). N=35 Phase I-II. Bortezomib 0.7-1 mg/m2 d 1, 4, 8 & 11 q 4 wk x 8 + LPAM 0.025-0.25 mg/kg d 1-4. MTD Bortezomib 1 mg/m2 same days + LPAM 0.1 mg/kg x 4d q 4 wk.OR 68% (CR 6%), at MTD OR 83%, MPFS 8 mo.

MULTIPLE MYELOMA- IMMUNETHERAPY

N Takebe et al (Clin Ca Res 2004;10:8301-8). Mycophenolate mofetil (Cellcept) inhibitor of inosine monophosphate dehydrogenase induce apoptosis in MM cell lines. N=11. MTD 5 g/d. Grade 1 fatigue. 1PR + 4 NC `6PD.

SB Rew et al (Clin Ca Res 2005;11:3377-84). Ag specific T cells generated with protein pulsed dendritic cells, tested by Elispot & CTL assays. HMI-24 type II glycoprotein expressed on myeloma cells.

MULTIPLE MYELOMA- BMT

B Barlogie et al (NEJM 2006;354:1021-30). =668, randomized trial. First 2 HD LPAM + ASCT & then Thalidomide 400 mg/d initial dose (100 mg/d at ASCT and then same dose maintenance 1 y & finally 50 mg qod (CR 62%, 5 y EFS 56% and 5 y OS 65%) vs control (CR 43%, 5 y EFS 44% and 5yOS 65%. No differences seen.

B Barlogie et al Intergroup S9321. (JCO 2006;24:929-36). N= 511, randomized study after French study showing ASCT>Standard chemotherapy. First Randomization LPAM 140 mg/m2 + TBI 12 Gy (7 y PFS 17% and 7 yOS 37%) vs conventional VCR+BCNU+LPAM+CPA+PRDN (7 y PFS 16% and 7 y OS 42%). After progression patients with conventional chemotherapy went into HD ChX+ASCT (N=87) with a MST 30 mo (patients on standard therapy had a MST 23 mo). Second randomization in patients with an OR/75%: IFN maintenance vs control (N=242) no differences in PFS or OS.

JP Fermand et al (JCO 2005). M F up 10 y Randomized study of HD ChX (LPAM or LPAM/BUS) + ASCT (MEFS 25 mo and MOS 47.8 mo) vs VCR+LPAM+CPA+PRDN (MEFS 19 mo, MOS 47.6 mo). No differences.

P Moreau et al French Myelome Group (Blood 2006;107:397-403). Aftwer tandem LPAM transplant patients were randomized to BE8 (anti IL6) MOS 46mo vs control MOS 51mo No differences.