5 years in the three eras was 79% (95% CI, 68%-87%), 85% (95% CI, 77%-90%) and 93% (95% CI, 83%-97%), respectively. At 10 years, in the two earlier eras, it was 56% (95% CI, 43%-67%) and 75% (95% CI, 65%-83%), respectively. Despite the significant reduction of deaths due to the FL and its treatment, differences in overall survival among the three groups were not statistically significant. This may depend on the advanced age of most patients and on short follow-up for patients of the most recent era. A longer observation will be needed to clarify the issue.
Conclusions: The cause-specific survival of patients with FL treated at the IOSI has improved over the last 25 years. This improvement may be a result of the sequential application of more effective therapies and improved supportive care; however it has not yet translated in an improvement of the overall survival.

6006 ORAL

DNA repair gene ATM polymorphisms and risk of chronic lymphocytic leukaemia

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One of the most frequently altered DNA repair pathway in cancer cells is the one that corrects double-strand breaks (DSBs). The ATM gene encodes a protein kinase that plays a key role in the detection and repair of DNA DSBs. Once activated, the ATM protein triggers phosphorylation of CHEK2 which, in turn, phosphorylates p53, Cdc25 and BRCA1, promoting cell-cycle arrest and DNA repair. Through their effect in DNA damage check point regulation, ATM gene polymorphisms may modulate individual susceptibility to cancer. Chronic lymphocytic leukaemia (CLL) is one of the most common malignant lymphoid diseases in the western world. ATM alterations have been observed in CLL and are related with a poor prognostic. In particular, recent studies have suggested a role for ATM in disease progression in B-CLL. Furthermore, a recent study has found an association between non-synonymous SNPs in ATM and risk of CLL.
In addition to SNPs in the coding region, SNPs in no coding region (intronic, 3′UTR, 5þTR) have been found to be associated with some diseases. Therefore, in this study, we have conducted a large association study between ATM and CLL. A total of 19 SNPs were genotyped. SNPs were chosen to map the ATM gene by linkage disequilibrium (LD), including adjacent non-transcribed regions at both edges, based mainly on LD data from the CEU population taken from HapMap phaseI (The International HapMap Consortium 2004). The tagger algorithm, as implemented in Haploview 3.0, was used to select TAG-SNPs. The selection was based on the number of additional SNPs for which they can act as tags and SNPs generating the common amino acid substitutions were specifically forced into the tagging. Genotyping was performed by using the MassARRAY SNP genotyping system (Sequenom Inc., San Diego, CA). Haploview 3.0 (Barrett et al., 2005) was used to estimate LD and to search for any deviation of Hardy-Weinberg equilibrium in controls. For haplotype analysis, we used a sliding windows approach, considering window sizes of two or three consecutive SNPs. All analyses have been done in 740 patients and 748 matched controls.
The data obtained from this extensive analysis are expected to further contribute to our understanding of the relationship between ATM polymorphism and the risk of CLL.
This work was supported by RETICS G 3/179 and Gobierno Vasco SAIOTEK

6007 ORAL

MDM2 SNP309 is associated with poor outcome in B-cell chronic lymphocytic leukaemia but can be preferentially targeted by the MDM2 inhibitor Nutlin-3a

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Background: A single nucleotide polymorphism (SNP) at position 309 in the promoter region of MDM2 leading to increased expression of MDM2 and attenuated function of p53 tumor suppressor protein has been negatively associated with onset and incidence of solid tumors. Since inactivation of p53 by deletion and/or mutations also negatively impact on the clinical course of B-chronic lymphocytic leukemia (B-CLL), we analyzed the association of SNP309 with the clinical course and its interaction with the p53 status in B-CLL.
Patients and Methods: The frequency of SNP309 T/T, T/G or G/G genotypes was assessed by RT-PCR in a cohort of 140 B-CLL patients. In addition, the p53 status (wild-type vs mutated p53, deletion of p53) was assessed by single-stranded conformation polymorphism (SSCP) and fluorescence-in-situ-hybridisation (FISH) analysis, respectively. SNP309 genotype and p53 status were correlated with treatment-free and overall survival of patients. In addition, in vitro sensitivity of B-CLL cells to apoptosis induced by nutlin-3a, a specific inhibitor of the MDM2/p53 interaction was determined and correlated with their SNP309 genotype.
Results: A significant negative association of the SNP309 T/G and G/G genotypes with overall survival (T/G genotype: RR 3.7 95% CI 1.2−11.5, p = 0.02; G/G genotype: RR 9.1 95% CI 2.4−35.1, p = 0.001) but no correlation with incidence or onset of B-CLL was observed. Multivariate analysis of SNP309 genotype and p53 status identified both as independent negative prognostic markers. Nutlin-3a treatment reactivated the p53 pathway in B-CLL cells and led to significant induction of apoptosis. Interestingly, the clinically unfavorable SNP309 T/G or G/G genotypes rendered B-CLL cells more sensitive to apoptosis induced by nutlin-3a.
Conclusions: The MDM2 SNP309 genotype was identified as an additional independent risk factor in B-CLL. The higher sensitivity of tumor cells from T/G and G/G SNP309 carriers to nutlin-3a might be exploited therapeutically.

Poster presentations (Mon, 24 Sep, 14:00−17:00)
Leukaemia, lymphomas, transplantation (adults)

6008 POSTER

Selenite is a superior cytotoxic agent to human primary leukemia cells

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Background: The selenium compound, selenite, is rising as a promising cancer therapeutic agent in several experimental studies. However, the mechanism of selenium-induced cytotoxicity is poorly understood. AML is the most common leukemia in adults but the cure rate remains low. Commonly used drugs, as cytarabines and anthracyclines, often lead to drug resistance.
Materials and Methods: This study was conducted on an ex vivo model with acute myeloid leukemia (AML) patient material. The primary cells were treated in a drug panel with conventional cytotoxic drugs, and evaluated in comparison to selenite treatment (5 μM).
Results and Conclusions: We show that selenite is the most effective drug in the panel compared to commonly used drugs against AML in concentrations that could potentially be administered to patients. Equally important, all conventional drugs in the panel showed a correlation to each other by having an effect on the same group of patients. Selenite does not show this correlation indicating the ability to treat an, in part, unique group of patients. mRNA and protein levels of thioredoxin reductase and mRNA levels of the glutaredoxins were also measured While a strong upregulation of thioredoxin reductase mRNA levels were observed, the protein level decreased. This possible translational impairment may explain a part of selenites cytotoxicity. Both glutaredoxin 1 and 2 mRNA levels increased suggesting both mitochondrial and cytosolic oxidative stress caused by selenite treatment.

6009 POSTER

Risk factors for early mortality, relapse and overall survival in new cases of APL treated by arsenic trioxide

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Background: there are several known risk factors for APL treatment by all-*trans* retinoic acid (ATRA) and chemotherapy, but risk factors for new cases of APL treated by arsenic trioxide (ATO) are unknown.
Material and Methods: Between May 2000 and September 2006, we treated 141 new cases of APL (Median age 28±12.8 y/o min = 11, max = 71) by 2 hours iv infusion of 0.15 mg/kg ATO until complete remission. Trial approved by IRB and consent form obtained. Diagnosis was by clinical and morphologic characteristics and confirmed by cytogenetic and RT-PCR for detection of t(15,17) and presence of PML-RAR?. After complete remission patients received consolidation by 28 days infusion of ATO for one or four courses. Known risk factors for APL treatment outcome