6013 POSTER

Risk factors for premature menopause following treatment for Hodgkin lymphoma

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Background: The long-term prognosis for Hodgkin lymphoma (HL) patients is nowadays favorable. Female HL survivors may, however, experience therapy-induced gonadal failure causing premature menopause, defined as cessation of menses before age 40. Although radiosensitivity of the human ovary has been studied in great detail, information on the effects of different chemotherapeutic agents is still limited.
Methods: We conducted a cohort-study among 518 female 5-year HL-survivors, aged 14 to 40 years (median 25 years) at treatment (1965–1995). In case the ovaries were situated in the radiation fields, the patients were excluded from analysis. Multivariable Cox-regression was used to quantify treatment effects on risk of premature menopause.
Results: After a median follow-up of 9.4 years, 97 women had reached menopause before age 40 (3 women had acute ovarian failure). Treatment with chemotherapy was associated with a 12-fold increased risk of premature menopause compared to radiotherapy only (Hazard ratio [HR] 12.3; 95% confidence interval [CI] 5.3−28.8). Women treated with mechlorethamine, vincristine, procarbazine, prednisone (MOPP; HR 5.7; 95% CI 3.6−9.1) or mechlorethamine, vincristine, procarbazine, prednisone/doxorubicine, bleomycine, vinblastine (MOPP/ABV; HR 2.9; 95% CI 1.6−5.2) were at increased risk for premature menopause, and these risks increased with higher dose. The chemotherapeutic agents responsible for the induction of premature menopause were the alkylating agents, and especially procarbazine (HR 8.1 95% CI 2.0−32.8) and cyclophosphamide (HR 3.5; 95% CI 2.0−5.9). The actuarial risk of premature menopause among women treated with high cumulative doses of procarbazine (>8.4 g/m^2) was 64% (95% CI 44%-78%), whereas the risk among those treated with low doses ($\leqslant$4.2 g/m^2) was 15% (95% CI 6%-23%) 10 years after their first treatment.
Conclusions: Alkylating chemotherapy (particularly with procarbazine and cyclophosphamide) induces menopause before the age of 40, which is in most cases not the result of acute gonadal failure. Although women treated with MOPP/ABV experience a lower risk for premature menopause compared to MOPP, treatment with MOPP/ABV is associated with a significantly increased risk for premature menopause compared to radiotherapy only. As long as alkylating agents (and especially procarbazine) will be used for curing HL, premature menopause will occur in these women, with various clinical implications.

6014 POSTER

G-CSF prophylaxis and neutropenic events in NHL patients receiving standard CHOP or R-CHOP – results from a retrospective study in the UK

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Background: In patients with non-Hodgkin lymphoma (NHL) receiving 21-day (R)CHOP chemotherapy, the incidence of febrile neutropenia (FN) is about 22% with current granulocyte colony stimulating factor (G-CSF) support. FN and related dose modifications can lead to poorer outcomes. We aimed to audit current practice neutropenia management in the UK and its impact on neutropenic events.
Methods: Consecutive NHL patients planned to receive full dose (R)CHOP chemotherapy at 12 UK centres during periods in 2001–5 were retrospectively studied. Patients were categorized by G-CSF use during chemotherapy: primary prophylaxis (PP), secondary prophylaxis (SP), treatment (T) and no G-CSF. Pegfilgrastim was considered to be 10 doses of daily G-CSF in number of doses calculation. Neutropenic events were recorded and included hospitalization due to FN, dose delays $\geqslant$1 week due to neutropenia and dose reductions $\geqslant$15% due to neutropenia. Relative dose intensity (RDI) was also calculated.
Results: 252/254 patients were analysed (59% male, mean$\pm$SD age: 60$\pm$14 yrs, 58% $\geqslant$ stage III disease) and 1548 cycles were delivered. The mean$\pm$SD number of G-CSF doses per cycle was 6.8$\pm$2.1, 4.4$\pm$2.2 and 1.7$\pm$1.3 in the PP, SP and T groups, respectively. Five or more G-CSF doses were used in just 20% of cycles. The incidence of neutropenic events in the different groups is shown (table). In cycle 1, 3% of PP patients were hospitalized for FN vs 12% of those receiving 'other' treatments. Furthermore, 97% of patients receiving PP had RDI $\geqslant$85% versus 83% of the 'other' treatment groups. Among those who had a neutropenic event, all PP patients achieved RDI $\geqslant$ 85% in contrast to just 70% of the 'other' treatment group.

	PP	Other			
	(n = 32)	SP (n = 42)	T (n = 67)	No G-CSF (n = 111)	All 'Other' (n = 220)
Hospitalization due to FN	4 (13%)	17 (40%)	32 (48%)	12 (11%)	61 (28%)
Dose delay $\geqslant$1 week due to neutropenia	2 (6%)	16 (38%)	29 (43%)	14 (13%)	59 (27%)
Dose reduction $\geqslant$15% due to neutropenia	0 (0)	8 (19%)	2 (3%)	2 (2%)	12 (6%)
All neutropenic events	4 (13%)	29 (69%)	43 (64%)	23 (21%)	95 (43%)

Conclusions: Relatively few (13%) NHL patients on 21-day (R)CHOP chemotherapy received PP G-CSF. Those receiving PP G-CSF had fewer neutropenic events than those receiving other neutropenia management and a greater proportion achieved RDI $\geqslant$ 85%. Half of those not planned to receive G-CSF subsequently required G-CSF SP or T. Results from studies such as these can aid implementation of new ASCO/EORTC guidelines which recommend PP with G-CSF when overall risk of FN is $\geqslant$20%.

6015 POSTER

FcgammaRIIIa and FcgammaRIIa polymorphisms do not influence overall survival in follicular lymphoma patients treated with rituximab

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Background: In follicular lymphoma (FL) genomic polymorphisms corresponding to the expression of valine (V) or phenyloalanine (F) in position 158 of Fc?RIIIa alter the binding affinity of immunoglobulin G1 (IgG1) and consequently response to rituximab. Recent data suggest that patients with FcγRIIIa-158V genotype have longer progression free survival (PFS) than those with 158F or 158 V/F genotypes. In contrast, the FcγRIIa-131 polymorphism is not associated with response to rituximab. In this study, we tested weather these polymorphisms may also influence overall survival (OS) in follicular lymphoma patients treated with rituximab.
Materials and Methods: DNA was extracted from the 2 ml of blood samples of 161 FL patients treated with rituximab. Polymorphisms were examined by PCR-RFPL method in a group. Median time of observation was 31 months (range 12–144 months).
Results: The study population consisted of 40% V homozygous, 20% F homozygous and 40% V/F heterozygous patients for gene FCGR3A and of 32% H homozygous, 16% R homozygous, 52% H/R heterozygous patients for FCGR2A. Fc?RIIIa-158 polymorphism did not influence overall survival. Although the differences in OS after 60 months and later were observed for FcγRIIa-131 polymorphism (95% for H, 90% for H/R but 58% for R), those differences were not statistically significant.
Conclusions: Although the presence of FcγRIIIa-158 V homozygous polymorphism elongate time to progression (TTP) in FL patients, our studies have shown that OS time is not influenced by any of the examined polymorphisms.

6016 POSTER

A novel organic arsenic S-dimethylarsino-glutathione (ZIO-101) experience in hematological malignancies

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Background: ZIO-101(S-dimethylarsino-glutathione), a novel organic arsenic, has a multifaceted mechanism of action which is mediated by

disrupted mitochondrial function, increased reactive oxygen species (ROS) production, modified signal transduction and anti-angiogenesis. ZIO-101 is active against diverse cancers in vitro and in animal models of AML and other leukemias. These features make ZIO-101 attractive for clinical evaluation in hematological malignancies.
Methods: Two studies a phase-1 study evaluating the safety and pharmacokinetic (PK) profile of ZIO-101and a phase II trial in patients with advanced hematological malignancies are ongoing. Patients received ZIO 101 IV for 5 consecutive days every 28 days until disease progression or significant toxicity.
Results: A total of 14 patients 13 with acute myelogenous leukemia (AML) (median 3 prior treatments) and 1 with MDS (median 2 prior treatments) Therapy with ZIO-101 has been well-tolerated to date. Preexisting anemia and thrombocytopenia increased by 1 grade in 4 and 3 patients each. Grade >3 neutropenia occurred in 2 subjects. No significant renal, hepatic or cardiac toxicity occurred. Six of the 13 evaluable AML patients, a decrease in the peripheral blood myeloblasts was noted. Bone marrow myeloblasts were unchanged. The studies are ongoing and continue to accrue patients.
Conclusions: Administration of ZIO-101 to patients with advanced AML was well tolerated and an antileukemic effect has been observed.

6017 POSTER

First line treatment of acute promyelocytic leukemia with arsenic trioxide without ATRA and chemotherapy

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Background: Standard treatment of APL is all-*trans* retinoic acid (ATRA) plus chemotherapy but arsenic trioxide (ATO) is most potent single agent against APL cells. Role of ATO in first line therapy of APL needs to clarify.
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 (one consolidation one month after CR and for some patients second, third and forth consolidations one month after first one and two another, one year and two year after CR).
Results: complete remission observed in 121 cases (85.8%) and early mortality rate was14.9% (most common cause of early mortality was APL syndrome, 61.9%). Median follow up was 28 months. For patients who achieved complete remission, one-, two- and three-year disease free survival rates were 95.6±2%, 76.9±4% and 57±6%, respectively. Many relapsed patients salvaged again with ATO alone so, two- and three-year overall survival for this cohort was 95.6±2% and 83.7±4%. Increasing number of consolidation from one to four couldn't increase DFS or OS in one and two years after CR.
Conclusion: ATO is effective in treatment of new cases of APL. Introduction of ATO in first line treatment of APL (with or without ATRA plus chemotherapy) needs a multi center randomized clinical trial.

6018 POSTER

Primary breast lymphoma and the risk of central nervous system disease – Should all patients receive prophylactic intrathecal chemotherapy?

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Background: Primary breast lymphoma (PBL) is rare. Existing practice is based upon studies limited by small patient numbers. It has been shown in a small retrospective study of twenty patients presenting with PBL, that patients may go on to develop central nervous system disease. 25% of the patients in this study had relapses with proven CNS disease [1]. This has led to a gradual change in clinical practice favouring the increasing use of prophylactic intrathecal chemotherapy. There is currently little data considering whether patients with limited disease at presentation should receive prophylactic intrathecal chemotherapy. Our main objective is to evaluate the appropriate use of prophylactic intrathecal chemotherapy.
Material and Method: We report a series of fifteen cases of patients with PBL presenting at New Cross Hospital, Wolverhampton, UK between 1991 and 2006. Patient age, histology, stage at diagnosis, treatment and outcome were recorded. The patients were followed up to observe for relapses involving the central nervous system and any necessary further treatment.
Results: The fifteen patients identified consisted of fourteen females and one male. Age at diagnosis ranged from 28 to 88 years. Of the fifteen patients seven had stage I disease, two had stage II disease and six had stage IV disease. Those with stage IV disease had either a positive bone marrow biopsy or abdominal disease present on CT scanning. None of the patients were identified to have evidence of CNS disease at presentation. Ten patients received CHOP/R-CHOP chemotherapy with seven achieving a complete response and three a partial response. Six of the patients achieving complete response also received radiotherapy. Three of the five patients not receiving chemotherapy were treated with radiotherapy and two of these achieved a complete response. In total five patients had relapses after first line treatment. Two involved CNS relapses. Both of these patients had initially presented with advanced (Stage IV) disease. None of the patients who presented with limited disease (Stage I-II) in our cohort went on to develop CNS disease.
Conclusions: It is becoming increasingly common for patients with PBL to receive prophylactic intrathecal chemotherapy with first line treatment. Our data suggests that whilst the use of prophylactic intrathecal chemotherapy is justified in patients presenting with advanced PBL, there is little evidence demonstrating any benefit in patients presenting with stage I or II PBL. This treatment is expensive and associated with significant morbidity. Further studies with larger numbers are needed before the use of prophylactic intrathecal chemotherapy should become routine practice in patients presenting with stage I or II PBL.

References

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6019 POSTER

Background and methodology of the ADAGIO study – a prospective, observational, multicenter study to determine the prevalence, predictors, and mediators of non-adherence in patients treated with imatinib

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Background: We describe the rationale and methodology of the "Adherence Assessment with Glivec®: Indicators and Outcomes" (ADAGIO) study, which examines determinants of adherence with imatinib treatment in chronic myeloid leukemia (CML) and gastro-intestinal stromal tumors (GIST) patients. Imatinib should be continued indefinitely in responding patients. Patient adherence with long-term medication regimens is influenced by patient-, clinician-, disease-, treatment-, and health system-related variables. The tolerance margin for imatinib nonadherence is narrow due to the relapse risk. Determinants and dynamics of nonadherence must be studied to design adherence-enhancing interventions.

	Month	
	0	3
Patient recruitment (screening, eligibility, informed consent)	X	
Patient characteristics (demographics, medical history, current comorbidity)	X	
Disease-related information		
Disease history	X	
Current clinical status	X	X
Concomitant medications: risk for drug-to-drug interactions	X	X
Physician variables (demographics, education, specialty, practice environment, number of CML/GIST patients, time spent with patients in diagnosis and treatment, use of scientific information; use of patient awareness and support materials, perspectives on patient compliance)	X	
System-related variables	X	
Patient adherence (patient and collateral interviews, pill count, appointment adherence, physician rating of adherence)	X	X
Patient variables (medication behavior self-efficacy, assessment of chronic illness care, symptom experience/distress, understanding of disease and treatment, functional status, knowledge-seeking behavior)	X	X
Response parameters		
CML: hematological, cytogenetic and molecular response	X	X
GIST: clinical, CT and PET	X	X
Treatment-related: CML/GIST-related GP and specialist visits t1 to t2		X