fraction from treated and nuclei from untreated cells we demonstrated that K-562 nuclei underwent apoptotic DNA fragmentation when incubated with cytosolic extract from Gem treated SKW-3 cells. The resistance of K-562 cells can be explained by the expression of BCR-ABL which prevents the apoptotic cell death. Cytosinearabinoside (Ara C) and Gem showed similar cytotoxic profiles on K-562 cells after 48 h incubation (IC50 > 100 μM for Ara C and IC50 > 40 μM for Gem). The simultaneous exposure (72 h) of K-562 to Gem and hexadecylphosphocholine (HPC) caused synergistic cytotoxicity. 24 h incubation of K-562 cells with 50 μM Gem followed by 50 μM HPC for 24 h caused optimal growth inhibition. Gem was found to be effective against freshly isolated blasts from a patient with relapsed AML as measured by the MTT-assay. Taken together our data indicate that Gem can be of benefit for patients with leukemias not responding to standard protocols.

1356 PUBLICATION

Cyclophosphamide, vincristine, epirubicin and prednisolone (ceop-100) in aggressive Non Hodgkin's lymphoma (ANHL)

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Combination chemotherapy (CT) with cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP) remains the standard treatment for aNHL. We replaced adriamycin with the less cardiotoxic antracycline, epirubicin, in a phase II trial. Between 1993– 1998, 89 patients (pts) with intermediate/high grade NHL were accrued into the trial. CEOP-100 consisted of cyclophosphamide 750 mg/m^2, epirubicin 100 mg/m^2, vincristine 1.4 mg/m^2 on day 1, and prednisolone 100 mg days 1–5 every 21 days. Growth factors were used for secondary propylaxis of neutropenic fever. The treatment plan included 4 cycles of CT followed by involved-field radiotherapy in stage I–IIA disease; advanced disease received 6 cycles of CT and radiotherapy to bulky nodes. WHO criteria for toxicity was used. Pts who didnot achieve complete response (CR) after the first 3 cycles were given salvage CT and taken off the study. The median age was 45 (range: 15–76), the male/female ratio 58/31. There were 19 pts with stage I, 34 with stage II, 25 with stage III and 11 with stage IV disease; 32 pts (36%) had B symptoms. Histology (Working Formulation) was intermediate grade in 79 and high grade in 10 pts. 449 cycles of CT were evaluable for toxicity; 81% of the pts completed the treatment. Delay >1 week occurred in 16% of the pts; 10% needed dose modification. Toxicity (grade III–IV) was recorded as follows: neutropenia 10%, anemia 8%, thrombocytopenia 3%, mucositis 5% of the cycles. Five episodes of neutropenic fever developed. One patient died with acute heart failure. Of the 85 pts with measurable disease, 76% achieved CR, 18% had partial response (PR); one patient progressed during CT. Fourteen pts (22%) with initial CR relapsed; 12 relapsed during the first year and died after being refractory to salvage CT. One of the 2 pts who relapsed after one year responded to salvage CT and is still in second remission. Median follow-up is 34 months; median disease-free survival is 15.5 and median overall survival is 19 months. The cumulative 3-year and 5-year survival is 49% (95% CI: 43–55) and 44% (95% CI: 37–51) respectively. The CEOP-100 regimen is an active and tolerable outpatient regimen applicable in aNHL. Ongoing trials of regimens with better CR rates will hopefully result in better survival.

1357 PUBLICATION

Prognostic factors in primary gastric non Hodgkin's lymphoma

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Fifty-two patients (pts) with primary gastric nonHodgkin's lymphoma (PGNHL) treated and followed between 1991–1998 were retrospectively analysed for presentation characteristics and prognostic factors. Histology (Working Formulation), performance status (PS-WHO), stage (Ann Arbor), bulky disease (>6 cm.), beta-2-microglobulin (B2MG), lactic dehydrogenase (LDH), surgery, and response to chemotherapy (CT) were included in the prognostic analysis. Median age was 60 (range: 23–75); male/female ratio was 1:1. Twenty-one pts had a distinguishable MALT (mucosa-associated lymphoid tissue) based lymphoma; 8 had low grade and 13 had high grade MALT histology. The other 31 pts did not have MALT association; 2 had folicular mixed, 16 had diffuse large cell, 9 had diffuse mixed cell and 4 had diffuse immunoblastic histology. The stomach was diffusely involved in 81% of the pts. Seventeen pts had stage I, 15 had II, 14 had III and 6 had IV disease; 42% had B symptoms. Thirty-seven pts applied after surgery; 14 had subtotal and 23 had total gastrectomy. CT was given to 34 (92%) of the pts after surgery; a total of 49 pts received CT and 98% of the CT given was antracycline-based. Pts with stage I disease and high grade histology received adjuvant CT after surgery. Response was evaluated in 35 pts who had measurable disease after surgery of unresectable gastric lymphoma; complete response (CR) was achieved in 74%. With combined of surgery and CT, the CR rate was 79%. PS > 2, stage IV disease, and lack of CR to CT were the adverse prognostic factors for survival. Surgery, LDH and B2MG levels did not affect survival. Of all pts who underwent surgery, only two pts did not receive CT, one of them is alive without disease. The 5-year overall survival was 65%; the 5-year survival was 69% in pts with unresected advanced stage disease, 73% in pts with subtotal gastrectomy and 60% in pts with total gastrectomy. There was no significant difference in survival between pts with or without surgery, although pts without surgery had advanced, unresectable disease. We conclude that the role of surgery in primary gastric lymphoma is still unclear. It is evident that only a fraction of pts can be cured by surgery alone, and the role of surgery in addition to CT remains to be determined in randomized studies.

1358 PUBLICATION

Aberrant immunoglobulin (IG) heavy chain glycosilation in igg multiple myeloma (MM)

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Glycosilation is the most important posttranslational modification of proteins in eukaryotic cells. While cells spend a large amount of energy on this process its importance in normal physiology and disease is largely unclear. Ig heavy chains are glycosilated mainly on the Fc portion and this is thought to be important in receptor binding and possibly control of clonal expansion. In MM tumor cells produce large amounts of a single Ig molecule. We compared glycosilation patterns in 18 IgG MMs and 19 matched controls by measuring levels of galactose and sialic acid moieties attached to heavy chains. IgG was purified using ammonium-sulfate precipitation and anion exchange chromatography, separated by denaturing electrophoresis and transferred onto PVDF membrane. Galactose and sialic acid moieties attached to heavy chains were detected using biotin-labeled RCA I and lectin, respectively. Galactosilation of MM chains was significantly less than that of normal controls (mean 283 relative units (RU), std. deviation 80 RU, vs. mean 352 RU, std. dev. 4 RU, p = 0.002). Sialylation was not different (mean 193 RU, std. dev. 83 RU, vs. mean 183 RU, std. dev. 30 RU), however some cases of MM had very low or very high sialylation. Neither galactosilation, nor sialylation correlated with clinical and biochemical parameters: sex, age, light chain type, disease status, disease duration, type of treatment, IgG or β2-microglobulin concentration. In MM the production of monoclonal immunoglobulin is accompanied by reduced galactosilation and in some cases aberrant sialylation. The clinical significance of these findings is presently unclear.

1359 PUBLICATION

Cyclophosphamide, liposomal doxorubicin and dexamethasone (CLAD) is safe and efficacious in multiple myeloma

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Previously we showed that the combination of Cyclophosphamid, bolus AdriamycinO (doxorubicin) and Dexamethasone (CAD) is an efficacious therapy with a 75% objective response rate in patients with multiple myeloma. Data in the literature suggest that prolonged infusion of doxorubicin is even more efficacious. Liposomal encapsulation of doxorubicin (Caelyx®) shows a half time of 39 hours. Furthermore, studies show that Caelyx is less cardiotoxic as the free drug which is important for patients with multiple myeloma with a mean age in the 6th live decade. Therefore we initiated a phase I/II, dose escalating trial in patients with multiple myeloma with a CAD regimen in which doxorubicin is substituted by Caelyx (CLAD).

Treatment regimen was: Cyclophosphamid 200 mg/m^2 day 1–4, Liposomal Doxorubicin (Caelyx) in two dose levels day 1 and Dexamethasone 40 mg day 1–4. Dose levels of calyx are 10 mg/m^2 and 20 mg/m^2. Treatment was repeated every three weeks.

So far, 6 patients (3 women, 3 men) were included in our study on dose level 1. Median age was 68 years (range 61–83). IgA- myeloma was seen in 1 patient, IgG in 14 patients and light chain disease in 1 patient. All patients

were in stage III according to Salmon/Durie, two had stage B. Five patients were pretreated, 2 with chemotherapy and 3 with radiation.

Four pts having received at least 2 cycles of CLAD are evaluable for response. Every pat reached a partial response (>50% reduction in m-protein). Median fall in M-protein after two cycles was 41% (range 30–49%). For safety 14 cycles were evaluated. Overall, treatment was well tolerated. In 1 cycle neutropenia grade III occurred and there was one episode of tachyarrythmia in combination with cardiac failure three weeks after chemotherapy cycle.

In summary, our data show that CLAD is a very promising therapy for patients with multiple myeloma.

1360 PUBLICATION

Clinical significance of p53 protein expression in Non-Hodgkin's lymphoma among Malaysian patients

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In Malaysia as in most developing countries, the majority of non-Hodgkins lymphoma (NHL) are of the aggressive type. Our treatment results with CHOP chemotherapy in aggressive NHL are considerably lower (<40%) than the rates reported from studies conducted in the West.

In this study we have investigated the fequency of p53 protein expression among newly diagnosed Malaysian patients with aggressive NHL and have correlated it with several clinical characteristics including treatment response and survival. Immunohistochemical staining with the p53 monoclonal antibody DO-7 was performed on specimens from 45 patients who were subsequently treated with conventional CHOP chemotherapy.

20 of the 45 lymphomas (45%) had >10% of the cells staining positively for p53. p53 staining correlated with increased LDH and a high IPI score. In addition p53 expression predicted for treatment failure with only 30% of patients with p53 positive tumours achieving a CR versus 55% of patients with p53 negative tumours. p53 expression was also significantly associated with a shorter overall survival.

Our results have shown a high frequency of p53 positive NHL among Malaysian patients and this may in part explain the relatively poor results obtained with CHOP chemotherapy.

1361 PUBLICATION

Long term follow-up of treatment of adult acute lymphoblastic leukemia with two protocols, LALA87 and YUALL. Single center experience

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Objective: 157 adult patients (pts) with acute lymphoblastic leukemia (ALL) of median age 38.1 yrs (range 15–65 yrs) underwent chemotherapy according to protocols LALA87 (112 pts, Group I) and YUALL (EORTC 6861) (45 pts, Group II) between 1989 to 1995. Both protocols include same induction, maintenance and CNS prophylaxis, and only difference is in consolidation with standard doses o drugs in LALA87 (DNR, AraC and L-Asp) and high doses in YUALL (L-Asp, CP and HD-AraC, 1000 mg/m^2/12^h 6 days, followed by VCR).

Results: Complete remission (CR) was achieved in Group I in 76 pts (76% evaluated, 68.2% of all) and in Group II in 31 pt (79.5% evaluated, 67.9% of all pts in the group). The Overall CR rate was 76.9% of all evaluated patients (11.5% died during induction), which comprises 68.2% of all treated patients. The predictive factor for achieving remission was age and FAB subtype. Median duration of CR in Group I was 14 mths and in Group II 11 mths. Median survival of patients achieving CR in Group I was 18 mths and in Group II 13.5 mths. There were no difference in CR rate, DFS and survival between two groups, except significantly better survival in the group of patients with T-ALL, especially Foon II group, but without difference in DFS.

Conclusion: These results are showing that in our two groups of patients there were no difference in overall survival depending on the modalities of consolidation chemotherapy. The long term results of treatment of adult patients with ALL are not satisfactory and need further improvement.

1362 PUBLICATION

ICE protocol as conditioning regimen in autologous bone marrow transplantation in high-grade non-Hodgkin's lymphoma

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Purpose: We report here the results of high dose chemotherapy with ICE (Ifosfamide 3000 mg/m^2 -6 -5 -4 -3, Carboplatin 500 mg/m^2 -6 -5 -4, Etoposide 300 mg/m^2 -6 -5 -4) in a group of high-grade NHL patients (pts).

Methods: We have treated 31 pts from 1993 tom 1997. Clinical characteristics were: female 15, male 16; stage III–IV 18; sistemic symptoms 11; 14 pts had mediastinic bulky disease; 16 were in first complete remission (CR), 5 were in second or third CR, 7 were partial responders and 3 refractory to chemotherapy.

Results: No treatment-related mortality was observed. Nonhematologic toxicity was minimal with 10% of severe mucositis (grade 3 WHO), 2 pts had hepatic toxicity (grade 2 WHO). No other clinically significant toxicities were observed. After a median follow-up of 24 months (range 1–53) overall survival (OS) was 88%. Stage was the only one statistically significant characteristic for OS. After a median follow-up of 21 months (range 1–51) 23 pts were freedom from disease, and disease-free survival (DFS) was 65%. The following characteristics were significantly associated with DFS: presence of bulky disease (93% vs 59% p 0.02), stage I–II (100% vs 55% p 0.004), CR at ABMT (81% vs 60% p 0.007).

Conclusion: We confirm the efficacy of this condictioning regimen and its feasibility in an heterogenic group of patients.

1363 PUBLICATION

Treatment of refractory or early relapsed lymphoma with *MINE* regimen

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Introduction: We report on the activity and tolerance of MINE regimen in patients with refractory or early relapsed intermediate or high grade NHL.

Methods: Seventeen patients, 12 men and 5 women, with refractory or early relapsed intermediate or high grade NHL were entered. The median age was 56 (32 to 75) years. Sixteen (94%) patients were in advanced stage III or IV and 12 (71%) were classified as high grade NHL (WF). According to the IPI, 10 (59%) patients with scores 3–5 were classified as high risk. All patients had been previously treated with either CEOP or CNOP (Novantrone instead of Epirubicin) and for various reasons, were not considered for megatherapy. After this first line treatment, the disease was proven to be resistant in 10 (59%) patients, while in seven patients the disease relapsed in 2–10 months after induced complete remission. The MINE regimen consisted of Mesna 1.33 gr/m^2, Ifosfamide 1.33 gr/m^2, Etoposide 65 mg/m^2 days 1–3, and Mitoxantrone 8 mg/m^2 day 1.

Results: The median number of cycles administered was 5 (2 to 7). Ten (59%) patients responded including 5 (30%) with CR. Four (40%) responders were observed among 10 patients with refractory disease and 6 (85%) among 7 with early relapse. Median survival was 18 months. *Toxicity:* Grade III neutropenia was observed in 10 (59%) patients. All patients exhibited alopecia grade III.

Conclusions: The MINE regimen with an acceptable toxicity is an alternative in the treatment of patients with early relapsed or refractory NHL. Its use may be important in the treatment of patients not eligible for more intensive regimens.

1364 PUBLICATION

Survival and prognostic factors in patients with Hodgkin's disease

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Purpose: The aim of this study is to determine the overall and progression free survival and to evaluate the prognostic factors in patients with HD.

Methods: 125 patients with histologically confirmed HD; treated and followed in our clinic between 1991–98 were evaluated retrospectively