consistently begin in the antrum and IM is common in chronic gastritis and increases in prevalence with disease duration. Earlier reports indicated the detection of atrophy and IM in DU patients and in some gastritis patients.[5] In this study, mild scores of such conditions might be reflected on the low incidence of gastric cancer cases in Libya. According to the world health organization (WHO) report, the annual rate in Libya is very low compared to those reported for Asian countries such as Japan (0.083% versus 57.65%). This fact demonstrates that geographic distribution and possibly genetic variability (as shown in our recent report were Turkish *H. pylori* strains were genetically similar to Western but not to Asian strains)[6] are important factors in the disease outcome. From this study, we conclude that *H. pylori* density at different gastric sites affects the severity of the gastric histology and the disease outcome. The mild histological scores and the few precancerous lesions detected might be correlated with the genotype of *H. pylori* strains in the Libyan patients examined. Further investigation in this regard is required.

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Fludarabine as a second-line treatment of advanced stage chronic lymphocytic leukemia

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Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults in the Western countries, accounting for approximately 25-30% of all leukemias. The traditional management of patients with CLL is chlorambucil with or without corticosteroids. They are in general safe, given on an out patients basis and significantly cheaper than purine nucleoside analogues. Chlorambucil alone or in combination with corticosteroids is associated with a complete and partial response rate of 30-70% in previously untreated patients.[1] Furthermore, until last year no effective alternative agents for the management of patients with CLL who were resistant to alkylating agents and corticosteroids. Fludarabine is indicated for the treatment of patients with B-cell CLL who have not responded to, or whose disease has progressed during or after treatment with alkylating agent-containing regimen. Response and survival after treatment with fludarabine in advanced CLL are strongly correlated with disease stage and degree of previous chemotherapeutic regimen. Resistance of disease to alkylating agents is also significant correlated to outcome. Fludarabine induces higher response rates with a substantial number of complete remissions, but no improvement in overall survival has been observed.[2]

In this report, from 2 center followed from May 1997 to September 2002, the clinical response rate and duration, toxicity and survival of 36 patients with 32 months follow-up of treatment with fludarabine in refractory CLL has been evaluated. The diagnosis was made according to physical examination and morphologic and immuno-phenotypic features of peripherally blood and bone marrow. Diagnostic criteria consisted of lymphocytosis with an absolute lymphocytes greater than 5.000/µl on at least 2 previous occasions one month apart and had more than 30% lymphocytes in the bone marrow. All of patients had surface marker analysis providing evidence of a monoclonal B-cell proliferation. The disease in each patient was assigned according to the Rai staging system at the time of fludarabine treatment.[3] Patients were included only if they had failed to respond or had relapsed during or after previous treatment with at least one therapeutic regimen containing an

alkylating agent. Refractory disease was defined as a failure to obtain a complete or partial response after therapy with an alkylating agent regimen or development of progressive disease while patients were still receiving alkylating agents. The patients also had World Health Organization (WHO) performance status of 0 to 2 and a life expectancy of more than 6 months. Patients were excluded from the study if they had received prior treatment with purine analogs, mitoxantrone or an anthracycline, severe or life-treating concomitant disease or autoimmune hemolytic anemia. Normal renal and hepatic functions (creatinine <2 mg% and bilirubin <2 mg%) were required. Fludarabine was administered at a dose of 25 mg/m^2/day in 30 minutes intravenous infusion for 5 consecutive days and repeated 4 weekly, for 6 months.

The primary efficacy measure was response to treatment, evaluated 3-5 weeks after the last treatment cycle. End-of-treatment assessment included a physical examination, hematological and biochemical parameters, documentation of adverse effects and WHO toxicity. A bone marrow or biopsy was carried out for all patients. For the interpretation of the response the criteria introduced by the International Workshop on CLL (IWCLL) were applied.[4] According to these criteria the patients were classified into complete responders (CR), partial responders (PR), progressive disease (PD), and stable disease (SD). Complete responders was defined as the absence of disease. Partial responders, SD and PD were also defined by these criteria. Baseline assessment included age, gender, ethnicity, height and weight. Physical examination were carried out at baseline, before the start of each treatment cycle and the final assessment. Grade of acute toxicity was carried out using WHO criteria (grade 0, absence of toxicity, to grade 4, severe toxicity). Assessments were made at baseline and again before each cycle of therapy. Adverse events not covered. The analysis was carried out using the Statistical Package for Social Sciences 11.0 statistical software.

Table 1 lists the characteristics of patients, survival, response rate and toxicity. All patients had previous treatment either chlorambucil alone or in combination with prednisolone. The median age was 63 years, with a range from 52-72. Thirty-two patients were male (89%) and 4 (11%) female. The median time from initial diagnosis to treatment was 55 months with a range of 36-84 months. The mean white blood cell count was 54.000/µl, with a range of 10.000/µl to 150.000/µl and median percentage of lymphocytes in the marrow was 78%. Thirty-two patients had Rai stage III and IV disease and 4 patients had stage II were entered to study. The mean number of fludarabine cycles necessary for achieving CR was 4 (range 2-6). According to IWCLL criteria 16 patients responded to treatment. The overall response rate was 44.4% with 4 CR and 12 PR. Twelve patients achieved SD and 8 PD. The median survival for responders was 18 months (range 12-30) for non-responders 8 months (range 6-10). Fludarabine was well tolerated with minimal side effects. Hypersensitivity reactions were not seen. Myelosuppression was seen in 8 patients. Median duration of myelosuppression was 15 days (range 10-21). In a total of 144 treatment courses, 24 febrile episodes were registered in 16 patients and successfully treated with empirical antibiotic regimen. In addition, 16 patients required blood and 4 patients required platelet transfusion during

Table 1 - Characteristics of patients, survival, response data and side effects of treatment.

Patients charateristics	**N**	**(%)**
Gender		
Male	32	(89)
Female	4	(11)
Age (year)		
Median	63	
Range	52-72	
Rai Stage		
II	4	(11)
III	22	(61)
IV	10	(27)
White blood cell (x 10^3/µl)		
Mean	54	
Range	10-150	
World Health Organization performance status		
0	7	(20)
1-2	20	(55)
3-4	9	(25)
Mean no of prior treatments	2	
Mean no of Fludarabine treatment (range)	4 (2-6)	
Median time from initial diagnosis to treatment (month)	55 (36-84)	
Median follow-up (months)	24 (6-32)	
Median survival (months)		
Responder	18 (12-30)	
Non-responder	8 (6-10)	
Response		
Complete response	4	(11)
Partial response	12	(33.3)
Stable disease	12	(33.3)
Progression	8	(22)
Neutropenia, grade 3 or 4	18	(50)
Thrombocytopenia, grade 3 or 4	10	(27.7)
Infection		
Patients	16	(44.4)
Cycles (144)	24	(16.6)
Transfusion		
Blood	16	(44.4)
Platelet	4	(11)
Treatment related mortality	0	

treatment. At the time of analysis, 16 (44%) patients remained alive. During follow-up, 16 patients died due to progressive disease, 2 patients due to myocardial infarction (in SD), and 2 patients due to pneumonia of unknown pathogen during progressive disease. Toxicity related mortality were no found.

The alkylating agents such as chlorambucil have been the mainstay of treatment in newly diagnosed patients with CLL for many years. No effective therapy for the management of patients who were resistant to these agents de novo or who developed resistance was available, until recently. The newer purine nucleoside analogues, fludarabine and cladribine have been synthesized recently and introduced into the treatment of CLL. Fludarabine was found the most active single agent in relapsed and refractory CLL. Response and survival after treatment with fludarabine in CLL are strongly correlated with disease stage and the degree of previous chemotherapeutic treatment. The response rate in patients who are refractory to alkylating agents is 35-40%, in previously untreated patients was associated with a response rate of 80%. In addition, patients with non-refractory CLL survive longer than patients with refractory disease (29 versus 9 months).[1] Many studies have shown longer response duration in patients treated with fludarabine than with alkylating agent based chemotherapy. Although, overall survival, progression free and events free survival were similar in patients treated with fludarabine and with conventional chemotherapy.[5] It is not clear whether it should be used immediately after failure of chlorambucil. However, more patients may respond if they have received more than 3 prior treatment regimens. Liso et al[6] published a series of patients in whom fludarabine had been used with success as third-line therapy after a sequential use of chlorambucil and cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or CHOP-like regimen. Authors reported that 5.2% of patients achieved a CR, 52.6% had a PR and the remaining 42.1% failed to respond to fludarabine treatment. Overall median survival from the start of fludarabine therapy was 30 months. Survival by tumor response did not show any difference between responders and non-responders.[6] Angelopoulou et al[7] showed that fludarabine treatment induces CR in 33% and PR in 25% of patients. The median number of fludarabine courses for achieving CR was 3 (range 2-5). Oral fludarabine treatment is other treatment modality. It has some advantages such as no needs hospitalization but diarrhea may be problem for these patients. The results of oral fludarabine is similar to intravenous fludarabine treatment.[8] In our study, the patients followed by median 24 months (range 6-32), median survival were 18 months (range 12-30) for responder patients while 8 months (range 6-10) for non-responder patients. Overall survival was observed in16 of 36 patients; SD was observed in 12 patients while progressive disease developed in 8 patients. Treatment related adverse effects were acceptable. Grade 3 or 4 neutropenia were occurred in 18 of 36 patients. Thrombocytopenia was appeared in 10 of 36 patients. Infection and transfusion requirement were occurred in 16 patients. There were no treatment related mortality.

In conclusion, fludarabine is indicated for the treatment of patients with B-cell CLL who have not responded to, or whose disease has progressed or after with at least one standard alkylating agent containing regimen. This study showed that fludarabine may be effective in patients with CLL refractory to conventional chemotherapy thus it may be given if patients still require treatment.

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