LETTER TO EDITOR / EDİTÖRE MEKTUP

The efficiency and side-effects of low-dose Fludarabine-Cyclophosphamide in the treatment of chronic lymphocytic leukemia

Kronik lenfositik lösemi tedavisinde düşük doz fludarabin-siklofosfamid'in etkinliği ve yan etkileri

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Dear Editor;

Chronic lymphocytic leukemia (CLL) is a malign disease of the bone marrow, originating from the relatively mature cell stage of B or T lymphocytes, during which mature-appearing small lymphocytes infiltrate the hematolymphoid organs. When fludarabine (F) is used alone, or in combination with cyclophosphamide (C), against CLL, especially the latter becomes a quite efficient chemotherapy combination for the first diagnosis or for resistant, or refractory, cases who previously a different therapy administered[1,2].

The aim of this study was to evaluate the efficiency, as well as the hematologic and non-hematologic side-effect profile of the low-dose oral F and C combination regime (FC) in cases, who were resistant against the first-line therapy, or in post-treatment relapsing CLL cases.

Accordingly, the efficiency of the FC combination therapy administered to 8 cases, who were either resistant against the first-line therapy, or relapsed following treatment, among a total of 38 CLL cases followed-up in the hematology outpatient clinic, have been retrospectively evaluated, together with developed any complications. The general features of all cases are summarized in Table 1, whereas those of the cases received the FC combination are given in Table 2.

Table 1. Characteristics of patients with chronic lymphocytic leukemia (n=38)

Male/female: 15/23
Mean age: 66 (44-81) years
Followed-up without medication, n (%): 13 (34.0)
Treated cases n (%): 25 (66.0)
Infections (n): 9 (multiple infection: 3, Varicella zoster virus: 1)
Hemolytic anemia (n): 2
IVIG (n): 4
Splenic RT (n): 2
CT protocols: CP (n=3), C (n=8), CVP (n=4), FC (n=8), different drug combination (n=2)
ARI (n=3)
TLS (n= 2)
Liver toxicity (n): 2 (Grade 1)
Exitus (n): 3 (2 due to infection-related sepsis, 1 due to TLS)
Neuropathy (n): 2 (due to vincristine)

ARI; Acute renal insufficiency, RT; Radiotherapy, CT; Chemotherapy IVIG; Intravenous immunoglobulin G, TLS; Tumor lysis syndrome, CP; Cyclophosphamide-Prednisolone, C; Chlorambucil, CVP; Cyclophosphamide-Vincristine-Prednisolone, FC; Fludarabine +Cyclophosphamide.

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Table 2. Features of cases administered with FC (n=8)

Disease: Refractory or relapse
Treatment Response, n (%): Complete response, 3 (37.0), Partial response, 5 (63.0)
Hematologic toxicity (first cure): Grade IV neutropenia (n=4), Grade 3 anemia (n= 3)
Infection (first cure): Neutropenic fever (n=3),
IVIG treatment (n=3), (1 hospitalized in the intensive care unit)
Exitus (n=1) (due to tumor lysis syndrome)

FC;Fludarabine+Cyclophosphamide, IVIG;intravenous immunoglobulin G, TLS;Tumor lysis syndrome

It was planned to administer F (30 mg/m2) and C (300 mg/m2) intravenously for three consecutive days, every 4 weeks. Prophylactic dose of trimethoprim-sulfamethoxazol was also administered for 12 months. The response and toxicity were evaluated according to National Cancer Institute (NCI) and WHO's current criteria.

Hematologic toxicity was observed in all cases during the first treatment course. Four cases developed grade IV neutropenia, three of them being diagnosed as grade III anemia too. Three cases developed neutropenic fever in the first treatment course. One case was hospitalized in the intensive care unit due to sepsis, and 2 other cases were treated according to neutropenic fever protocol. All other cases developed mild lung infection, for which oral antibiotic therapy was observed as sufficient. Varicella zoster virus infection developed after treatment in one case. Three cases were administered a total of four doses intravenous immunoglobulin G (400 mg/kg/day - 1 dose/month) due to the occurrence of more than two severe infections and hypogammaglobulinemia. Dose modifications were made in other treatment courses due two developing hematologic and non-hematologic side-effects, so that F (20 mg/m2/day) and C (200 mg/m2/day) were administered p.o. three consecutive days every 28 days. At the end of a total of 6 treatment courses, complete response and partial response were achieved in 3 and 5 cases, respectively (total response 100%). Two cases with partial response had been administered palliative radiotherapy approximately 6 months prior to the FC therapy due to massive splenomegaly (with the longer axis of spleen exceeding 20 cm, and with a sense of fullness over the spleen) and for pain palliation purposes. In these cases, which spleen sizes were reduced by 50% following the splenic radiotherapy, the spleen was further reduced almost to the normal size after the FC therapy.

Alkylating agents, such as chlorambucil, as an initial treatment, have been in use for a long time. Initial treatment of CLL has started to change with the introduction of nucleoside analogs like F into treatments. Although complete response and disease-free survival are enhanced with F and FC therapies, no difference is established in the total survival. Nowadays, the complete response rates have been further increased with the combinations of rituximab (R)-like agents with F. The clinical risk assessment can be conducted better in new diagnosed CLL patients by cytogenetic analysis and other biological prognostic factors, and the initial treatments are planned according to the patient's age, medical state, cytogenetic and other prognostic factors, aiming at palliating the symptoms of disease with complete response, disease-free survival, or minimal toxicity[3].

There are clinical studies, showing that combination therapies of FC and R-FC are quite efficient in treating CLL, as compared to chlorambucil or to F alone[2,4].

Although the combination of FC is an efficient treatment against CLL at conventional doses, it may lead to severe hematologic and non-hematologic toxicity in the elders. It has been reported that the FC regime is efficient and well-tolerated even at lower oral or intravenous doses of FC administered to CLL cases, including the relapsing and refractory cases[5-7].

The FC chemotherapy regime was administered to our relapsing and refractory cases, without genetic and other prognostic indicators being worked in detail, and without a prognostic staging being performed, due to limited technical capabili-

ties. While similar response rates have been attained in our cases to those from the literature, the hematologic toxicity in conventional FC was markedly higher than that in the low-dose FC (50% vs. 31%).

In conclusion, although oral F and C combination is efficient in refractory or relapse cases which previously treated by different modalities, its hematologic and non-hematologic side-effects make the use of this combination complicated. Especially, because of hematologic toxicity is higher in the elders and neutropenia-related infections occur frequently, it may become necessary to modify the dose according to the age and clinical picture of the respective patient. The protocol F (20 mg/m2/day) and C (200 mg/m2/day), administered p.o. three consecutive days every 28 days, seems to be an efficient treatment modality with a lower side-effect profile for refractory CLL cases. Further comparative studies including a wide number of cases are needed in this field.

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