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Different schemes of B-cell chronic lymphocytic leukaemia (B-CLL) treatment in the population affected by the Chernobyl accident

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Summary

Background Remarkable advance in the knowledge of the biology and treatment of chronic lymphocytic leukaemia (CLL) has been noted in recent years. CLL resembles several heterogeneous diseases with variable morphological features. New agents with antileukemic activity have been introduced recently for CLL patients, which improved the treatment results. Fludarabin has shown its efficacy in CLL both as a treatment of choice and in combination with conventional cytostatic agents. Clinical and haematological features of B-CLL in persons affected by the Chernobyl accident in the last period are presented.

Aim The aim of this study was the comparison of two chemotherapy different schemes for B-CLL treatment.

Materials/Methods The study was based on 32 patients with diagnosis of B-CLL who were treated at the Hematology Department. Depending upon the protocol all patients were classified in two subgroups: I – fludarabine monotherapy treatment, II – fludarabine with combination with other chemotherapy preparations.

Results of the treatment are analyzed for 16 patients after different chemotherapy regimens. A combined fludarabine and cyclophosphamide regimen has been shown to improve long-term complete and partial remission in the majority of patients as compared with a more conservative approach.

Key words **chronic lymphocytic leukaemia • Fludarabine • immunophenotype • treatment**

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Background

Clinical and haematological features of B-cell chronic lymphoid leukaemia and results of management with various chemotherapy protocols are presental for persons exposed to ionizing radiation after the Chernobyl nuclear power plant accident (CNA). A combination of fludarabine with cyclophosphamide was found to induce a long-term complete or partial remission in a large part of patients in contrast to the use of traditional protocols. Cytopenia is regarded as one of the side-effects of the fludarabine treatment along with infections and bleeding related to decreased platelet counts.

A clinical course of B-cell chronic lymphoid leukaemia (B-CLL) in people exposed to ionizing radiation when working in emergency situations at the CNA and *living* on radio-contaminated territories long time after the accident is characterized by a rapid progress and resistance to traditional chemotherapy protocols [1].

Application of purine analogue (i.e. pentostatine, cladribine, fludarabine) a prospective drugs in the management of B-CLL [2–6] for the last two decades has led to a significant improvement in the treatment outcome [7,8].

The B-CLL origin is now thought to be related to a decrease of in cell sensitivity to apoptosis. The fludarabine effect involves a direct apoptotic impact on B-cells through the depression of DNA synthesis and especially DNA repair [9].

Clinical trials with fludarabine have proven its action on the lymphoid cell line and its efficacy in chronic lymphoproliferative disorders**,** including the B-CLL cases progressing under alkylating agents and standard chemotherapy protocols [10–13].

Fludarabine monotherapy was not always effective enough; therefore, some other cytostatic agents have been added to improve the response. A combination of fludarabine with cyclophosphamide provides a response in 71–89% [7].

Aim

We present here the results of our study of the efficacy of different treatment schemes in the population affected by the Chernobyl accident.

Methods

The study was carried out on 12 participants of emergency work at the CNA and four residents of radio-contaminated territories all with B-CLL, aged 42–76, and treated at the Hematology Department of SCRM of MSA of Ukraine (1st group). Doses of external exposure were estimated during dosimetry control after decontamination work in four patients and varied from 0.04 to 0.25 Gy. Out of 8 clean-up workers 5 were exposed in the period from April to October 1986, and other three – in 1987. According to dosimetry estimates [14] the mean doses to those workers in 1986 were 0.13 Gy and to those in 1987 – were 0.05 Gy. Total doses of chronic exposure residents of the contaminated territories varied from 0.05 to 0.04 Gy. The control group included 16 B-CLL patients who were exposed to natural ionizing radiation (2nd group). Age and gender were comparable in both groups. The latent phase in the 1st group was 1–10 (6.9±2.02) months. The pre-clinical phase in the control group ranged between 12 and 96 (23.1±7.4) months. Clinical and hematological characteristics of the patients is showns in Table 1.

Table 1. Clinical-hematological characteristics of patients.

		Patients	
		1st group (n=16)	2nd group (n=16)
Males		16	16
Age		53±7	54.5±6.71
Phase B		13	10
Phase C		3	6
Hb	≤100 g/L	6	8
	≥100 g/L	10	8
Platelets	≤100×10^9/L	3	2
	≥100×10^9/L	13	14
WBC	≤100×10^9/L	11	13
	≥100×10^9/L	5	3

Peripheral lymph nodes enlargement (1 to 5 cm) in two regional groups and was found in both groups with splenomegaly (150/80–180/80 mm) and ventral lymph nodes enlargement (10 to 49 mm) by ultrasonography.

Elevated white blood cell counts, of 13–531×10^9/L (mean 100.8±79.71) 54–95% lymphocytosis (mean 77.9±9.58) were observed. Lymphocytes with mature cell morphological signs (high cytoplasm/nucleus ratio, condensed nuclear chromatin, basophilic cytoplasm) were prevalent in lymphocytograms. There were 10–30% of prolymphocytes (in *2/1* patients respectively), which corresponded to B-CLL morphologically atypical form. The hemoglobin level was 28–154 g/L (mean 102.9±18.16),and the platelets count was 30 to 300×10^9/L (mean 156.25±50.53).

Myelograms showed an increase in myelokaryocytes count of up to 360,000 (mean 213,200) at the expense of a high number of lymphocytes (80±11 mean) and narrowing of myeloid and erythroid hemopoietic roots. Megakaryocytes were represented by single cells.

Trepanobiopsy studies from the iliac bone indicated hyperplastic bone marrow with lymphoid elements of a mature lymphocyte type filling out all the intertrabecular spaces. A diffuse type of bone marrow damage was prevalent. A focal-diffuse type of the BM injury was observed at the initial stage A. Myeloid (granulocytic) and erythroid hemopoietic tissues were represented by single small islets. The megakaryocyte root was narrowed with a small amount of mostly mature forms. Pronounced reduction of adipose tissue was registered with a myeloid/adipose tissue ratio of 5–7:1. Moderate bone tissue resorption with fibrotic foci formation, deformation of sinuses and their quantitative decrease were present.

Table 2. Number of patients treated by chemotherapy including fludarabine.

Courses	Patients	
	1st group	2nd group
7	2	2
6	7	4
5	1	0
4	5	2
3	1	1
2	1	2

Table 3. Results of treatment.

Patients	Response			
	CR	PR	SS	PD
1st subgroup n=16	3	8	3	2
2nd subgroup n=16	0	3	3	10

What was typical was loss of structure odue to diffuse infiltration with a lymphoid tissue, mainly of small lymphocytes.

Immunophenotype studies of B-cell markers have shown that 50 to 92% of the circulating blood or BM cells in the exposed persons, and 54 to 90% cells in the 2 group represented a $CD45^{+}10^{-}19^{+}20^{+}5^{+}22^{(dim)+}23^{+}DR^{+}$ phenotype. The T-cell showed an altered ratio of $CD4^{+}$ and $CD8^{+}$ cells with the prevalence of the latter. The phase of leukaemia was defined for all patients using available data according to clinical phase classification by Binet [15,16].

Depending upon the applied protocols, patients from both groups were classified in two subgroups. The first subgroup of exposed patients included 14 (males aged 41–72, mean 53 years) who received fludarabine as monotherapy or in combination with other chemotherapy agents. In three cases, resistance was found to previous standard chemotherapy with leukeran and prednisolone both with that to CHOP, CHOP-Bleo, COP and VAMP programes. Other 11 patients received fludarabine as an initial agent. The second group included two patients, aged 51 and 74 who received standard polychemotherapy protocols. In the control the first subgroup of 12 persons received fludarabine, and the other group included four patients treated traditionally.

Fludarabine monotherapy was administered in a 50 mg/day dose i.v. with a low infusion rate for 5 days; the same protocol was used in combination with cyclophosphamide (fludarabine 50 mg/day and cyclophosphamide 600 mg/day i.v. at a low rate) for 3 days. Treatment courses were repeated every 4 weeks.

Table 2 shows the number of patients treated by chemotherapy including fludarabine.

Chemotherapy outcomes were assayed by the National Cancer Institute (NCI) Standard Scale (USA) [17].

Results

Complete clinical-hematological remission lasting 16, 15 and 9 months was obtained in three (21.4%) of patients exposed Who receivied fludarabine. In one case, complete remission was established after 5 courses with previous resistance to standard chemotherapy. In two other cases, the complete remission was registered after 4 and 6 courses.

Partial remission lasting over 6 months was observed in 8 patients (51.4%) after 2, 3, 4 and 5 courses; two of them were resistant to prior therapy (5–6 courses of leukeran with prednisolone, lymphocyte plasmopheresis, or either CHOP or COP).

Discussion

The general response rate in fludarabine therapy in this group was 72,8% which is corresponding the available data from medical literature. Progression was observed in two patients with infectious complications, in whom the use of fludarabine induced the pronounced anaemia, therefore application of the drug was discontinued. Toxic effects such as alopecia or kidneys involvement were not observed, nausea and vomiting were stopped by antiemetics. In three cases prolonged leukopenia (28–37 days, WBC count 1.2×10^{9}/L) occurred after 3 or 4 courses of fludarabine. After the period of rest between courses the therapy was continued for up to 45 days; a new course of fludarabine was initiated when the WBC count was over 2.0×10^{9}/L. In the second subgroup which receivied leukeran or cyclophosphamide as monotherapy or in combination with prednisolone or courses of CHOP or COP polychemotherapy no complete clinical-hematological remission was observed, whereas partial remission in three patients lasted less than 3 months. The progression of the disease was been in 62.5% of patients from the second subgroup.

Table 3 shows the result of treatment.

Conclusions

The period of the WBC count doubled was faund to be much shorter in the Chernobyl NPP accident survivors than that in the controls. The course of B-CLL in the exposed patients is characterized by resistance and low sensitivity to traditional treatment. Fludarabine can be successfully used during period of acute clinical-hematological manifestations of B-CLL in patients resistant to standard polychemotherapy protocols as it provides long-term remission with an increase of the survival time. The present study is to be followed up in the future.

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