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The use of methotrexate, vincristine, L-asparaginase and dexamethasone for salvaging adult acute lymphoblastic leukemia and lymphoma: a real-life experience

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Abstract

Objective: Despite recent improvements in the treatment options, adult relapsed/refractory Acute Lymphoblastic Leukaemia (ALL) and lymphoblastic lymphoma (LBL) exhibit poorer cure rates than in childhood. Since, the mainstay difference of childhood multidrug regimens is L-Asparaginase, we sought to salvage adult patients with a protocol containing methotrexate, vincristine, conventional L-asparaginase, and dexamethasone (MOAD). In this study, we aimed to summarize our experience.

Methods: Adult patients with relapsed/refractory ALL and LBL followed-up in our institution between 2017 and 2018 were reviewed and those treated with MOAD protocol were retrospectively included in the study. Clinical data, treatment responses, and adverse events were summarised. The protocol featured 28-day cycles of methotrexate 200 mg/m2 intravenously (IV) on days 1 and 15; vincristine 1.4 mg/m2 IV on days 1, 8, and 15; L-asparaginase 10,000 IU/m2 IV twice weekly; and dexamethasone 40 mg IV or orally on days 1–4 and 15–18.

Results: A total of eight patients were enrolled, of median age 37 years (range: 21–58 years). Four patients were recovered after transplantation. Complete remission was evident in 38%. Two such patients underwent allogeneic hematopoietic stem cell transplantation after the protocol. Another patient with lymphomatous disease achieved partial remission and underwent successful transplantation. L-asparaginase did not trigger any clinically evident hypersensitivity reaction; the most common adverse events associated with the protocol were hypofibrinogenemia, anemia, and febrile neutropenia.

Conclusions: The MOAD protocol was effective and tolerable, enabling to salvage before and after transplantation, particularly in patients with relapsed/refractory T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma.

Key-words: Acute lymphoblastic leukemia, Lymphoblastic lymphoma, methotrexate, vincristine, L-asparaginase, dexamethasone

Introduction

Acute lymphoblastic leukemia (ALL) is a disease that is poorly curable in adults, despite initial complete remission (CR) rates of 80–90% in newly diagnosed cases (1-2). Most patients relapse and up to 20% develop resistant disease. An effective salvage therapy is required, but attempted salvage using conventional chemotherapies after the first relapse yields CR rates of only 30–40% (2-4). After a second or later relapse, the outcomes are even poorer (5).

Currently, the only available potentially curative treatment is allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, it is important to achieve remission prior to allo-HSCT in those with relapsed/refractory disease (6). Lymphoblastic lymphoma (LBL) is a rare disease that is biologically closely allied to ALL, but features only minimal or no bone marrow (BM) involvement. In adults, initial ALL-type regimens afford survival rates of about 70%, thus better than those of ALL patients.

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However, management of relapsed/refractory disease remains very difficult. Second-line therapies using the available drugs are associated with poor survival; to ensure effective salvage, HSCT is imperative (7).

Apart from the conventional multi-drug regimens, new agents seek to increase the response rates to re-induction therapy for both ALL and LBL (8-13). However, the high cost and limited availability of such agents compromise their use; and adult cure rates are still lower than those of children. The childhood multidrug regimens include L-asparaginase, this drug may be toxic to adults because toxicity increases with age (14). In a recent phase 2 study in adults of median age 42 years, a PEGylated formulation of L-asparaginase was successfully combined with methotrexate, vincristine, and dexamethasone to salvage relapsed/refractory ALL (15). Previously, a similar combination of methotrexate, vincristine, conventional L-asparaginase, and dexamethasone (MOAD) was given to adults newly diagnosed with ALL (16). However, to the best of our knowledge, only a few studies have used the MOAD protocol (thus including conventional L-asparaginase rather than the PEGylated form) to treat relapsed/refractory patients. Here, we summarise our experience with the MOAD protocol in patients with relapsed/refractory ALL or LBL; we used the protocol to bridge patients to allo-HSCT or to salvage them after HSCT.

Materials and Methods

Study design: We retrospectively reviewed adults followed-up in our institution for 2 years (2017–2018) who were diagnosed with relapsed/refractory ALL or LBL and treated using the MOAD protocol. Their demographic and clinical characteristics, responses to treatment, and adverse events were noted. Data were extracted from a dedicated electronic database created in accordance with the guidelines of the Joint Accreditation Committee: International Society for Cellular Therapy and European Blood and Marrow Transplantation (JACIE) (Nucleus ver. 9.3.39; Monad Software Co., Ankara, Turkey); all data were verified by an independent audit group. Side effects were recorded using the Common Terminology Criteria for Adverse Events (ver. 5.0).

Evaluations/definitions: BM aspiration, flow cytometric analysis, and/or BM biopsy were scheduled for ALL patients after the first course of salvage chemotherapy. Additionally, patients with extramedullary lymphomatous disease were subjected to detailed radiological imaging. Complete response or complete remission (CR) featured all of the following: normalization of peripheral blood data (absolute neutrophil count (ANC) >1x109/L, platelet count >100x109/L, BM blasts <5%, and no circulating blasts or extramedullary disease).

Refractory disease (RD) was defined as a failure to achieve CR, and relapsed disease was defined by re-appearance of blasts in the blood or BM (>5%) or in any extramedullary site after CR had been attained. Progressive disease (PD) was defined as an increase ≥25% in the absolute number of circulating or BM blasts, or development of extramedullary disease. A partial response (PR) in those with lymphomatous extramedullary disease was defined as a >50% decrease in lymphomatous enlargement (17). Progression-free survival (PFS) was the time from treatment initiation to disease progression or death.

The MOAD Protocol

The MOAD treatment cycle ran for 28 days and featured intravenous (IV) methotrexate 200 mg on days 1 and 15 (reduced by 50% if the creatine clearance rate was 10–50 mL/min); vincristine 1.4 mg/m2 (maximum 2 mg) IV on days 1, 8, and 15 (reduced to 1 mg in those with pre-existing neuropathy and/or a bilirubin level 2–3 mg/dL and not given to those with a bilirubin level >3 mg/dL); L-asparaginase 10,000 IU/m2 given IV twice weekly on days 2, 5, 9, 12, 16, 19, 22, and 25 (withheld if the bilirubin level was >3 mg/dL and/or if pancreatitis, thrombosis, or disseminated intravascular coagulation developed); and dexamethasone 40 mg IV or orally on days 1–4 and 15–18 of each cycle (Table 1). The levels of amylase and lipase; the prothrombin time (PT) and activated partial thromboplastin time (PTT); and the fibrinogen, bilirubin, and liver transaminase levels were measured prior to each administration of L-asparaginase. Intrathecal chemotherapy was used for prophylaxis or to treat active central nervous system disease if no contra-indication was evident. Fluconazole 200 mg/day (withheld on days of vincristine administration to reduce the risk of toxicity), valacyclovir 500 mg/day, and levofloxacin 500 mg/day, were given to prevent infection.

Statistical analysis: SPSS software ver. 24.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Descriptive data are shown as numbers with percentages for categorical data, and as means with standard deviations (or ranges) for continuous data.

The study protocol was approved by the Baskent University Institutional Review Board (approval no. KA19/78) and adhered to all relevant tenets of the Declaration of Helsinki.

Table 1. The MOAD protocol

Day	1	2	3	4	5	8	9	12	15	16	17	18	19	22	25
Methotrexate (200 mg/m^2)	M								M						
Vincristine (1.4 mg/m^2)	V					V			V						
L-asparaginase (10000 IU/ m^2)		A			A		A	A		A			A	A	A
Dexamethasone (40 mg)	D	D	D	D					D	D	D	D			

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Results

In the interval 2017–2018, eight patients with relapsed/refractory ALL or LBL were treated using the MOAD protocol and all were included in analysis. Their median age was 37 years (range: 21–58 years). In four of the patients, MOAD served as salvage therapy after HSCT. The ALL lineage was B-cell in nature in four patients, but all patients were negative for the Philadelphia chromosome. Table 2 summarizes patient demographic and clinical characteristics. In terms of initial diagnosis, all patients presented with leukemic disease except for one presenting with lymphoma without BM involvement. Three patients with initial leukemic presentations relapsed prior to MOAD; they developed lymphomatous disease without BM involvement. The total number of completed MOAD cycles was 10; 3 uncompleted cycles were also noted.

Commencing on the first day of therapy, the mean follow-up period was 212 days (range, 10–623 days). One patient received the same protocol twice at different times, once prior to HSCT because of refractory disease and once after HSCT because of relapse. Table 3 lists the details for each case. Three (38%) of the eight patients achieved CR after the first MOAD protocol. For two of these, MOAD served as a bridging regimen to allo-HSCT. However, all three eventually developed progressive disease, including the two who relapsed despite allo-HSCT. Two patients (25%) with lymphomatous disease (patients 1 and 5 in Table 3) entered PR after the first MOAD cycle. One retained PR status after the second cycle but progressed after the third cycle; the other proceeded to allo-HSCT and is being continuously followed-up – that patient is in PR (without progression) 4 months after transplantation.

Table 2. Patient characteristics (n=8)

Median age (years), mean (range)	37 (21–58)
Gender (male:female), n	5:3
Lineage, n (%)	
B	4 (50%)
T	4 (50%)
Disease status prior to MOAD, n (%)	
Leukemia	4 (50%)
Lymphoma	4 (50%)
Number of chemotherapies prior to MOAD, n (%)	
1–2	2 (25%)
>2	6 (75%)
HSCT prior to MOAD, n (%)	
Yes	4 (50%)
No	4 (50%)

Table 3: Summary of clinical courses.

Patient	Sex/ age (years)	Origin	Prior chemotherapy	Response to MOAD	MOAD cycles	HSCT after	Follow-up after MOAD	Follow-up period (days)	Outcome
1	M/26	T	HyperCVAD, FLAG, linker protocol, allo-HSCT, high-dose methotrexate/cytarabine, nelarabine, MEC, radiotherapy	PR after the first cycle	3	No	Progression evident after the third cycle	113	Exitus
2	M/50	B	HyperCVAD, FLAG, allo-HSCT, MEC, rituximab, high-dose methotrexate	CR after the first cycle	3	No	Progression evident after the third cycle	389	Continuing on inotuzumab
3	F/21	T	HyperCVAD, ICE, IGEV, autologous HSCT, high- dose methotrexate/cytarabine, nelarabine	CR	1	Yes	Progression evident on day 123 after HSCT	623	CR developed after liposomal vincristine
4*	F/58	T	HyperCVAD	CR	1	Yes	Progression evident on day 90 after HSCT	150	Exitus
4*			HyperCVAD, MOAD, allo-HSCT	NA	1**	No	NA		Exitus
5	F/58	T	HyperCVAD, ICE	PR	1	Yes	PR persisted to month 4 after HSCT	339	Continued PR
6	M/21	B	HyperCVAD, BFM protocol, FLAG	RD	1	No	NA	68	Exitus
7	M/43	B	HyperCVAD, FLAG, MEC	NA	1**	No	NA	10	Exitus
8	M/22	B	HyperCVAD, FLAG, MEC, blinatumomab	NA	1**	No	NA	11	Exitus

Discussion

Adult patients with relapsed/refractory ALL or LBL have dismal prognoses, respond poorly to salvage regimens, and survive only briefly (2,7). The only option is to seek a second CR followed by allo-HSCT; the goal of salvage treatment is therefore a new CR. Apart from the conventional multi-drug regimens, new targeting agents increase the chance of re-induction (18), but these are expensive and not always available, so take-up is low. Moreover, most such agents target B-lineage disease; few new salvage options for T-lineage disease are available. Alternatively, the response rate can be increased by incorporating agents (such as L-asparaginase) that are widely used to treat pediatric ALL into adult regimens. This is not always easy, because the childhood drugs may be toxic to adults. Here, we report our experience with the MOAD protocol (which includes L-asparaginase) in patients with relapsed/refractory ALL and LBL; we sought to bridge them to allo-HSCT or salvage them after allo-HSCT. We found that 38% of patients (n=3) achieved CR that persisted for a median of 105 days after MOAD; 25% (n=2) evidenced PR. Two leukemic patients in CR and one lymphoma patient in PR proceeded to allo-HSCT after MOAD; all had T-cell disease. Thus, the protocol served as a useful bridging regimen, particularly for patients with T-cell disease for which new salvage options are few, in contrast to B-cell disease. Three patients underwent allo-HSCT prior to MOAD, and that regimen was used to salvage relapsed ALL in these patients. One achieved a short CR (62 days), one died without completing the protocol, and the third (with a lymphomatous relapse) achieved PR but for less than 3 months. Salvage after allo-HSCT is intended to reduce tumour load, which enables a therapeutic allogeneic effect; chemotherapy is not used in an effort to attain CR (19). Thus, two of three patients benefited from MOAD used as a salvage regimen after allo-HSCT.

A few studies have used similar drug combinations in relapsed/refractory settings and reported different CR rates and durations. Esterhay et al. (1982) prescribed the same drugs as we did, but with a different schedule, to 14 previously treated patients: the CR rate was 79% and the median CR duration was 7.5 months (20). Aguayo et al. studied 32 patients of median age 34 years (range, 20–74 years): the CR rate was 22% and the median CR duration was 16 weeks (21). The principal differences between the regimen used in these cited works and MOAD were the use of dexamethasone rather than prednisolone, and incorporation of the PEGylated form of L-asparaginase (polyethylene-glycol conjugated-asparaginase). Tapan et al. also used PEGylated L-asparaginase in combination with methotrexate, vincristine, and dexamethasone to treat patients with relapsed/refractory disease of median age 42 years (range, 22–69 years): the CR rate was 28% and the median CR duration was 4.3 months (15). In contrast, our protocol included the conventional form of L-asparaginase, which is an advantage because conventional L-asparaginase is more readily available than the PEGylated form, although the latter drug exhibits better pharmacokinetic properties and tolerance, and is associated with fewer side effects (22). In our present study, no patient experienced an allergic reaction during L-asparaginase administration. Additionally, all other treatment-related side effects were self-limiting; the most common side effect was hypofibrinogenemia.

One limitation of this study is that we included only a relatively small number of patients. However, very few reports have focused on relapsed/refractory patients who require allo-HSCT; our real-life clinical experience contributes to the knowledge in this area.

Conclusion

In conclusion, we suggest that a combination of methotrexate, vincristine, dexamethasone, and conventional L-asparaginase is well-tolerated, and can serve both as a bridge to allo-HSCT and as a salvage regimen after allo-HSCT, particularly in patients with relapsed/refractory T-cell ALL and LBL. Nevertheless, more work with larger numbers of patients is required to have more precise remarks and we hope our study will pioneer new prospective works about the issue.

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