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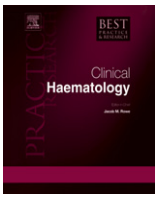

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What is the impact, present and future, of novel targeted agents in acute lymphoblastic leukemia?

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The absence of a standard of care for adults with acute lymphoblastic leukemia (ALL), the inadequate outcome of all adult regimens, and the lack of improvement in treatment outcomes over the past decades suggest a critical need for new approaches to treating adults with this disease. Several new strategies are now being considered, including the use of novel targeted agents alone and in combination with other chemotherapeutic drugs. This paper discusses several of these approaches and their impact on overall outcome.

Introduction

There is no universally accepted standard of care for adults with acute lymphoblastic leukemia (ALL). First, multiple different chemotherapy regimens have been studied all resulting in similar outcomes, with only few comparable trials [1,2]. Therefore the choice of a specific treatment is arbitrary, based on prior experience, training, practice preference and convenience. Second, children with ALL are treated differently from adults, with better outcome. Furthermore, it is becoming clear that

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adults with ALL at different ages should not be treated uniformly. Three age groups may be considered separately: adolescents and young adults (AYA) aged 15–39 years, adults aged 40–60/65 years, and adults older than 60/64+ years [3]. Finally, the role of allogeneic hematopoietic stem cell transplantation (HSCT) in front-line ALL is uncertain. Thus, the absence of a standard regimen, the inadequate outcome of all adult regimens, and the lack of improvement over the past decades imply a critical need for new approaches. Several new strategies are now being considered; one of them is the introduction of novel targeted drugs. This review will discuss several concepts of applying targeted agents as single drugs and in combination with chemotherapy in adult ALL, and their current and potential future impact on overall outcome.

Current treatment approaches

In adult acute lymphoblastic leukemia (ALL), the cure rate has not improved over the past 2-1/2 decades, as shown in epidemiological surveys in all age groups [4] and in multiple large clinical trials [1]. Table 1 presents several of the more recent large trials. They vary by upper age limit, selection of specific chemotherapy agents, and indication for allogeneic HSCT yet have an almost identical long-term survival of 35%–40% [5–12]. If Ph+ ALL is excluded, the overall survival (OS) is approximately 45% [9].

In general, the treatment of ALL is complex, consisting of several different chemotherapy cycles with a variety of agents. The regimens can be roughly grouped into several treatment models. The first are multidrug combinations based on the treatment model developed by Dr. Bayard Clarkson from Memorial Sloan-Kettering Cancer Center (MSKCC), called L-20, with daunorubicin, prednisone, vincristine and cyclophosphamide [13]. This concept was modified in children to the Berlin-Frankfurt-Munster (BFM) ALL model that consists of two-phase inductions: the first with four drugs (daunorubicin, prednisone, vincristine and asparaginase) and the second phase with cyclophosphamide, cytarabine, and 6-mercaptopurine. Post remission cycles vary, but all include asparaginase and a cycle of delayed reinduction (a modified repetition of the induction), which in high-risk children has proven to be advantageous [14]. Hoelzer et al. applied the principals of the BFM treatment model to adult ALL [15,16]. Several other regimens listed in Table 1 [5,6] and others [16–19] are variants of the BFM model principles. The largest ever front-line adult ALL study (UKALL XII/ECOG 2993) was conducted by a joint effort of the US Eastern Cooperative Oncology Group (ECOG) and the British Medical Research Council (MRC), which used a variant BFM model [8,9].

The second treatment model, hyperCVAD, consists of fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine [12]. It is probably the most commonly used regimen in adult ALL in the United States despite having no proven advantage, greater marrow toxicity, requires longer hospitalization, does not include asparaginase, but has a simpler structure.

The third treatment model is an aggressive “AML-style” induction that was studied in the hope that more rapid complete response (CR) would lead to more cures. The MSKCC ALL-2 regimen combined

Table 1
Newly diagnosed adult ALL: recent large clinical trials.

Study	Years	*N*	Age	Treatment	CR (%)	DFS (%)
GMALL 05/93 [5]	’93–’99	1163	35	Variants of a BFM model	87	35
CALGB 8811 [6]	’88–’91	198	35		85	36
CALGB 19802 [7]	’99–’01	163	41		78	35
MRC/ECOG-UKALLXII/E2993[a] [8,9]	’93–’06	1913	15–64	BFM model ± SCT	90	OS 39
UCSF 8707 [10] [b]	’87–’98	84	27	VPDA + intensified	93	52
L-2 [11]	00–06	78	33	HD-MITOX + HD-ARA-C	85	34
HyperCVAD [12] [b]	’92–’00	288	40	A) Cyclophosphamide, DEX, ADR, V B) HD-MTX + HD-ARA-C	92	38

Abbreviations: A, asparaginase; ADR, adriamycin; BFM, Berlin-Frankfurt-Munster ALL treatment model; D, daunorubicin; DEX, dexamethasone; DFS, disease-free survival; HD-ARA-C, high-dose cytarabine; HD-MITOX, high-dose mitoxantrone; HD-MTX, high-dose methotrexate; OS, overall survival; P, prednisone; V, vincristine.

[a] Randomized.

[b] Single institution.