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Current Prospects for Clinical Care of Acute Leukemia

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Current therapy for acute leukemia can be chosen from among three proven methods and one most promising but preliminary method of treatment: chemotherapy, radiation therapy, bone marrow transplantation, and the up and coming modality of specific immunotherapy. Chemotherapy clearly remains the standard against which all newer treatments must be measured. Bone marrow transplantation relies upon chemotherapy and radiation for maximum effect but has become the treatment of choice for carefully specified patient populations at specific times during their illness. *Specific* immunotherapy (IT) has emerged from the ashes of earlier, and largely catastrophic, trials of nonspecific immunoactive substances to its present state, in which specific reagents not only have potential of their own, but can broaden the scope of bone marrow transplantation through the removal of specific cell populations from the donor cell pool.

Within these modalities exist numerous options, the most important of which are listed in Table 1. These include oral and i.v. chemotherapies at several levels of intensity and complexity, bone marrow allografts of several levels of risk and effectiveness, several forms of immunologically active agents: drugs, antisera, and monoclonal antibodies; and ancillary measures up to and including total body irradiation.

In parallel, the means of identifying different classes of leukemia have been developed along the lines indicated in Table 2. In the process it has become apparent that in terms of the success of therapy the leukemias range from the very responsive, usually curable common ALL with normal chromosome constitutants and minimal evidence for T- or B-cell differentiation (CALLA+, T–, CIg– und SMIg–, normal or hyper-diploid) on the one hand, to Burkitt-like leukemia (TdT–, SMIg+, L3

Table 1. Options for treatment of acute leukemia

Chemotherapy p.o., i.v.
Vincristine, prednisone
Vincristine, prednisone, daunorubicin (or adriamycin), asparaginase
Methotrexate, asparaginase
Standard dose araC
Standard dose AraC, anthracycline ± thioguanine
High-dose araC, asparaginase
High-dose araC, anthracycline
Mercaptopurine, methotrexate
High-dose cyclophosphamide
Intermediate-dose methotrexate
IT methotrexate ± araC ± hydrocortisone
Bone marrow transplant
Isograft
Allograft, HLA and DR identical
Allograft, haplotype identical
Allograft, unmatched, T depleted
Autograft,leukemia cell depleted
Ancillary treatment
Antibiotic prophylaxis
Heparin prophylaxis
Cranial irradiation 18 – 24 Gy
Immunotherapy
Levamisole
Anti-CALLA
Anti T cell (4)
Anti-TdT

Table 2. Identification of different classes of leukemia

Usually curable:
Common ALL, children, hyperdiploid, Ph 1-, CALLA+, sIg and CTg-, CSF-, L_1, or L_2
Occasionally curable:
AML, children, normal karyotype, no prior treatment, M_1, M_2
AML, adult, normal karyotype, no prior treatment, M_1, M_2
Common ALL, adult, hyperdiploid, Phl-, CALLA + SIg and cIg-, L_1 or L_2
APL
Significant palliation and ultimate relapse:
T-cell ALL
AML, adult, abnl, karyotype, no prior R_x
AMoL
ALL, common CALLA+, Ph 1+
ALL, common (pre-B variant) CALLA+, SmIg−, CyIg+
Very refractory to rx:
Blastic crisis, lymphoid
Blastic crisis myeloid
B-cell ALL, SmIg+, L_3, Ia+
Pre-leukemia progressing to AML
AML, AMML, AEL following prior radiation exposure and/or cytotoxic chemotherapy

morphology, ±14q−), myeloid blast crisis (TdT±, SMIg−, CyIg−, Ph 1+ or ++), and other secondary leukemias on the other, with all other types falling somewhere in between the two extremes. A third component of the problem includes patient factors such as race, sex, age, the availability of stem cell donors, and past medical history. On the general level, it is the responsibility of the leukemia therapist to select the appropriate therapeutic options for each combination of leukemic and patient subtype, so as to maximize the likelihood of response, while keeping the risk of acute, chronic, and delayed toxicities to an acceptable minimum.

The current oncological-hematological literature is replete with examples of combined modality treatments including bone marrow transplantation. This volume includes a number of examples (e.g., the papers by Creutzig et al., Hoelzer et al., Thomas et al., Weinstein et al., and Zintl et al.) and also methods of segregating patients into known prognostically significant categories (e.g., the paper by Chen et al. and the overview by Greaves). Taken together one can draw the following *generalities* concerning treatment (Table 3). The most sensitive class of disease and the form with the best prospect of cure is common ALL in childhood. These individuals usually achieve remission with the combination of vincristine plus prednisone, and are kept in hematological remission with mercaptopurine plus methotrexate. Meningeal and gonadal involvement are frequent in common ALL; CNS prophylaxis must be given in all such cases, and there is evidence accumulating that the use of intermediate-dose methotrexate infusions will further reduce the risk of CNS leukemia and eradicate gonadal leukemia as well.

Common ALL is curable also in a small segment of adults, but appears overall more resistent to both induction and maintenance treatment. The addition of asparaginase and either daunorubicin or adriamycin are required for best response during remission induction. In both children and adults with uncomplicated common ALL bone marrow transplants should be reserved for patients who are in early relapse or who have been reinduced into a second remission, since with initial drug treatment many patients will be cured.

The strategy for good risk AML, AMML, and APL, i.e., those patients without an-

Table 3. Treatment preferences

Leukemia	Initial presentation		First relapse	
	Remission induction	Treatment in CR	Remission induction	Treatment in CR
Common ALL, child	VCR + P	MP, MTX, V, P, CNS XRT + MTX or MD-MTX	VCR, P, ASN, ANT	Allogeneic BMT or autograft with CALLA treatment
Common ALL, adult	VCR, P, ASN, ANT	XRT + Maint IT-MTX or MD-MTX	VCR, P, ASN, ANT or MTX, ASN, VCR, P	
Common ALL, Pre-B	VCR, P, ASN, ANT	TBI, CPA, BMT Allogeneic		
T-Cell ALL	VCR, P, ASN, ANT, AraC, CPA	TBI,CPA, BMT Allogeneic		
B-cell ALL	VCR, P, ANT, ASN, AraC, CPA	TBI, CPA BMT Allogeneic		
AUL	VCR, P, ANT, ASN, AraC, CPA	TBI, CPA, BMT Allogeneic		
Good-risk AML	AraC, ANT, ± TG ± HIDAC, antibiotics	AraC, ANT ± TG (intensive, 6 months) (CNS prophylaxis in children)		
APL	AraC, ANT, ± TG ± HIDAC, antibiotics, heparin	AraC, ANT, ± TG (intensive, 6 months)		
AMML, EL	AraC, ANT ± TG ± VP16, ± HIDAC	AraC, ANT, ± TG (intensive 6 months)	HIDAC, ANT	CPA, TBI BMT
AMOL	VCR, P; AraC, ANT, ± TG, antibiotics, Leukapheresis PRN	AraC, ANT, TG, intensive IT-MTX	± heparin	
Secondary AML	HIDAC	TBI, CPA, BMT		
CML, Blast crisis, lymphoid	VCR, P; HIDAC	TBI, CPA, BMT, or MTX		
CML, Blast crisis, myeloid	HIDAC	TBI, CPA, BMT		

AraC, cytarabine; HIDAC, high-dose cytarabine; ASN, asparaginase; ANT, anthracyclene (daunorubicin, adriamycin); CPA, cyclophosphamide; MP, 6-mercaptopurine; MTX, methotrexate; IT, intrathecal; MD-MTX, intermediate-dose MTX; TG, 6-thioguanine; BMT, bone marrow transplantation; VCR, vincristine; VP16, etoposide

tecedent bone marrow disease or cytotoxic treatment and without major cytogenetic abnormalities (excepting translocation 15:17) is in many ways analogous to that for common ALL. Patients are induced into remission, in this case with araC + anthracycline (7 + 3 or 10 + 3) or ara−C + anthracycline + thioguanine (TAD), and given limited but intensive maintenance therapy. No additional therapy will be required by as many as 30% of responders. For those who relapse a second remission may be achieved by the same drugs, following which allogeneic bone marrow transplantation is performed if a suitable donor is available and if the patient is 40 years of age or less.

For patients with other varieties of acute leukemia, who can be induced into remission but rarely remain there, e.g., T-cell ALL, pre-B-cell ALL, Ph 1+ ALL (or AML), and patients with very high blast cell counts, transplantation should be performed where possible early in the first remission using the most appropriate available resources and techniques.

Until recently, there was little to offer individuals who developed acute leukemia in marrows previously injured by other malignancy, radiation, or cytotoxic drugs. Patients with lymphoid blastic crisis of CML would occasional remit with vincristine ± prednisone, but for the majority, with myeloid secondary acute leukemias, treatment was fruitless. The use of high-dose cytarabine introduced by Rudnick et al. [7] and further evaluated by several groups [1–3] has been recently shown by Preisler and co-workers and Capizzi [1, 6] to be remarkably effective in controlling (albeit transiently) these formerly refractory secondary leukemias (see Table 4). Although remissions to date have been brief, they may permit these individuals to be successful recipients of bone marrow from normal donors, or of autologous marrow from which malignant cells have been eradicated (Ritz et al., Rodt et al., Kersey et al., McCaffrey et al., this volume).

The harnessing of the new techniques of immunodiagnostics and monoclonal antibody production have led to remarkable clinical results in leukemia and lymphoma ([4], Ritz et al., Levy et al., Kersey et al., this volume). Although of recent vintage the effects of antibodies or antisera in vivo, and in vitro in conjunction with autografting, have been so successful that larger trials to confirm and extend these approaches are mandatory. The pursuit of alternative methods of eliminating tumor cells on the one hand or T-effector T cells on the other in order to broaden the application of autografting and allografting for the management of malignancy ([5], Santos, Redt, this volume) are also of high priority.

The ultimate goal for the clinician is to have available a treatment for every type of leukemia in every clinical setting, and a rapid, reliable assay to determine which treatments are required. Progress is being made in this direction ([6], Izzaguira, McCaffrey, this volume). For the present choices must in the main rely on generalities drawn from clinical experience, but progress in assaying and classifying leukemia has been so rapid as to encourage great optimism for the management of acute leukemia in the immediate future.

Table 4. Treatment of secondary leukemias[a] with high-dose cytarabine (HIDIC)

Treatment	No. of patients	No. of CR	No. of PR	Duration (months) of response	Reference
HIDAC	10	6	2	1–4+	[6]
HIDAC + asparaginase	14	9	2	–	[1]

[a] Includes acute leukemia developing in patients diagnosed and treated for CML, polycythemia vera, and preleukemic (myelodysplastic) syndromes

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