Editorial

MANAGEMENT OF CHILDHOOD ACUTE LEUKEMIAS: PRESENT CONCEPTS

Acute leukemias are defined as malignant clonal proliferation of hematopoietic precursor cells, of unknown eitiology, leading to replacement of normal hematopoiesis by blast cells, comprising 30% or more of bone marrow cells, and infiltrating the spleen, liver, lymphnodes or other organs. Childhood acute leukemias are classified as acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).

Acute Lymphoblastic Leukemia

The malignant transformation in ALL may occur at any stage of early (immature) B-cell or T-cell differentiation. At initial presentation the usual tumor burden is 10^{11-12} cells. To induce complete remission (CR), induction must reduce the total number of leukemic cells by 99%. Although the basic two drug combination of vincristine (VCR) and predisolone (PRED) could induce CR in 85% of all patients, the addition of L-Asparaginase (L-ASP) and/or daunomycin (DR) has improved the CR to 95% and has also improved the duration of remission. Central nervous system (CNS) prophylaxis is an important concept in the treatment of ALL based on the fact that CNS acts as a sanctuary site for leukemic cells. The administration of cranial irradiation and intrathecal methotrexate (MTX) reduces the incidence of CNS relapse to less than 10%. Following induction and CNS prophylaxis, consolidation is a period of intensification of chemotherapy, particularly in high risk patients. Finally, in slow proliferating malignancies, maintenance therapy with daily cytotoxic treatment for about two years is necessary to maintain complete continuous remission. Drug dosage during maintenance should be adjusted to keep the total count at 1.0-3.0 $\times$ 10^9/L. With awareness of dose intensification, combination chemotherapy has become successful in curing patients with ALL(1). At the same time better supportive care with blood component therapy; bacterial, fungal and *Pneumocystic carinii* prophylaxis; broad spectrum antibiotic combinations; empirical antifungal therapy; enteral and parentral nutrition; has helped to decrease non-leukemic fatality during chemotherapy to less than 5%.

Early bone marrow relapse occurs within 6 months of stopping the treatment and has an extremely poor prognosis even high dose cytotoxic therapy. Bone marrow transplant (BMT) by a compatible donor is perhaps the only hope in these patients. Late bone marrow relapse occurs more than 6 months after cessation on therapy, and may be successfully treated with infusion of high dose MTX and cytosine arabinoside (ARA-C). CNS relapse occurs in 3-8% of patients even after adequate prophylaxis. Local therapy to the meninges by intrathecal chemotherapy combined with systemic therapy and CNS irradiation in non-irradiated children will cure 40% of patients. Testicular relapse usually occurs after completion of treatment in 10% of the boys. Localized involvement of a single testes should be treated with local irradia-

tion, followed by systemic therapy for atleast one year. Combined relapse most often involves bone marrow and CNS and has an extremely unfavorable prognosis.

At our institute we have made considerable progress in the treatment of childhood ALL in the last two decades. Between 1974-78(2) the induction CR was 53% with VCR/PRED, and 70% with VCR/L-ASP/PRED. The overall survival (OS) at 3 years for 153 evaluable patients was 22%. During 1984-86(3), the induction CR improved to 91% in 128 evaluable patients, using a four drug induction-consolidation regimen with VCR/ADR/ARA-C/PRED. The 5 year disease free survival (DFS) was 32%. Since June 1986, we have started a prospective clinical trial in collaboration with the National Cancer Institute (NCI) MCP-841 protocol. The induction therapy I-1 consists of VCR/L-ASP/DR/PRED. Patients in CR receive cranial prophylaxis with cranial radiotherapy (18 Gy) and intrathecal MTX. This is followed by a repeated induction course I-1, followed by consolidation therapy and 1½ years of maintenance treatment. For 457 patients treated from June 1986 to December 1991, the CR is 90.5%. The induction mortality is about 7.5%. The OS at 5 years is 55%.

The cure rate in ALL has increased from 15% in early 1970's, to 51% in 1980's, to almost 70% now. As a result careful monitoring of late antileukemic therapy has obtained importance to judge the quality of cure. Irradiation and alkylating agents can produce chromosomal abnormalities in normal cells resulting in second malignancies 2-20 years after treatment. Abnormal tomographic scans of the brain and slight impairment of the psychomotor skills and attention deficits have been noted after irradiation. Adolescent males are at a risk for spermatogenic dysfunction following cyclophosphamide. Thus, it has become essential to tailor the treatment according to the risk groups(4).

Acute Myeloid Leukemia

AML is more frequent is adults than in children and hence the management of AML is attributable to studies done in adults. Significant development was first seen in 1960's with the introduction of ARA-C and daunomycin. Further progress in the last two decades is attributable to: the application of high dose (HD) therapy, *i.e.*, HD ARA-C or HD busulphan plus CP with rescue autologous BMT; identification of major histocompatibility complex leading to successful allogenic BMT; and the development of bacterial and fungal prophylaxis for prevention of potentially lethal infections.

The current induction therapy is a combination of ARA-C and an anthracycline. A third agent (thioguanine or epipodophyllotoxin), has shown an improvement in the results in recent studies. In the current MMC AML-10 trial(5), the CR rate in children is 91%. About 5% of the children have resistant disease and another 5% succumb to infections and hemorrhage during remission induction. Recent studies with all-trans retinoic acid (ALTRA) has shown that remission may be induced through differentiation in AML-M3. Further post remission intensification therapy is designed to eliminate clonogenic cells assumed to be detectable as "minimal residual disease (MRD) by immunological or combined immunological and cultural methods. The options include: further cycles of therapy similar to the remission induction therapy: HD ARA-C containing chemotherapy; and myeloablative therapy followed by bone

marrow rescue. Bone marrow transplant with an HLA matched marrow has a dramatic impact on the relapse risk, reducing it from 50% to about 10-15%. There is little doubt that elective matched allogenic transplantation in first complete remission in childhood AML results in best relapse-free survival. For patients who do not have a donor, autologous bone marrow rescue following high dose chemoradiation remains of unproven benefit.

Patients exposed to HD anthracyclines may develop cardiotoxicity and premature deaths. More information is available about long term sequelae in BMT patients. One third of BMT patients treated with cyclophosfamide and total body irradiation (TBI) develop compensated hypothyroidism and about 8% require hormone deficiency and two-thirds of the pre-pubertal children have delayed onset of secondary sexual characteristics and may require hormonal therapy. Most post pubertal boys and girls will develop gonadal failure.

At our institute, ARA-C and DR were used for induction therapy from 1975-85, resulting in a CR rate of 44% and induction mortality of 32.4%(6). These patients were given 1½ years maintenance therapy. The 2-year DFS was 10%. With improved supportive care and the same induction therapy (1986-87), the CR rate improved to 75% in 53 evaluable patients. This was followed by two courses of consolidation therapy with the same drugs. The 2-year DFS was 24% and the OS was 18%. In the next phase (1988-90), 126 patients received the same induction followed by post induction escalation of ARA-C. The CR rate was 65% and the DFS at 2 years was 28%. These results clearly indicate the need for improvement in the treatment of AML and efforts are now on to institute allogenic BMT in the first remission.

Thus, while intensive therapy yields a high remission rate (>80%) only a variable proportion of these children are cured (20-50%). However, following BMT, 60-80% become long term survivors.

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REFERENCES

1. Pinkel D. Lessons from 20 years of curative therapy of childhood acute leukemia. Br J Cancer 1992, 65: 148-153.
2. Advani SH, Giri NK, Pai SK, *et al.* Acute lymphoblastic leukemia in childhood: Treatment, results and prognostic factors. Indian J Cancer 1989, 26: 180-188.
3. Advani SH, Iyer RS, Pai SK, *et al.* Four agent induction/consolidation therapy for childhood ALL: An Indian Experience. Am J Hematol 1992, 39: 242-248.
4. Barr RD, DeVeber LL, Pai MK, Andrew M, *et al.* Management of children with acute lymphoblastic leukemia by the Dana-Farber Cancer Institute Protocols: An update of the Ontario Experience. Am J Ped Hematol/Oncol 1992, 14: 136-139.
5. Eden OB, Lilleyman JS, Richards S, Shaw MP, Peto J. Results of Medical Research Council childhood leukemia. Br J Hematol 1991, 78: 187-196.
6. Saikia TK, Rajni A, Gopal R, Nair CN, *et al.* Long term results in acute non-lymphoblastic leukemia. J Assoc Phys India 1988,36: 505-507.