FUTURE ONCOLOGY

TECHNOLOGY, PRODUCTS, MARKETS AND SERVICE OPPORTUNITIES

A NEW MEDICINE PUBLICATION JANUARY 1996 VOLUME 1, NUMBER 9

STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

LEUKEMIA AND MYELOPROLIFERATIVE/ MYELODYSPLASTIC DISORDERS

MEETING COVERAGE

18TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM, SAN ANTONIO, TX, DECEMBER 10-13, 1995

ADVANCES IN THE MANAGEMENT OF BREAST CANCER

STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

LEUKEMIA AND MYELOPROLIFERATIVE/ MYELODYSPLASTIC DISORDERS

EPIDEMIOLOGY, ETIOLOGY AND CLASSIFICATION

Primary disorders of the hematopoietic system are relatively rare causes of morbidity and mortality, worldwide (see Exhibits 1 and 2). These diverse disorders are classified broadly according to their biologic behavior and malignant cell of origin. Leukemias are classified either as acute, which are associated with immature hematopoietic cells and progress rapidly, or chronic, which involve more mature cells and progress more slowly. Based on the cytology of leukemic cells, leukemias are also classified as lymphocytic and myelocytic (granulocytic).

With the exception of acute lymphocytic leukemia (ALL), leukemia is a disease primary occurring in middle age with incidence rates increasing with age; rates are estimated at 50.5 per 100,000 among those over 65 years-of-age. Leukemias are particularly deadly types of malignancies, with 5-year overall survival rates estimated at about 38.3% (see Exhibit 1).

In children, the most common leukemia is ALL. About 2,000 children are diagnosed with ALL every year, accounting for more than 50% of new ALL cases in the USA. In contrast, fewer than 500 children are diagnosed with AML, only about 100 with CML and CLL is rarely encountered in childhood.

Incidence rates vary among ethnic groups and geographic regions but, because of generally low incidence rates, reliable statistics are not available worldwide. The estimates presented in Exhibit 2 are based on USA and UK rates extrapolated for all of Europe. Incidence of leukemia is very low in Japan, except for adult T cell leukemia that is estimated to affect about 3 per 100,000 population.

Acute Leukemia

Acute leukemia, an uncommon disease in adults, is the most common malignancy of childhood. In the USA, estimated incidence is 4.5 cases per 100,000 people, and it is the twentieth most common cause of death from cancer. Acute leukemias are divided into two categories according to the cell of origin:

- acute myelogenous leukemia (AML) which arises out of the myeloid line
- acute lymphoblastic leukemia (ALL) which originates from lymphoid precursors

Acute myelogenous leukemia (AML) is primarily idiopathic but has also been associated with radiation and chemical (particularly benzene) exposure, certain genetic diseases (e.g., Down's syndrome, Bloom's syndrome, and Fanconi's anemia), and underlying hematopoietic disorders (e.g., paroxysmal nocturnal hemoglobinuria, myelodysplastic and myeloproliferative syndromes). It was recently reported (Shu XO, etal, J. NCI, January 3, 1995, 88:1:24-31) that maternal alcohol consumption was associated with increased risk (60% higher risk compared to controls) of infant AML; the risk rose to 10.5 times that of controls in mothers who drank during the last six months of pregnancy. Proximity to electric and magnetic fields was also thought to be a risk factor, but larger epidemiological studies have not confirmed a relationship (McDowall ME, Br J Cancer, 1986, 53:271).

"Secondary" or treatment-related AML may follow high dose alkylating therapy or exposure to epipodophyllotoxins (Pui C-H, etal, NEJM 1991, 325:1682). In July 29, 1994, the National Surgical Adjuvant Breast and Bowel Project and the National Cancer Institute reported that five cases of AML occurred in women 50 years-of-age or older with breast cancer that had spread to underarm lymph nodes, who were treated with dose-intensive, or high-dose regimens of Bristol-Myers Squibb's Cytoxan (cyclophosphamide) between April 1992 to February 1994. The women were treated with Cytoxan doses that were two to four times above the standard dose, a standard Adriamycin dose, tamoxifen (Nolvadex; Zeneca) and colony stimulating factors. AML cases occurred in each of the three treatment groups that received differing high doses of Cytoxan. Two of the five women who developed AML died from leukemia. The risk of developing chemotherapy-induced leukemia is 0.1%; the incidence of AML in this treatment group to date was 0.2%. Because of the increased use of high-intensity chemotherapy for many cancers, it was suggested that NCI-supported clinical trials report diagnoses of secondary AML.

AML is classified into 8 subtypes according to the cell type and stage of differentiation (Exhibit 3). Determination of the precise classification of AML subtypes depends on morphology, histochemistry, immunophenotyping, and cytogenetics. Although not part of the original classification scheme, advancements in immunophenotyping have allowed recognition of two other categories. Extremely primitive cells are now classified in the M0 subtype. Biphenotypic leukemias bear markers for both myeloid and lymphoid lineages.

AML is a particularly deadly cancer associated with an estimated 5-year survival rate of 10.4%. Survival is determined by age with rates for those under 65 years-of-age estimated at 17.3%, compared to 1.9% for those over 65.

Acute lymphoblastic leukemia (ALL) is also primarily idiopathic, although radiation has been associated with a few cases and heredity may play a role in some types. Whereas 80% of AML cases occur in adults, 70% of ALL occurs in children. ALL is classified into 3 subtypes on the basis of morphology and immunophenotyping; 75% of adult ALL has a B-cell phenotype, while 25% is T cell. (Exhibit 4). ALL is associated with 5-year survival rates of about 52.3%; survival varies dramatically with

Exhibit 1
Estimated Incidence, Death Rate and 5-year Survival Rates of Leukemia by Type in the USA in 1995

Leukemia	Incidence (#)	Rate*	Total (%)	Deaths (#)	Rate*	5-Year Survivors	Rate (%)
By Cell Type							
Lymphocytic	11,000	4.2	42.8	6,400	2.4	6,955	63.2
ALL	3,933	1.5	35.8			2,025	51.5
CLL	6,403	2.4	58.2			4,399	68.7
Other (mostly HCL)	664	0.2	6.0			531	80.0
Myelocytic	11,100	4.2	43.2	8,400	3.2		
AML	6,029	2.3	54.3			627	10.4
APL	800	0.3					
CML	3,272	1.2	29.5			775	23.7
Other (includes ATL)	1,799	0.7	16.2				
*Other & Unspecified**	3,600	1.4	14.0	5,600	2.1		
Total	25,700	9.8	100.00	20,400	7.8		38.3
By Progression							
Acute	11,761	4.5	45.8				
ALL	3,933	1.5	33.4			2,025	51.5
AML	6,029	2.3	51.3			627	10.4
Other (includes ATL)	1,799	0.7	15.3				
Chronic	10,339	3.9	40.2				
CLL	6,403	2.4	61.9			4,399	68.7
CML	3,272	1.2	31.7			775	23.7
Other (mostly HCL)	664	0.2	6.4			531	80.0

**per 100,000 population*

age, estimated at 56.8% in patients under 65 years-of-age compared to 3.5% for those over 65.

Adult T-cell leukemia (ATL) is a late complication of human T-cell lymphotropic virus type I (HTLV-I) infection. HTLV-I is the only virus definitely associated with acute leukemia. Despite active infection, risk of malignant conversion is low and only 2% to 4% of those with antibodies to HTLV-1 develop adult T cell leukemia/lymphoma (Tajima K, Int J Cancer, 1990, 45:237), usually 20 to 40 years after the initial infection. Nevertheless, strong evidence exists supporting the causative role of HTLV-I. The virus is found monoclonally integrated only in leukemic cells. HTLV-I is a retrovirus primarily found in the Caribbean basin, sub-Saharan Africa, northeastern South America, southwestern Japan, and the southeastern USA. It is spread parenterally, transplacentally, and by sexual contact. There are four different subtypes of ATL, smoldering, chronic, acute and lymphomatous, which usually appear in sequence.

Chronic Leukemia

Chronic leukemia is distinguished from acute leukemia by a more indolent biologic behavior and longer survival times. Although the malignant cell in chronic leukemia has a more mature phenotype, it is believed that the genetic defect occurs in a primitive cell.

Chronic myelogenous leukemia (CML) is classified as both a myeloproliferative disorder and a chronic leukemia. It accounts for about 15% of all cases of leukemia with an incidence of 1.2 per 100,000. Although radiation and benzene exposure have been reported to cause CML, most cases are idiopathic. Mean age at diagnosis is 60. Three phases of CML are recognized clinically, stable phase, accelerated phase, and blast crisis (see Exhibit 5). CML is associated with meager 5-year survival rates, estimated at 23.7%; rates decline from 32.7% for those under 65 years-of-age to 12.4% for those over 65.

Chronic lymphocytic leukemia (CLL) is a malignant clonal expansion of mature appearing lymphocytes. The disease progresses through stages characterized by the amount of tumor burden. Early stages are associated with lengthy median survival times. CLL is more common in men than women and is primarily a disease of old age. It is the most prevalent leukemia accounting for 30% of all leukemias. CLL is associated with the highest 5-year survival rates, estimated at 68.7% with age-related rates being similar at 74.9% for those under 65 years-of-age, compared to 65.0% for those over 65.

Hairy-cell leukemia (HCL) has a striking male predominance and also occurs primarily in older individuals. The disease progresses slowly; the median survival period of untreated patients is 53 months.

Myeloproliferative Disorders

Myeloproliferative disorders are primary diseases of hematopoietic progenitor cells which result in uncontrolled expansion. They are characterized according to whether the myeloid, erythrocyte, megakaryocyte or fibroblast lines is primarily involved. The four classic subtypes are CML (discussed above), polycythemia vera (PV), essential thrombocytosis (ET), and agnogenic myeloid metaplasia with myelofibrosis (AMMM). The mean age of diagnosis for myeloproliferative disorders is 60. PV occurs in approximately 1 per 100,000 people and is usually diagnosed in adulthood. Radiation has been associated with the development of the myeloproliferative disorders, but other etiologic agents have not been identified.

Myelodysplastic Syndromes (MDS)

Myelodysplastic syndromes which are rare disorders characterized by dysplastic and disordered hematopoiesis (MDS), are divided into 5 subtypes (Exhibit 6). Patients with MDS suffer from cytopenias despite a hypercellular bone marrow. These syndromes have proven quite refractory to treatment, and the only known curative procedure is bone marrow transplantation. Nevertheless, patients may survive for prolonged periods of time with supportive care only.

PATHOGENESIS AND GENETIC ABNORMALITIES

Acute Leukemia

Many chromosomal defects have been observed in the acute leukemias and are undergoing characterization. Better understanding of the role of these markers, is expected to allow clinicians to fine-tune therapeutic regimens to better manage patients. For instance, in the case of the M3 subtype (promyelocytic) of AML, successful therapy has been targeted to this translocation. In all other cases, however, knowledge of these genetic defects has not lead to successful specific therapies.

t(15;17)(q22;q11.2) documented by cytogenetics or PCR, is diagnostic of acute promyelocytic leukemia (M3). This translocation fuses the promyelocytic leukemia gene (PML) on chromosome 15 to the retinoic acid receptor alpha gene (RARa) on chromosome 17 (Kakizuka A, etal, Cell, 1991, 66:663-74; de The H, etal, Nature, 347:558-61) resulting in a PML-RARa fusion transcript. This product may act as a dominant negative inhibitor of the wild type RARa.

Exhibit 2
Estimated Incidence of Chronic and Acute Leukemia in the USA, Canada, Europe* and Japan in 1995

Leukemia Type	Europe (#)	Total (%)	USA and Canada (#)	Total (%)	Japan (#)	Total (%)	Total (%)
Acute	22,692	55.2	12,900	53.3	7,600	65.5	43,192
ALL	7,564	33.3	4,313	33.4	1,600	21.0	13,477
AML	11,598	51.1	6,611	51.3	2,500	33.0	20,709
APL	1,513		300		876		2,689
Other (includes ATL)**	3,530	15.6	1,976	15.3	3,500	46.0	9,006
Chronic	18,405	44.8	11,313	46.7	4,009	34.5	33,727
CLL	12,102	65.7	7,010	62.0	2,500	62.4	21,612
CML	5,042	29.4	3,576	31.6	1,200	29.9	9,818
Other (mostly HCL)	1,261	6.9	727	6.4	309	7.7	2,297
Total	41,097	53.4	24,213	31.5	11,609	15.1	76,919

** Excludes the former USSR*
*** About 3 per 100,000 in Japan*

t(8;21)(q22;q22) is associated primarily with the M2 subtype of AML and portends a more favorable prognosis. This translocation fuses the AML1 gene on chromosome 21 with the ETO gene on chromosome 8 (Erickson P, etal, Blood, 82:1825-31; Miyoshi H, etal, PNAS, 1991, 88:10431-4; Miyoshi H, etal, EMBO J, 12(7):2715-21). The active portion of the AML1 gene is not incorporated into the fusion protein and thus the translocation product may act as a dominant negative inhibitor of the wild type AML1 gene (Meyers S, etal, Mol Cell Biol, 13:6336-45).

inv(16)(p13q22), found as a variant of the M4 subtype of AML known as M4Eo, associated with a better prognosis. This inversion fuses the core binding factor (CBF) beta subunit with a myosin heavy chain gene, MYH11. The molecular results of this translocation are still under investigation.

t(9;22) which is equivalent with the Bcr/Abl rearrangement, is found in 30% of adult ALL and 5-10% of AML and portends a particularly poor prognosis. The breakpoint is usually downstream of the common translocation found in CML, and results in a 190 kD protein with unknown function.

In ALL and AML, the ALL1 gene, located on 11q23, is fused to one of a variety of genes located on various chromosomes. The t(4:11) translocation involving 11q23 is frequently found in childhood leukemia. This translocation is found in 5% of adults and is associated with a particularly poor prognosis.

In ATL, HTLV-1 is monoclonally integrated into malignant T lymphocytes and is believed to be a key factor in its pathogenesis. Malignant lymphocytes are activated CD4+ T cells [they manifest the CD3+, CD4+, CD8-, CD7-, CD25+ (IL-2R a subunit) phenotype].

In late 1994, Raggio-Italgene (Pomezia, Italy) researchers and academic collaborators reported that a gene, TCL1, was preferentially expressed early in T- and B-lymphocyte differentiation (Virgilio L, etal, PNAS USA, Dec 1994, 91:1250-12534).

Chronic Leukemia

CML is characterized by the t(9;22) abnormality which translocates the breakpoint cluster region of chromosome 22 to the abl oncogene of chromosome 9. This so called Philadelphia chromosome results in a 210 kD protein, encoding a tyrosine kinase product. When transfected into mice, the bcr-abl construct appears capable of regenerating the CML phenotype (Daley GQ, etal, Science, 1990, 247:824).

Progression to acute leukemia is usually the terminal event in CML. Although the majority of patients will acquire additional chromosomal abnormalities at this time, it is unclear what the transforming event is or how to predict it. In 2/3 of cases, blast cells are myeloid, while in 1/3, lymphoid blasts are identified suggesting that acute leukemia derives from a primitive cell capable of differentiating along either line. Recently, p16 mutations were found in 5 of 10 CML patients progressing to lymphoid blast crisis (Sill H, etal, Blood, April 15, 1995, 85:2013-6).

CLL and HCL are primarily B cell diseases. T cell CLL is seen in 5% of cases. Although there is sufficient basis to implicate a genetic factor in the cause of CLL, no specific genes have been identified. About 50% of CLL patients have a detectable cytogenetic abnormality, most commonly trisomy 12 and abnormalities involving chromosome 14. However, hypotheses about pathogenesis

Exhibit 3
Morphology, Cytogenetics, Clinical Features and Incidence of AML Subtypes Based on the French French-American-British Classification System

FAB Subtype	Morphology	Cytogenetics	Clinical Features	Incidence (#)
M0 (2%)	Myeloblast-undifferentiated			120
M1 (10%)	Myeloblast-undifferentiated, granules and Auer rods rare	Trisomy 8, monosomy 5 and 7		603
M2 (40%)	Myeloblast-with differentiation	Trisomy 8, monosomy 5 and 7, t(8;21)		2,412
M3 (13%)	Promyelocyte-abundant Auer rods, atypical primary granules	t(15;17)	DIC common, may treat with ATRA	800
M4 (15%)	Myelomonocytic	Trisomy 8, monosomy 5 and 7, M4Eo inv(16)	Extramedullary sites common	904
M5 (10%)	Monocytic	t(4;11), t(9;11)	Extramedullary sites common	603
M6 (5%)	Erythroleukemia	Trisomy 8, monosomy 5 and 7	Long prodromal phase, rheumatic signs	301
M7 (5%)	Megakaryocytic		Associated with myelofibrosis	302

are not well developed. It was also recently observed that CLL B cells from most patients coexpress both membrane-bound and soluble CD27, along with its ligand, CD70. The expression of soluble CD27 may prevent leukemic B cells from stimulating T cells via CD70, thereby potentially impairing their ability to function as effective antigen-presenting cells (Ranheim EA, etal, Blood, 1995 June 15, 85(12):3556-65).

Myeloproliferative Disorders

In PV, ET and AMMM, proliferation at extremely low levels of growth factors has been demonstrated. In the case of PV, endogenous levels of erythropoietin (EPO) are usually quite low and clones with extreme sensitivity to EPO have been isolated and are believed to be the malignant cells. Myelofibrosis associated with the myeloproliferative disorders is thought to be caused by overproduction of fibroblast growth factors. Fibrosis is reversible with bone marrow transplantation. Fibroblast expansion is known to be polyclonal, further supporting its reactive nature.

In contrast, marrow fibrosis associated with AMMM is highly correlated with the number of dysplastic megakaryocytes in the marrow. Increased type III collagen is attributed to fibroblast growth factors. Multiple clonal cytogenetic abnormalities are seen, but none are diagnostic.

Myelodysplastic Syndromes

Many suspect that chemical exposure plays a significant role in the development of MDS. Clonal cytogenetic changes such as 5q-, monosomy 7, trisomy 8, and 20q-, are seen in 50% of patients. Secondary MDS is closely linked with deletions of chromosomes 5 and 7. All MDS syndromes are characterized by a maturation defect, although the degree of perturbation of the various lines determines the clinical picture. The 5q- syndrome is the best characterized. The chromosome loss of 5q13-33 is the site of many growth factors, including GM-CSF, IL-3, IL-4, IL-5, M-CSF and M-CSF receptor.

PRESENTATION AND DIAGNOSIS

Acute Leukemia

Patients developing AML and ALL are often acutely ill and are hospitalized for immediate therapy. Pancytopenia from marrow replacement with leukemic cells results in symptoms of anemia, thrombocytopenia and neutropenia. Diagnosis is based on hematologic parameters and special studies to fully characterize the aberrant cell. Patients with acute leukemia usually undergo bone marrow biopsy and aspiration to obtain material for morphology, histochemistry, flow cytometry, and cytogenetics. Cytogenetics and molecular diagnostics are now part of the standard workup and are important in prognosis and detection of residual disease. Since treatment for AML and ALL differs, definitive therapy is implemented only after a final diagnosis is obtained.

No specific staging studies are required, because leukemia, typically, does not involve significant extramedullary disease. Also, treatment of leukemia with curative intent always requires systemic therapy which would address any sites of visceral disease.

HTLV-I-associated ATL presents with adenopathy, hepatosplenomegaly, hypercalcemia, skin lesions and lytic bone lesions. Patients with ATL are immunosuppressed and, as a consequence, more likely to contract opportunistic infections.

Chronic Leukemia

Given their generally indolent nature, chronic leukemias are often diagnosed incidentally on routine physical exam.

CML is characterized by splenomegaly, a high white blood count with an immature spectrum of cells, and a tendency to progress to a more aggressive acute stage. Patients may present with constitutional symptoms, hypermetabolic symptoms, early satiety due to splenomegaly, or be completely asymptomatic. Diagnosis is made by a characteristic blood smear and documentation of the Philadelphia chromosome (Ph1).

Oncor (Gaithersburg, MD) received FDA permission in September 1995 to export to several European countries, its investigational *in vitro* gene-based system, Mbcr/abl, for the diagnosis of CML. Multicenter evaluations for this test kit have been completed in the USA and a PMA has been filed with the FDA.

CLL is diagnosed by the demonstration of increased numbers of circulating B cells on flow cytometry. CLL characteristically expresses CD5 in addition to the B cell markers CD19, CD20, and surface light chains. Patients are often asymptomatic although they may also present with adenopathy, hepatosplenomegaly, constitutional symptoms or one of the associated autoimmune diseases. Autoimmune hemolytic anemia in conjunction with CLL is called Evan's syndrome. Immune thrombocytopenias may also be seen. Both are due to autoantibodies and usually improve with steroids or treatment of CLL.

HCL is characterized clinically by pancytopenia, splenomegaly and infectious complications. Diagnosis is made on the basis of morphology showing characteristic "hairy" lymphocytes with abundant projections, staining for tartrate resistant acid phosphatase (TRAP), and flow cytometry documenting CD11c (myelomonocytic marker) and CD25 (IL-2R). Hairy cells are CD5 negative.

Myeloproliferative Disorders

Polycythemia vera often presents with nonspecific symptoms attributed to hypervolemia and hyperviscosity. Headaches, cardiovascular symptoms, plethora, pruritus (particularly after a shower) are common. The greatest danger in the proliferative phase is thrombosis, particularly when the hematocrit is greater than 45% (Pearson TC and Wetherley-Mein, Lancet, Dec 9, 1978,

Exhibit 4
Classification of ALL subtypes Based on the French-American-British System

	L1	L2	L3
Morphology	Small, uniform	Large, nonuniform	Large, prominent vacuoles
Population	Children	Adults	
Surface markers	c-ALLA		Surface immunoglobulin
Molecular markers			t(8;14)
Prognosis	Standard	High risk	High risk, Burkitt's type

Exhibit 5
Phases of CML

Phase	Clinical Features	Therapy	Median Survival
Stable phase	Stable disease, mildly symptomatic, counts easily controlled	Alkylator therapy or IFN-α	3-5 years
Accelerated phase	Constitutional symptoms, difficulty controlling counts with medication, increased blast count		6-10 months
Blast crisis	Circulating blasts, myeloblastoma	Antileukemic therapy	3-6 months

pp 1219-2). Thrombosis occurs in 30% of patients and is the major cause of death. Bleeding also occurs and complicates management. In its spent phase, PV is characterized by marrow fibrosis and failure, with compensatory splenomegaly from extramedullary hematopoiesis.

The polycythemia working group has proposed a set of criteria to aid in the diagnosis of PV (Exhibit 7). The diagnosis of PV requires all three criteria in category A, or A1+A2 and B2 from category B, and also requires ruling out other causes of polycythemia. A basic workup includes measurement of erythropoietin (EPO) levels, and workup for EPO secreting tumor if EPO is found to be elevated. A blood gas with P50 excludes relative hypoxia and hemoglobinopathies. Cardiopulmonary disease must also be ruled out. Many clinicians measure red cell volume, although this is usually unnecessary if the hematocrit is >60%; if suspected, iron deficiency anemia must be investigated since it could falsely lower the red cell mass.

Essential thrombocytosis may be asymptomatic or associated with bleeding or thrombotic complications. Bleeding episodes tend to involve mucocutaneous surfaces while thrombosis of both venous and arterial systems is seen. Another manifestation is erythromelalgia, a painful vaso-occlusion of the lower extremities which can lead to gangrene. Improvement in symptoms when the platelet count is controlled or the patient is treated with arachidonic acid inhibitors, support the importance of platelets in this symptom. Neurologic symptoms including seizures and strokes have also been seen. Platelet function studies may show decreased aggregation with epinephrine (due to loss of membrane alpha-adrenergic receptors) which distinguishes this disorder from reactive thrombocytosis.

As with other low grade disorders, AMMM is often diagnosed on routine exam when splenomegaly or abnormal blood counts are noted. Patients may be asymptomatic or they may present with signs of marrow failure and discomfort due to splenomegaly. As the bone marrow in AMMM becomes increasingly fibrotic, hematopoietic activity shifts to extramedullary sites such as the spleen and then the liver, resulting in massive hepatomegaly.

Myelodysplatic Syndromes

Patients with myelodypsplasia usually come to medical attention when an abnormal complete blood count is noted, or they become symptomatic from anemia, thrombocytopenia or neutropenia. MDS subtypes and associated survival are presented in Exhibit 8. A common presentation is anemia with an elevated mean corpuscular volume noted in the elderly. Bone marrow biopsy is diagnostic and usually shows a hypercellular marrow with dysplastic changes. Nuclear abnormalities of red cells, ringed sideroblasts, and micromegakaryoctes are particularly suggestive. Chromosome analysis is performed to identify abnormalities associated with MDS.

PROGNOSIS

Acute Leukemia

Prognostic factors are divided between those present at the time of diagnosis, and features that become evident

as therapy proceeds. In general, age, comorbid disease, and certain subtypes or genetic abnormalities have prognostic significance. Acute leukemia developing from underlying hematopoietic disorders is associated with a particularly poor response to therapy and short survival. Response to primary therapy is also indicative of future biologic behavior. Prompt remission offers the best prognosis, while more resistant, refractory, or quickly relapsing disease are poor prognostic signs.

AML is associated with approximately 50-70% first remission rate. Higher complete remission rates have been achieved with more intense induction therapy and result in better overall survival (Mitus A, etal, JCO, 1995, 13:560-9). Of patients with AML entering a remission, 20-50% appear to be long term disease free survivors. Median survival for the entire population is 1 year. In patients with AML who relapse, approximately 50% can be re-induced into a second complete remission often using the original treatment regimen. However, these second and subsequent remissions are often short-lived and cure is extremely rare.

ALL has a more optimistic prognosis. Newer regimens show a complete response rate of 70%-90% with an overall cure rate of 30%-50% at 5 years (Larson RA, etal, Blood, April 15, 1995, 85:2025-37). However, ALL associated with t(11;14) and t(9;22) has less than a 10% long term survival rate with conventional chemotherapy alone, so BMT should be offered in first remission. Detectable PCR product from these translocations is equivalent to residual disease which will eventually relapse.

ATL is associated with very poor prognosis with overall survival of 50% at five months.

Exhibit 6
Rai Staging System for CLL

Stage	Clinical Characteristics	Median Survival (years)
0	Lymphocytes greater than 15,000/ml in the blood and 40% lymphocytes in the marrow	12.5
I	Adenopathy	8.0
II	Hepatosplenomegaly	6.0
III	Anemia (hgb<11 g/dl)	1.5
IV	Thrombocytopenia (plt<100K)	1.5

Chronic Leukemia

CML is associated with a median survival of 3-5 years. Progression to the accelerated or blast phase is an extremely poor prognostic sign and is usually associated with the development of additional cytogenetic abnormalities. Blast crisis may be either myeloid or lymphoid, the latter being associated with a somewhat better, but still dismal prognosis. The Sokal criteria (Sokal JE, etal, Blood, 1984, 63:789-9) divide patients into low, medium and high risk disease. Although these criteria are useful for population studies, the stratification lacks predictive ability for the individual patient. The accelerated phase lacks clear diagnostic criteria. In general, it is characterized by the need for increased medication to control symptoms and/or the development of constitutional symptoms such as weight loss, night sweats, or fevers. Increasing basophilia and blast count is suggestive of accelerated disease. Some centers classify patients with chromosomal abnormalities other than the Philadelphia chromosome as accelerated, contributing to the difficulty in interpreting studies of these patients. Patients in accelerated phase are at an increased risk for leukemic transformation with a median time to progression of 3-6 months.

CLL is not universally-treated upon diagnosis unless accompanied with complications or is progressive. Prognosis closely tracks its staging system which is fairly predictive of survival. Cytogenetic information is also important as normal cytogenetics has a much better prognosis. Median survival is 15+ years compared with 7.7 years for those with cytogenetic abnormalities. T-CLL has a more aggressive course and poor response to chemotherapy. The development of an aggressive lymphoma in the setting of CLL is called Richter's syndrome and occurs in 3%-10% of patients. Evidence both for and against the clonal evolution of the malignant cell is in the literature (Foon KA, etal, Ann Int Med, Oct 1, 1990, 113:525-39). Response to chemotherapy is poor and median survival is 4 months. Recently, deletion of the p53 gene in CLL has been associated with poor response to purine analogs and decreased survival (Dohner H, etal, Blood, March 15, 1995, 85:1580-9).

HCL is an indolent disease characterized by long periods of control with current therapies. Nevertheless, median survival is 4-5 years.

Myeloproliferative Disorders

Median survival of ET and PV is greater than 10 years with death resulting from thrombosis, hemostasis, or progression to the spent phase, or leukemic transformation. Although patients may be asymptomatic for a prolonged time, catastrophic events may occur at any time. In the case of PV, attempts at early treatment with antiplatelet agents resulted in no protection against thrombosis and was associated with a higher risk of bleeding (Tartaglia AP, etal, Sem Hematol., July 1986, 23: 172-6). Surgery poses a particular problem to PV patients and a very high risk of surgical complications is seen if the hematocrit is not controlled prior to surgery. Complicating management is the observation that, when phlebotomy is first initiated, there is a higher rate of thrombotic events.

Younger patients with ET are also difficult to manage. Despite the clinical belief that younger patients are relatively protected from complications of ET, a study of

patients under age 45 with ET showed that the risks of hemorrhage and thrombosis are substantial with 39% of patients experiencing one of these (Mitus AJ, etal, Am J Med, April 1990, 88:371-5).

Median survival after diagnosis of AMMM is 5 years and death usually results from progression of marrow failure. Better prognosis is associated with lack of symptoms, maintenance of adequate blood counts, and absence of hepatomegaly.

Myelodysplastic Syndromes

Prognosis is closely tied with stage of disease. Survival ranges from 5 months to 5 years. Patients with cytogenetic abnormalities have significantly shorter survival rates. Death in the more indolent stages often occurs because of marrow failure and resulting complications of pancytopenia. In the more advanced forms, death is usually due to leukemic transformation which occurs in approximately 25% of patients. AML originating from MDS is usually refractory to therapy and remission, if achieved, is of short duration.

Exhibit 7
Polycythemia Working Group Criteria for the Diagnosis of PV

Category A	
A1	Increased red cell volume
A2	Normal arterial oxygen saturation
A3	Splenomegaly
Category B	
B1	Thrombocytosis > 400K
B2	Leukocytosis > 12K
B3	Elevated leukocyte alkaline phosphatase score > 100
B4	Elevated B12 level or unbound B12 binding capacity

TREATMENT OPTIONS FOR MYELOPROLIFRATIVE AND MYELODYSPLASTIC DISORDERS

Myeloproliferative Disorders

The goal of chemotherapy is to control cell proliferation and symptoms. Allogeneic bone marrow transplantation is also curative in appropriate candidates.

In PV, therapeutic phlebotomy is used to maintain the hematocrit below 45% by inducing a state of iron deficiency. Control of hematocrit is particularly critical during pregnancy and surgery when risk of bleeding and thrombosis are higher. In older patients, radioactive phosphorus (32P) has also been used but appropriate consideration of the leukemogenic potential is required. Chlorambucil was used in the past, but was associated with an increased incidence of leukemia and has been abandoned.

ET is treated with hydroxyurea when cytotoxic therapy is required. In asymptomatic patients with extremely high platelet counts, use of antiplatelet agents is controversial but most clinicians elect to treat despite the higher risk of bleeding. Anagrelide (Agrelin; Roberts Pharmaceutical), a phosphodiesterase inhibitor, interferes with megakaryocytic maturation and decreases platelet counts. It may be associated with cardiovascular symptoms, headache, nausea, vomiting, and rebound in the platelet count when stopped (Anagrelide study group, Am J Med, Jan 1992, 92:69-76; Blood 1992; 79:1931). Agrelin, an orphan drug, was licensed by Roberts Pharmaceutical (Eatontown, NJ) from Bristol-Myers Squibb. An NDA has been submitted for the drug in the USA and approval is also being sought in Europe.

Many therapeutic approaches have been tried for AMMM with little success. Danazol appears to help the anemia in some patients. Busulfan and interferon have been tried. Splenic radiotherapy may result in symptomatic relief but carries the risk of an abscopal event and pancytopenia. Splenectomy in these patients is often high risk and should only be done for symptomatic relief and to decrease transfusion requirements.

Myelodysplastic Syndromes

Although many therapies have been tried, most have proven unsuccessful. Hormones (androgens, danazol, growth factors, vitamin repletion (folate, B12, pyridoxine), steroids, retinoids and interferons have only shown anecdotal benefit. Allogeneic transplantation in young patients with matched donors is appropriate. Overall survival for MDS patients after allogeneic transplantation is 30-40%, somewhat lower than for other diseases because of a higher relapse rate (up to 20%).

CURRENT TREATMENT OPTIONS IN ACUTE AND CHRONIC LEUKEMIAS

Most leukemias, particularly adult leukemias, are difficult and expensive to treat, may require long periods of maintenance treatment after successful induction therapy, and multiple hospitalizations (see Exhibit 9) for both cancer therapy and intervention associated with complications of the treatment and the disease. A retrospective review of charges associated with ATRA-based chemotherapy in 30 patients with APL, conducted at Memorial Sloan-Kettering Cancer Center, revealed that, excluding physician charges, the median cost of treatment was $97,944 for those treated by standard chemotherapy (during the 1985-1990 period) compared to $61,756 (during the 1990-1992 period) for those treated with ATRA (Eardley AM, Leukemia, Vol 8, No 6 June 1994, pp 934-939).

In spite of several novel drugs having entered the clinic recently, outcomes of leukemia patients are disappointing, remissions are short-lived and only a relatively small percent of patients survive past five years (see Exhibit 1). One approach that has been used successfully in failed chemotherapy patients and is now being increasingly

Exhibit 8
French-American-British Classification of MDS and Median Survival

MDS Subtype	Peripheral Blood	Bone Marrow	Median Survival (months)
Refractory anemia (RA)	<1% blasts	<5% blasts	44
Refractory anemia with ring sideroblasts (RARS)	<1% blasts	<5% blasts; ringed sideroblasts >15% of nucleated cells	55
Chronic myelomonocytic leukemia (CMML)	<5% blasts; peripheral monocytosis	5-20% blasts	29
Refractory anemia with excess blasts (RAEB)	<5% blasts	5-20% blasts	17
Refractory anemia with excess blasts in transformation (RAEB-T)	>5% blasts	20-30% blasts or Auer rods	5
AML		>30% blasts	

From Bennett JM, etal, Br. J. Haematol. 1982,51:189-99.

used to sustain remissions, is transplantation of bone marrow (BMT) and/or peripheral blood stem cells (PBSCT). Leukemia represents the most common indication for allogeneic BMT (alloBMT), accounting for 74% of all such transplants worldwide, 73.4% in the USA and 75.4% in Europe in 1993. Autologous BMT (autoBMT) has been less popular in leukemia, accounting for 9.4 % of such procedures in the USA and 23.4% in Europe. Estimated alloBMT and autoBMT procedures in the USA and Europe in 1993 are presented in Exhibits 10 and 11; estimated worldwide procedures in 1995 are presented in Exhibit 12.

Chemotherapy in Acute Leukemia

Acute leukemia is treated as soon as diagnosis is confirmed. Routine pre-chemotherapy studies are performed to establish adequacy of organ function prior to treatment. Central access catheters are implanted to insure adequate venous access for drugs, blood transfusions, and blood sampling. Total parenteral nutrition may be given although it is usually not necessary.

In cases where definitive treatment must be delayed while awaiting conclusive diagnosis, hydroxyurea and leukapheresis may be used to control blast counts. Therapeutic leukapheresis is performed if symptoms, such as mental status changes, develop. Allopurinol and urine alkalinization help prevent metabolic abnormalities from tumor lysis syndrome when cytotoxic chemotherapy is given.

Therapy for both AML and ALL involves prolonged periods of pancytopenia. Patients are aggressively supported with blood products and antibiotics, as needed. It is not unusual for patients to require empirical treatment with aminoglycosides, beta lactam antibiotics, vancomycin and amphotericin because of persistent fevers. Colony stimulating factors such as G-CSF, have been avoided in the past because of concerns about stimulation of the malignant clone in AML, although no significant supporting evidence for such an effect has been produced. Patients who do not wish or are not candidates for aggressive chemotherapy, usually die within weeks from infection, bleeding, or other complications.

AML is treated with cyclic chemotherapy, and is divided into induction and consolidation phases. Induction regimens usually combine an anthracycline, typically daunorubicin or idarubicin (Idamycin (USA) and Zavedos; Pharmacia and Upjohn), with cytosine arabinoside (ara-C, Cytosar; Pharmacia & Upjohn). Thioguanine (Burroughs Wellcome/Glaxo Wellcome), a purine analog, which was commonly used in the past, does not contribute substantially to complete remission. Following remission, monthly cycles of chemotherapy attempt to "consolidate" this outcome. Modifications to standard regimens which increase the intensity of induction and consolidation cycles have resulted in improved survival (Mayer, etal, NEJM, Oct 6, 1994, 331:896-903; Mitus A, etal, JCO, 1995, 13:560-9). Total duration of primary AML therapy is approximately 6 months. Options for patients who do not wish aggressive chemotherapy include hydroxyurea.

AML patients who relapse are unlikely to experience durable second remissions and the median survival is 3-4 months. Nevertheless, a second remission may be obtained in 50% of these patients. Originally-employed chemotherapy regimens are sometimes successful, especially if the duration of remission has been substantial. Other active agents include mitoxantrone, amsacrine, and VP-16 (etoposide) which are used in various salvage regimens.

M3 AML, or acute promyelocytic leukemia (APL), is an unusual disease. Treatment with all-trans retinoic acid (ATRA) results in differentiation of the blast cells and re-establishment of normal hematopoiesis, although the response is not durable without other chemotherapy. Patients treated with ATRA, sometime during therapeutic intervention, may have a survival advantage (Fenaux P, etal, 1993, Blood 82:3241; Tallman MS, etal, Nov 15, 1995, 86 (Suppl):125a). One of the limitations of oral

ATRA therapy is declining plasma levels of the drug. An intravenous liposomal formulation, is being developed by Aronex (The Woodlands, TX) to ensure adequate plasma levels during the recommended treatment period. This and the development of other retinoids in hematologic malignancies will be discussed in a future issue of FUTURE ONCOLOGY.

All-trans retinoid acid (ATRA, Vesanoid; Roche) was approved by the FDA on November 22, 1995, as second-line treatment of APL, the first retinoid to receive approval as an anticancer agent. Vesanoid was unanimously recommended for approval by FDA's Oncology Drugs Advisory Committee (ODAC) in its December 12-13th, 1994, meeting and has been available to patients under a compassionate treatment program. Vesanoid has been designated an orphan drug for the APL application. The approved indication is limited to induction (short-term) therapy of APL patients who have failed anthracycline treatment, cannot be treated by anthracyclines or have relapsed post-treatment. Vesanoid is to be delivered orally twice daily (total dose is 45 mg/m^2) on an inpatient basis and treatment is not to last longer than 90 days. Patients are to receive a standard consolidation and/or maintenance chemotherapy regimen for APL after induction therapy with Vesanoid, unless contraindicated.

Treatment with ATRA may be complicated by the retinoic acid syndrome, experienced by about 25% of those taking the drug, which has a significant mortality rate and is marked by increasing white count, fever, pulmonary compromise and capillary leak syndrome. (Frankel SR, etal, Ann Int Med, 1992, 117:292). Discontinuation of ATRA and prompt treatment with steroids may abort the syndrome. Other side effects include fever, headache, nausea and vomiting, skin dryness/rash, visual changes, cardiac arrhythmia, bone pain and abnormal liver enzymes, among others.

Issues regarding treatment protocols to maximize ATRA's benefit remain unresolved. Results of a National Cancer Institute-sponsored trial of ATRA were more favorable when the drug was used as first-line and/or maintenance therapy, improving one-year disease-free survival from 77% for standard chemotherapy induction followed by ATRA to 88% when ATRA was used pre- and post-induction. CR rates with ATRA range from 48% to over 90% depending on patient status. Survival rates were most striking among newly diagnosed patients treated with ATRA and anthracycline-based chemotherapy, with more than 50% surviving longer than three years. Survival rates in relapsed patients treated with ATRA are not as high, with about 20%-30% of patients surviving for one year. A 400 patient phase III trial comparing ATRA to standard chemotherapy is underway in the USA.

Vesanoid was launched in the USA in December 1995, for the treatment of APL. It is available in 10 mg soft gelatin capsules. In March 1995, Nippon Roche launched Vesanoid in Japan for the treatment of APL where it is priced at $11.0 per 10 mg capsule, for a total 30-day treatment cost of $2,673.

ALL is also treated with cyclic chemotherapy with a multidrug regimen containing anthracyclines, cyclophosphamide, ara-C, methotrexate, 6-mercaptopurine (Purinethol; Burroughs Wellcome/Glaxo Wellcome), prednisone, vincristine, and L-asparaginase (Elspar; Merck and Erwinase; Speywood Pharmaceuticals). Intensification of chemotherapy regimens has been particularly successful in children, significantly increasing five-year disease-free survival to 71% compared to 57% with standard chemotherapy (Chessells JM, etal, Lancet, Jan 21, 1995; 345:143-8).

Pegaspargase (Oncaspar), a PEGylated form of L-asparaginase was approved in the USA in February 1994 for the treatment of ALL. Developed by Enzon (Piscataway, NJ) and marketed by Rhône-Poulenc Rorer (RPR) in the USA, it is administered in combination with other agents, IV or IM (2,500 IU/m^2, every 14 days). This formulation of L-asparaginase was developed to treat those patients who develop hypersensitivity to L-asparaginase which occurs in approximately 70% of patients on L-asparaginase but only in 20% of those on Oncaspar. Attaching strands of polyethylene glycol to native L-asparaginase shields the latter from the patient's immune system, extending its plasma circulating life and improving its effectiveness. Oncaspar is also administered under a more convenient dosing schedule. Based on an average wholesale price of $1,225 for 3,750 IU, the average monthly cost of Oncaspar therapy is $2,940.

In early 1995, Enzon and RPR revised the terms of their December 1993 licensing and marketing agreement for the North American rights of Oncaspar. Under the new terms, Enzon will receive a 10% royalty in 1995 and 23.5% in the 1996 to 2007 period, on sales up to an agreed amount and an additional royalty (23.5% in 1995 and 43.5%) on sales exceeding that amount with a limit of total royalties paid at 33% of net sales. Oncaspar was approved for marketing in Germany in late 1994. Oncaspar is designated as an orphan drug. Sales of Oncaspar are estimated at about $50 million in the USA in 1995.

Following remission, intensification and consolidation chemotherapy is administered followed by maintenance for a total of 2-3 years of therapy. In adults, central nervous system prophylaxis with cranial irradiation and intrathecal methotrexate and ara-C is common. The CNS is a sanctuary site and 30% of ALL patients will relapse

Exhibit 9
Hospitalizations of Patients with Leukemia in the USA

ICD-9-CM	Type of Leukemia	First-listed Diagnosis		All-listed Diagnoses	
		1992	1993	1992	1993
204	Lymphoid	23,000	22,000	49,000	45,000
204.0	Acute	15,000	15,000	17,000	17,000
204.1	Chronic	8,000	7,000	30,000	27,000
205	Myeloid	22,000	18,000	23,000	18,000
205.0	Acute	18,000	14,000	16,000	11,000
205.1	Chronic	6,000	6,000	7,000	7,000
Total		45,000	40,000	62,000	63,000

in this site if untreated (Omura GA, etal, Blood 1980, 55:199). Initial CNS involvement is a poor prognostic sign. Options for patients who do not wish aggressive chemotherapy include vincristine/prednisone.

Prognosis following relapse with ALL varies somewhat depending upon the duration of remission. Approximately 20%-50% of relapsed patients can be re-induced into a second complete remission. However, as in relapsed AML, second remissions from ALL are usually of short duration. In relapsed ALL alloBMT is considered in appropriate candidates.

ATL treated with chemotherapy is associated with a disappointing outcome. Recently, however, patients with adult T cell leukemia/lymphoma responded to a combination of AZT (zidovudine; Retrovir; Glaxo Wellcome) and IFN-α. In a clinical trial involving 19 ATL patients with acute and lymphomatous forms of ATL (including seven who relapsed or failed to respond to chemotherapy) treatment with oral AZT (200 mg five times daily) and subcutaneously-delivered Intron-A (5 IMU to 10 IMU daily), 58% of the patients experienced a major response, with 26% achieving complete remission (Parkash SG, etal, NEJM, June 29, 1995, 332:26:1744-1788). Similar results were observed using AZT and Roferon-A (Gill,etal, Gallo RC, etal, Hermine O, etal, NEJM, June 29, 1995, 332:26:1749-1751).

Chemotherapy in Chronic Leukemia

CML may only be cured with bone marrow transplantation. Palliative therapy is designed to control proliferation of the myeloid cells and the resulting symptoms. This may be accomplished with single agent alkylator therapy such as hydroxyurea. Busulfan was the standard agent in the past but was associated with more complications and a worse outcome. IFN-α induces cytogenetic and molecular remissions but is associated with significant flu-like symptoms in many patients. Several randomized trials have suggested that treatment with IFN-α significantly improves survival compared with hydroxyurea treatment (Tura S, etal, NEJM, March 24, 1994, 330:820-5; Allan NC, etal, Lancet, June 3, 1995, 345:1390-7; Kantarjian HM, etal, Ann. Int. Med., Feb 15, 1995, 122:254-61). Splenectomy does not affect the natural history of the disease and is used only for symptomatic relief.

Roferon-A, Hoffmann-La Roche's recombinant IFN-α 2a, was approved in the USA on October 19, 1995, for the treatment of Ph1+ CML patients who are minimally pre-treated (within one year of diagnosis). Roferon-A, designated an orphan drug for this indication, is the only IFN approved in the USA for the treatment of CML. It has also been approved for CML in 43 countries around the world. Intron-A has been approved for this indication in several countries outside the USA, and Glaxo Wellcome is planning to submit an application for approval of its Wellferon for CML in Europe.

Roche originally filed for FDA approval for Roferon-A in April 1994, and subsequently to receiving a "not approvable" letter from the FDA, resubmitted its application in February 1995. In April 1995, FDA's Biological Response Modifiers Advisory Committee (BRMAC) unanimously approved Roferon-A for the treatment of CML based on data from two 1993 studies, a phase II clinical trial of 91 patients treated by Roferon-A at M. D. Anderson Cancer Center, and a randomized multicenter phase III study of 335 patients (226 treated by Roferon-A and 109 by chemotherapy) conducted in Italy. In this latter study, median survival after start of therapy was 69 months in the Roferon -A-treated group (44% of these patients were also treated with chemotherapy during the trial due to insufficient hematologic response with IFN alone), compared to a median survival of 55 months in those treated by chemotherapy alone. Adverse events occurred in 66% and 31% of patients in the two studies, respectively. Therapy was discontinued because of side effects in 15% and 23% of patients for each study, respectively. Severe or life-threatening side effects included anemia (15% of allpatients), leukopenia (20%) and thrombocytopenia (27%).

Exhibit 10
Estimated Allogeneic and Autologous Transplants by Type of Leukemia in the USA (1993)

Indication	Total (#)	Total (%)	Allogeneic (#)	Total (%)	Autologous (#)	Total (%)
AML	1,411	40.6	925	65.6	486	34.4
ALL	733	21.1	623	85.0	110	15.0
CML	1,005	28.9	955	95.0	50	5.0
MPD/MDS	200	5.8	200	100.0		0.0
Other	125	3.6	125	100.0		0.0
Total	3,474	100.0	2,828	81.4	646	18.6

Exhibit 11
Estimated Allogeneic and Autologous Transplants by Type of Leukemia in Europe (1993)

All Transplants			Allogeneic		Autologous			
Indication	Total (#)	Total (%)	BMT (#)	Total (%)	BMT (#)	PBSCT alone or with BMT+(#)	Total (#)	Total (%)
AML	1,397	40.9	762	54.5	564	71	635	45.5
ALL	976	28.5	627	64.2	274	75	349	35.8
CML	854	25.0	779	91.2	25	50	75	8.8
MDS	171	5.0	154	90.1	14	3	17	9.9
CLL	21	0.6	10	47.6	6	5	11	53.4
Total	3,419	100.0	2,332	68.2	883	204	1,087	100.0

In order to minimize toxicity, the advisory committee recommended that dose response studies be carried out to determine the lowest effective dose of Roferon-A. Roche is conducting phase IV dosing studies in Europe. The recommended Roferon-A dose for CML is 9 MIU, administered daily subcutaneously or intramuscularly. Grading the dose during the first week of treatment from 3 MIU to 9 MIU daily may improve short-term tolerance. Treatment duration to reach complete hematologic response was 5.3 months and the time required for optimal response was between 18 and 24 months. The longer period was associated with complete or partial cytogenetic responses in approximately 10% of IFN-treated patients, compared to only 2% of those undergoing chemotherapy. Based on an AWP of Roferon-A of about $90 per day, total costs for this treatment range from $14,000 to $64,800.

CLL is traditionally treated with alkylator therapy (such as chlorambucil) and steroids. For non-responders or for those who relapse after standard therapy, purine analogs such as fludarabine, 2-CDA or deoxycoformycin (pentostatin) are used. However, high doses of purine analogs used in early trials resulted in substantial neurotoxicity. With dose reduction, myelosuppression and infections, often with atypical organisms, are the primary complications. Lymphocyte counts, particularly CD4 cells, remain depressed for extended periods and late infections may be seen. Addition of steroids results in poorer outcome due to increased infections. CSFs and EPO are used to treat neutropenia and anemia, respectively.

Fludarabine (Fludara; Schering AG), a purine analog, is marketed worldwide for the treatment of CLL. Fludarabine resulted in a response rate of 70% in 33 patients without prior therapy (Keating MJ, etal, J Clin Oncol, Jan 1991, 9:44). The response rate in 68 previously treated patients was approximately 57% (Keating MJ, Blood, 1989, 74:19). The drug may also salvage patients failing other purine analogs. Autoimmune manifestations of CLL usually respond better to steroid treatment than to purine analogs. Fludarabine, in combination with ara-C and granulocyte-colony stimulating factor (G-CSF), was also shown effective in the treatment of poor-prognosis acute non-lymphoid leukemia. It was also used in Ph1+ CML unresponsive to IFN-α that had progressed to acute phase after 5 months of treatment with 6-mercaptopurine and hydroxyurea (Visani G, etal, Br. J. Haematol, 1994 Feb, 86(2):394-6). AWP of one fludarabine cycle, administered IV (25 mg/m^2 daily over 30 minutes for 5 days, every 28 days), is about $784.

Immunoglobulin is used to treat hypogammaglobulinemia encountered in many CLL patients, that may predispose them to sinopulmonary infections. Although replacement immunoglobulin is costly, in selected cases it has been shown to decrease infection rates. Baxter Hyland's (Glendale, CA) Gammacard, approved in the USA in 1986 for the prevention of infection in CLL patients, was removed from the market in February 1994, because it was contaminated with hepatitis C virus (HCV). A newer version, Gammacard S/D, treated with organic solvents and detergents to prevent transmission of HCV was approved in the USA in May 1994, for infusion at a concentration of 10%.

HCL requires treatment if pancytopenia or splenomegaly results in symptoms. Splenectomy was commonly used in the past, but has limited value because patients frequently relapse and require treatment with chemotherapy. IFN-α is somewhat effective but usually results in partial remissions and is associated with flu-like side effects. Several purine analogs that were shown effective in the treatment of HCL are commercially available.

Pentostatin (deoxycoformycin, Nipent/Oncopent; Parke-Davis) was approved in the USA in October 1991 and launched in 1992 as second-line therapy for HCL. It was subsequently approved as first-line therapy in 1993. Pentostatin was associated with a CR rate of 69% compared with 10% receiving IFN in a randomized study of 302 patients (Grever M, etal, Proc Am Soc Clin Oncol, 1992, 11:868).

Cladribine (2-CDA, Leustatin/Leustat; Ortho Biotech) which was approved and launched in the USA in 1993 and in the UK in late 1995, was associated with a CR of 85% and a PR of 12% in 144 HCL patients (Saven A and Piro LD, Cancer Invest, 1993, 11:559-64). 2-CDA is the treatment of choice among the purine analogs because of a better toxicity profile. 2-CDA is a prime example of a rationally designed drug. Its development stemmed from the observation that adenosine-deaminase deficiency was associated with lymphopenia due to toxic buildup of deoxyribonucleotides. Synthetic purine analogs were evaluated for efficacy and toxicity, with the eventual development of 2-CDA. (Carson DA, etal, PNAS, 1980, 77:6865-9). Cost of one treatment cycle (continuous IV infusion of 0.09 mg/kg/day for seven consecutive days), based on AWP, is estimated at $2,117.

Recombinant IFN-α was licensed by the FDA in 1986 for the treatment of HCL. This was the first biological to be licensed for cancer therapy. The FDA based its licensing decision on clinical studies showing that more than 50% of HCL cases responded to treatment with only minimal side effects. Both Intron-A and Roferon-A are marketed in the USA for this indication under an orphan drug designation, and Wellferon (Glaxo Wellcome) is available for this indication in Europe. A small number of HCL patients undergoing IFN-α treatment, who developed resistance to the agent, ultimately responded to treatment with deoxycoformycin (dCF). However, treatment with dCF led to marked suppression of the immune system.

Bone Marrow Transplantation in Acute Leukemia

Bone marrow transplantation is offered to selected AML and ALL patients after a relapse because long-term disease-free survival is rare when these patients are treated with standard chemotherapy.

The use of allogeneic transplantation for acute leukemia in first remission is somewhat controversial. Some centers routinely transplant all AML patients in first remission believing that this strategy will maximize long-term, disease-free survival. Other institutions defer allogeneic transplantation until relapse occurs, then attempt to salvage patients with transplantation Although the survival rate following allogeneic transplantation at qualified centers is clearly higher than that attained with chemotherapy alone (Appelbaum FR, etal, Blood, July 1, 1988, 72: 179-84), toxicities of therapy and graft versus host disease (GvHD) decrease the benefits of the survival advantage. However, transplantation of patients with particularly poor prognostic signs or difficulty attaining remission is warranted given their dismal chances with conventional chemotherapy. Several studies are now also examining the role of autologous transplantation in acute leukemia, with or without purging of marrow.

A large multicenter prospective study involving 623 patients concluded that autologous or allogeneic (HLA-identical sibling) BMT during first complete chemotherapy-induced remission, results in a more favorable outcome in terms of disease-free survival (55% treated by alloBMT and 48% treated by autoBMT survived for four years) than intensive consolidation chemotherapy with high-dose cytarabine and daunorubicin (30% disease-free survival at 4 years). Of the 239 patients who were treated by transplantation, 144 were treated by alloBMT from HLA-matched siblings and 95 were treated by autoBMT (Zittoun RA, etal, NEJM, Jan 26, 1995; 332:217-23). This ratio between alloBMT and autoBMT is much higher than what has been the historic norm, signaling a change in BMT trends toward autologous source of bone marrow in spite of risks associated with transplanting occult cancer cells because of lack of fool-proof purging techniques. Also better management techniques have reduced the mortality and morbidity associated with BMT in AML,

Exhibit 12
Estimated Allogeneic and Autologous Transplants by Type of Leukemia Worldwide (1995)

Indication	Total (#)	Total (%)	Allogeneic (#)	Total (%)	Autologous (#)	Total (%)
AML	3,792	37.5	2,537	66.9	1,256	33.1
ALL	2,365	23.4	1,851	78.3	514	21.7
CML	3,024	29.9	2,884	95.4	140	4.6
MPD/MDS	618	6.1	599	96.9	19	3.1
Other	301	3.0	289	95.9	12	4.1
Total	10,101	100.0	8,160	80.8	1,941	19.2

encouraging the use of this treatment approach in an increasing number of patients under 60 years-of-age.

Decision analytic studies of ALL have convincingly demonstrated that standard-risk adults should not be transplanted in first remission (Horowitz MM, etal, July 1, 1991, 115:13-8). Many of these patients can be salvaged with transplantation following relapse, and the better success of primary therapy for ALL does not justify the risks of alloBMT. However, for high-risk patients, such as those with t(4;11) or t(9;22) cytogenetic abnormalities, the prognosis for long-term, disease-free survival is dismal enough to warrant transplantation in first remission.

Bone Marrow Transplantation in Chronic Leukemia

Experience in syngeneic transplants shows a relapse rate of approximately 50%, suggesting that a graft versus leukemia effect is important as well as ablative therapy in curing the disease. Nevertheless, work to isolate normal stem cells from CML individuals for transplantation is ongoing. AlloBMT is currently the only curative option. Acceptable candidates must have minimal comorbid disease and should be under 55 years-of-age. Survival rates for patients in stable phase are 40-80% in major centers. The relapse rate in non-T-cell depleted transplants is approximately 10%. Success of transplantation is related to time from diagnosis for unclear reasons. Deaths occur due to regimen-related toxicity rather than from relapse. Major morbidity and mortality are the result of the conditioning regimen, the profoundly immunosuppressed state which follows transplantation, and GvHD. Some evidence suggests that normal stem cells (lacking Ph1) can be identified in CML patients and potentially selected for autologous transplantation after high dose chemoradiation conditioning (Dube ID, etal, Br. J. Haematol, 1984, 56:633).

Transplantation for CLL is uncommon but is being increasingly considered in young patients with high-risk CLL. Data from 54 CLL patients treated by alloBMT, collected by the European and International Bone Marrow Transplant Registries, indicated that 38 (70%) experiencedremission and 24 (44%) were alive a median of 27 months (5-80 months) post-transplantation. The probability of survival at three years was 46%. Most deaths (46%) were caused by the complications of treatment rather than progressive leukemia (9%). The death rate from treatment complications was significantly higher in this series than the 10% generally reported. The median age of the patients was 41 years (21 to 57 years). AutoBMT is also employed in CLL but the data is insufficient to arrive at a conclusion regarding its effectiveness (Rozman C and Montserrat A, NEJM, Oct 19, 1995; 333:1052-1057).

Growth Factors

Growth factors have been used as adjunct therapies in leukemia to improve recovery from chemotherapy and increase dose intensity. However, the use of these agents is controversial. A study of GM-CSF (molgramostim, Leucomax; Schering-Plough/Sandoz) in elderly AML patients failed to show improved outcome (Stone R, etal, NEJM, 1995, 332:1671-7). A similar study conducted by the AML Cooperative Study Group, using G-CSF (lenograstim; Chugai/RPR) in elderly AML patients failed to improve survival among patients over 65 years-of-age but G-CSF-treated patients experienced higher rates of CR (Dombret, etal, NEJM, June 22, 1995; 332:1679-1683). G-CSF in ALL was of some benefit in older patients, but results did not reach statistical significance, according to a study by the Cancer and Leukemia Group B (CALGB 9111). A study of 76 ALL patients randomized to G-CSF or placebo during induction therapy showed a significant decrease in the time to completion of chemotherapy (39 v 44 days, p=0.008) but did not show any survival advantage at 20 months (Ottmann OG, etal, Blood, July 15, 1995, 86:444-50). On a positive note these growth factors did not stimulate growth of leukemic cells, as was feared, and were deemed generally well-tolerated and safe.

In contrast to the above findings, in April 1995 FDA's BRMAC recommended approval of sargramostim (Leukine; Immunex) for use after induction chemotherapy in AML patients over 55 years-of-age. If approved by the FDA, sargramostim, a GM-CSF produced by recombinant DNA techniques, will be the first among the colony stim-

ulating factors (CSFs) to gain approval for acceleration of neutrophil recovery after chemotherapy. CSFs are in commercial use as prophylactics in patients treated by neutropenia-inducing chemotherapy.

MEETING COVERAGE

18TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM, SAN ANTONIO, TX, DECEMBER 10-13, 1995

ADVANCES IN THE MANAGEMENT OF BREAST CANCER

NEW IMAGING APPROACHES IN BREAST CANCER

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is fast becoming a valuable imaging modality for the diagnosis and evaluation of breast diseases. MRI is proving extremely useful in the evaluation and staging of breast tumors, not possible with other methods. In addition, with the help of contrast agents such as gadolinium, MRI was highly sensitive in detecting invasive breast cancer, since it is not limited by the density of the breast. Furthermore, MRI may be used for staging because it can detect the degree of tumor invasion and pinpoint its location. MRI is currently considered an investigational procedure for the diagnosis and evaluation of breast cancer. Also, its high cost makes it unsuitable for routine screening. A major problem with MRI, because of its low specificity (40%-70%), is imaging benign growths and, thus, increasing the need for biopsies (Bassett LW, 18th San Antonio Breast Cancer Symposium, Plenary Session).

Italian investigators demonstrated the value of dynamic contrast enhanced MRI in identifying suspicious breast lesions in 30 patients. Following surgery, histological results were correlated with dynamic contrast enhanced MRI, mammography and ultrasound findings. MRI showed a strong, early contrast enhancement of all 23 invasive carcinomas, confirmed by histology, and a low early contrast enhancement of four fibroadenomas and one proliferative dysplasia. No contrast enhancement of two sclerosis adenosis was noted (Ventrella V, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 70: #219).

Positron Emission Tomography

Positron emission tomography (PET) has been proven useful in cancer patient management, often precluding invasive procedures in breast cancer patients with complicated clinical or diagnostic profiles. In ten patients with complicated diagnosis studied with whole body PET imaging using F-18 fluorodeoxy-glucose, a radiolabeled metabolically trapped analogue of natural glucose, the reported sensitivity for imaging primary breast cancer is about 94%, with a specificity of 100%, and an accuracy of 94%.

PET imaging was especially useful in difficult diagnostic situations including dense breast tissue, post-biopsy/surgical changes, silicon injections, or presence of adjacent implant to the suspicious lesion. In patients with recent surgery (within one week of PET study) elevated tracer uptake was demonstrated, compared to patients with much earlier surgery, whose studies were negative. Local recurrence was detected in two of four women with prior lumpectomies or excisional biopsies and residual mass on follow-up mammogram. Neither of two patients with silicon implants, referred for possible development of a new lesion, demonstrated abnormal tracer uptake, which was later confirmed during observation (Conti PS, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 71: #223).

HORMONAL THERAPY

Tamoxifen (Nolvadex; Zeneca)

A decision analysis model study comparing tamoxifen use for two years, five years, and a lifetime in elderly breast cancer patients reached the conclusion that prolonging adjuvant tamoxifen use for a lifetime is both reasonable and cost-effective because adjuvant tamoxifen leads to a substantial survival gain in women over 65 years-of-age. Data was compiled from the tumor registry of the Moffitt Cancer Center and Research Institute (Tampa, FL) and from reports published prior to May 1, 1995. Based on this model the impact of lifetime therapy was about 10% of life expectancy. Co-morbidities had a major impact on prognosis. Cardiovascular protection by tamoxifen had a stronger impact on survival than its effect on breast cancer mortality. Although life-long tamoxifen therapy is an expensive treatment strategy, it is marginally cost-effective in this context (Extermann M, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 97: #337).

Anastrozole (Arimidex; Zeneca)

Anastrozole, a new, orally active, third-generation aromatase inhibitor, offers an alternative therapeutic approach for postmenopausal women with advanced breast cancer, who progress on tamoxifen therapy. To determine the clinical efficacy and tolerability of anastrozole in comparison with megestrol acetate (Megace; Bristol-Myers Squibb), two prospective phase III clinical trials were evaluated, a 386-patient North American trial and a 378-patient trial conducted in Europe, Australia, and South Africa. In both studies, patients whose disease progressed on tamoxifen therapy were randomly assigned to either anastrozole (1.0 mg or 10 mg once daily), or megestrol acetate (40 mg four times a day). Median follow-up was six months plus.

Objective response rates were similar in each arm of both studies. Combining the data from the two trials, the objective response rate (CR + PR + disease stabilization for more than six months) for anastrozole was 35.4% in the 1.0 mg group and 31.5% in the 10 mg group, compared

to 34.0% in the megestrol acetate group. Median time to disease progression was 141 days, 153 days and 139 days, respectively. Approximately 15% of patients died in each study and, so far, there were no differences in survival in any arm of either trial.

There were no statistically significant differences for any efficacy endpoints in the three treatment groups of either trial, but there were considerable differences with regard to drug-related adverse effects. Significantly, more patients on megestrol acetate experienced edema, dyspnea, and thromboembolic events than did those on either dose of anastrozole. In addition, women treated with megestrol acetate gained significantly more weight, 11.9% versus 4.1% on anastrozole 10 mg and 1.5% on anastrozole 1 mg (Buzdar AU, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 37 #20).

Arimidex was approved by the FDA in December 1995 for the treatment of postmenopausal women with advanced breast cancer whose disease progresses on tamoxifen. It had been recommended for approval by FDA's ODAC in its October, 1995 meeting, after an NDA was submitted in March 1995. Zeneca launched Arimidex in January 1996 in the USA at the recommended dose of 1 mg, once-daily. Zeneca has also started a 60-patient multicenter randomized, double-blind study of Arimidex in Europe in August 1995 that compares it to foremestane (Lentron; Ciba-Geigy). A large multicenter study, expected to enroll 400-500 patients, is slated to begin in North America in early 1996 to compare the drug with tamoxifen as first-line therapy in breast cancer patients who have not been treated by hormonal therapy. Zeneca has filed applications for approval of anastrozole in several countries and has launched the drug in the UK where it was approved in September 1995.

ICI 182.780 (Zeneca)

Treatment with ICI 182.780, a 7-alpha substituted estradiol that is a pure anti-estrogen, results in comparable response rates to those achieved with megestrol acetate, but a significantly longer duration of response in women with tamoxifen-resistant breast cancer. In a clinical trial, 19 women who received ICI 182.780 in a long-acting, monthly depot of 250 mg, were each matched with three patients (57 women in total) treated with megestrol acetate (40 mg four times daily); all women had cancer that progressed on tamoxifen therapy. Patients were matched for metastatic sites, prior tamoxifen therapy (adjuvant or advanced disease), and therapeutic response to tamoxifen. The objective response rate was 69% (13/19) among the women treated with ICI 182.780, versus 63% (63/57) among those on megestrol acetate. Duration of response was significantly different between the two therapeutic modalities, 26 months for those on ICI 182.780, compared to 14 months for those on megestrol acetate. These clinical findings confirm earlier experimental *in vitro* data that showed that ICI 182.780 binds more potently to the estrogen receptor and, thus, induces prolonged regression of tamoxifen-resistant tumors *in vivo* (Robertson JFR, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 33:#3).

Liarozole (Liazazole) Fumarate (R85246, Janssen Research Foundation)

Liarozole (Liazazole) fumarate, a new P450 retinoic acid hydroxylase inhibitor developed primarily for the treatment of prostate cancer, shows promise in both receptor-positive (ER+) and receptor-negative (ER-) postmenopausal metastatic breast cancer. Sixty-three postmenopausal women with ER- disease in first relapse, ER+ or ER-unknown disease resistant to hormonal therapy, or metastatic disease refractory or resistant to chemotherapy, have been enrolled into a phase II study to date. The women have been treated with oral liarozole at 150 mg twice daily, increased to 300 mg orally twice daily at two weeks, tolerability permitting, until disease progression. Response was assessed at two-month intervals. Among 49 evaluable women, there were four responses and disease stabilized in seven patients within a maximum follow-up of 11 months. Toxicities observed are dose-dependent and are mainly mild to moderate in severity, being related primarily to a hypervitaminosis A syndrome. Enrollment in the study is ongoing (Goss PE, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 71:224).

Leuprorelin Sustained Release (TAP-144SR, TAP Pharmaceuticals)

TAP-144 SR, a gonadotropin-releasing hormone agonist microencapsulated in polylactic and polyglycolic acid which allows sustained release, appears to be a safe and effective treatment of premenopausal women with metastatic breast cancer. Over a two and one-half year period, 106 premenopausal women (100 eligible) with metastatic breast cancer, whose estrogen receptor in the primary lesion or metastatic lesion was positive (66 patients) or unknown (34), were randomized to either TAP-144 SR 3.75 mg (49 patients) or 7.50 mg (51) administered subcutaneously every four weeks. The best objective response rate (5CR + 12 PR) was 35% in the low dose group compared to 29% (1 CR + 14 PR) in the high dose group. Duration of treatment ranged from one to 120+ weeks (median 24) and from four to 128+ weeks (median 21) in the low and high dose groups respectively. All patients became amenorrhic within 12 weeks of treatment. Most common side effects were hot flashes, headache, nausea and vomiting, dizziness, and mild hepatotoxicity, all of which subsided within the first 12 weeks. No patients discontinued treatment because of side effects (Watanabe T, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 74:#233).

CHEMOTHERAPY

Taxanes

For a detailed review of taxanes in the treatment of cancer see FO, V1#7/8, pp 175-185.

Docetaxel (Taxotere; Rhône-Poulenc Rorer) is proving to be highly effective as first-line chemotherapy in advanced breast cancer as demonstrated in three consecutive phase II studies carried out by the EORTC-CSG with docetaxel as first-line chemotherapy in metastatic breast cancer. In the first study, 34 women received docetaxel 100 mg/m^2 as a one-hour intravenous infusion every three weeks, without routine premedication. In a second 39-patient study, the dose was reduced to 75 mg/m^2 every three weeks, without routine premedication, to reduce the incidence and severity of fluid retention observed in the first trial. Since fluid retention was still present, in a third trial, 37 patients received docetaxel at a dose of 100 mg/m^2 every three weeks, with premedication from cycle one consisting of oral corticosteroids and H_1/H_2 blockers. Overall objective response rate was 68% (16% CR) in 31 evaluable patients in the first trial, 52% (13% CR) in 31 patients in the second trial, and 68% (5% CR) among 37 patients in the third trial. Considering the state of these patients, while docetaxel showed a lower response rate at 75 mg/m^2, its activity was still remarkable. Median response duration was 44 weeks and 34 weeks in the first two trials, respectively, and was not reached, at the time of the report, in the third. Median duration to disease progression was 37 weeks, 24 weeks, and 31 weeks, respectively. Grade four neutropenia was seen in the majority of patients (91%, 82%, 89%) but was of short duration (7 days) and reversible. Non-hematologic toxicities were similar to those reported in other studies and, except for fluid retention, were mild. Fluid retention was the main toxicity, but it was not life threatening and was managed with three to five days of corticosteroids (Kerbrat P, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 36:#13).

Docetaxel exhibits definite and consistent activity in heavily-pretreated women with metastatic breast cancer and is significantly active in anthracycline-resistant breast cancer. Forty-two women with histologically proven metastatic breast cancer who had undergone at least two prior chemotherapeutic regimens for metastatic disease and who were exposed to anthracyclines (20 were anthracycline-resistant), were treated with docetaxel (100 mg/m^2 as a one-hour infusion every three weeks) and with five days of premedication with corticosteroids. Patients were treated until progression or unacceptable toxicity occurred, for a maximum of nine courses. In 36 evaluable patients, the overall response rate was 22%, including 8 PRs; disease stabilized in 15 patients (42%) and progressed in 13 (36%). The response rate in anthracycline-resistant cancer was 33% (6/18). Neutropenia, experienced by most patients (69% of patients with grade 4 and 29% with grade 3), was dose-limiting. Dose reduction was required in six women (14%) and in 15 cycles (11%). Fluid retention was noted in 14 patients (33%), and led to treatment discontinuation in two. Thus far, no unacceptable toxicity has been observed in this heavily-pretreated population (Antoine E, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 88:#301).

Docetaxel, alternating with epirubicin and cyclophosphamide, in an escalated and accelerated schedule using concomitant recombinant human granulocyte colony stimulating factor (rHuG-CSF), appears highly feasible for the treatment of advanced breast cancer. In a phase I study, ten chemotherapy-naive women with advanced breast cancer, were administered two to three courses of docetaxel (100 mg/m^2 as a one-hour infusion), alternating with epirubicin (120 mg/m^2) and cyclophosphamide (830 mg/m^2), together with subcutaneously-delivered rHuG-CSF (150 mcg/m^2 on days 2 to 10 post-chemotherapy). Intervals between the two regimens were 21 days in the first five patients and 14 days in the second five patients. The first five patients experienced a documented partial response after only two courses of therapy. No unexpected side effects were noted. The median nadir of white blood cells (WBC) was 5.2 X 10^9/l after docetaxel and 0.7 X 10^9/l after epirubicin plus cyclophosphamide. There were two febrile episodes in two patients, but no thrombocytopenia. Concerning non-hematologic toxicities, there was no fluid retention or cardiac toxicity (Ten Bokkel Huinink WW, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 89:#308).

Paclitaxel (Taxol; Bristol Myers Squibb) was shown to be a safe and substantially effective treatment regimen for metastatic breast cancer patients exposed to prior chemotherapy. In a phase II study, 65 patients received paclitaxel by a three-hour continuous infusion at a dose of 210 mg/m^2, every three weeks, along with premedication with dexamethasone, diphenhydramine, and ranitidine. G-CSF was permitted in cases of grade 4 neutropenia lasting for more than three days or grade 2 fever. Among 60 evaluable women, the overall response rate was 35%, with two CRs (3%), 19 PRs (32%) and one MR; disease stabilized in 17 and progressed in 20. Treatment was discontinued in one case because of hypotension. Grade 4 neutropenia was observed in 45 patents (75%) and neutropenic fever in 14 (23%). G-CSF was used in 14 women (23%) in 41 treatment cycles (14%). Other common grade 2/3 toxicities included neurosensory effects (33%), myalgia (25%), arthralgia (27%), and alopecia (87%) (Wantanabe T, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 90:#311).

Combination of paclitaxel and 5-fluorouracil (5-FU) was also shown active in heavily pretreated women with metastatic breast cancer. In a phase I study, 21 women with advanced breast cancer and at least one prior chemotherapy course, were treated with a three-hour infusion of paclitaxel at 125 mg/m^2, 150 mg/m^2, 175 mg/m^2, or 200 mg/m^2, followed by 5-FU as a 24-hour continuous infusion, every 21 days. No G-CSF was allowed. Maximum tolerated dose (MTD) of this combination was not reached at a paclitaxel dose of 200 mg/m^2 and a 5-FU dose of 1200 mg/m^2, every 21 days. This combination therapy, with its modest toxicity, met the goals of a palliative outpatient regimen. In 19 evaluable patients (two early deaths), grade 3/4 leukocytopenia was seen in 8%,

grade 1/2 anemia in 46.6%, and grade 1/2 thrombocytopenia in 4%. Non-hematologic toxicities included alopecia (grade 1/2 in 40% and grade 3/4 in 51.9%), grade 1/2 arthralgia/myalgia(9.8%), grade 1/2 peripheral neuropathy(25.5%), and grade 1/2 nausea and vomiting (26.9%) (Gleissner B, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 90:#312).

Paclitaxel and epirubicin were also safe and effective as first-line therapy in patients with metastatic breast cancer. In a phase II study, 45 chemotherapy-naive patients with metastatic breast cancer were treated with epirubicin (60 mg/m^2 as a one-hour infusion), followed by paclitaxel (175 mg/m^2 as a three-hour infusion), after standard premedication with steroids, antihistamines and H_2 blockers, every three weeks. Toxicities permitting, paclitaxel dose was escalated to 200 mg/m^2 and 225 mg/m^2. Among 23 patients evaluable for response to date, the overall response rate was 56.5%, with one CR (4.3%) and 12 PRs (52.2%). Ten women had stable disease (43.5%). Regarding toxicity, among 28 evaluable patients no cases of cardiotoxic events were observed; grade 3/4 and grade 1/2 leukocytopenia was seen in 53.3% and 38% of patients, respectively, and grade 3/4 and grade 1/2 anemia in 1.1% and 42.4% of patients, respectively; no thrombocytopenia was observed. No non-hematologic toxicity over grade 2 occurred except for grade 3/4 in 71.9% of patients. Grade 1/2 arthralgia/myalgia, peripheral neuropathy, and nausea and vomiting were common in over 50% of patients (Lück HJ, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 88:#304).

Vinorelbine (Navelbine; Glaxo Wellcome)

In an open-label study, vinorelbine proved a reasonable therapeutic approach for refractory metastatic breast cancer. Overall, 365 patients with advanced breast cancer who did not respond or were intolerant to doxorubicin or some other anthracycline and paclitaxel or another taxane, and had failed tamoxifen (if hormone-receptor positive), received vinorelbine (30 mg/m^2 weekly for 12 weeks and then every other week). Patients were evaluated every four weeks for a subjective response, defined as disease improvement, stabilization, or progression. In 247 evaluable patients the confirmed responses were improvement in 38 (15%), disease stabilization in 101 (44%), and disease progression in 80 (32%). Time to disease progression was 13 weeks, with 40% of the women remaining progression-free at 16 weeks. Incidence of grade 3/4 granulocytopenia was 74%, a rate comparable to that seen in previous clinical studies. Incidences of grade 3/4 anemia and grade 3/4 thrombocytopenia were 18% and 14%, respectively. Only 2% of patients withdrew from the study due to drug-related toxicity (McGuirt C, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 75: #237).

A new combination of vinorelbine, doxorubicin, and 5-FU was highly active as first-line treatment of poor-prognosis metastatic breast cancer. In a phase II study, 82 women who had completed adjuvant chemotherapy at least six months prior to relapse, were given vinorelbine (25 mg/m^2 as a short infusion on day 1 and 8), doxorubicin (20 mg/m^2 bolus on day 1 and 8), and 5-FU (250 mg/m^2 continuous infusion from day 1 to 15). Dose reduction was allowed to mitigate toxicity. A total of 537 cycles was administered; the median number of cycles per patient was eight. The overall response rate in 70 evaluable patients was 64.2% (45/70), with 5 CRs (7.1%) and 40 PRs (57.1%). The median duration of response was 32 weeks (17-95), with a median follow-up of 62 weeks (2-118). Among 78 patients, the primary toxicity was grade 3/4 neutropenia (81.3%), with six episodes of febrile neutropenia (7.3%) and grade 3/4 mucositis (29%) (Dieras V, etal, Breast Cancer and Treatment, Vol 37, Suppl 1996; Pg 75:#238).

A vinorelbine and paclitaxel regimen, delivered as a simultaneous three-hour infusion together with G-CSF support, was a highly feasible approach against treatment-resistant metastatic breast cancer. In a phase I study, 13 women with invasive ductal breast cancer, 54% of whom had prior adjuvant chemotherapy, were administered vinorelbine (25 mg/m^2, 30 mg/m^2, 36 mg/m^2, 42 mg/m^2, or 46 mg/m^2) and paclitaxel (150 mg/m^2) every three weeks. G-CSF was given on days 2 to 12 of each cycle. Overall, 95 cycles were administered, with a median follow-up period of 6.9+ months. Nine women (69%) experienced grade 3/4 granulocytopenia, with neutropenic fever observed in two patients (15.3%). Dose-limiting toxicities were fatigue and pelvic pain. MTD of the combination was 36 mg/m^2 vinorelbine and 150 mg/m^2 paclitaxel. The overall response rate was 69%. There were two CRs (15%), five PRs (39%), and two MRs (15%); disease stabilized in 15% and progressed in 15% of patients (Ibrahim NK, etal, Breast Cancer and Treatment, Vol 37, Suppl 1996; Pg 44: #107).

High Dose Chemotherapy

Dose-intensive chemotherapy with etoposide and cyclophosphamide without stem cell support is an effective, well-tolerated regimen in metastatic breast cancer, yielding results comparable to regimens requiring stem cell support. One hundred women with metastatic breast cancer were administered etoposide (2400-4200 mg/m^2 as a continuous infusion), followed by cyclophosphamide (50 mg/kg/day for four days). Hematopoietic growth factors were usually, but not always, administered to help accelerate marrow recovery. In this group, 42 patients were still responding to standard therapy, disease progressed in 48, and 10 were not administered additional therapy (untested relapse). The regimen was well-tolerated, with a 6% treatment-related mortality. The median duration of granulocytopenia was 17 days and of thrombocytopenia, 18 days. Among 93 evaluable patients, 19% experienced CR and 44% PR. The median duration of CR was 15 plus months and of PR, six months. Responses lasting more than one year were seen in 19% of patients (Herzig R, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 44:#106).

Aggressive induction chemotherapy, followed by double high-dose polychemotherapy (HDCT) with mitoxantrone, cyclophosphamide and vinblastine or carboplatin and autologous peripheral blood stem cell transplantation (APBSCT), is feasible and yields a high CR rate in women with metastatic breast cancer. Fifty women were treated with two courses of 5-FU (500 mg/m^2 on days 1 and 8), doxorubicin (50 mg/m^2 on day 1), and cyclophosphamide (500 mg/m^2 on day 1) (FAC), followed, in those responding to treatment, by two courses of FAC with increased doses of cyclophosphamide (2000 mg/m^2) and also G-CSF. The first HDCT consisted of mitoxantrone (63 mg/m^2), cyclophosphamide (6 mg/m^2) and vinblastine (0.3 mg/kg), with subsequent APBSCT. A second HDCT was proposed with the same drugs but replacing vinblastine with carboplatin (800 mg/m^2). In 37 patients evaluable for response, all women experienced a major response after completion of induction chemotherapy; 30% experienced CR; more than 60% experienced CR after one HDCT. The main toxicity of the first HDCT was hematologic with 100% of patients experiencing grade 4 neutropenia and thrombocytopenia. Almost 50% of patients also experienced grade 3 mucositis. The second HDCT with APBSCT was performed in one-third of the patients and resulted in CR in all but one woman. Drug-related toxicities were comparable to those seen in the first HDCT, except that three patients experienced grade 3 cardiac toxicity, five had grade 2 diarrhea, and there was one toxic death from infection. This study represents the experimental arm of an upcoming multicenter trial comparing conventional FAC chemotherapy to HDCT in the treatment of metastatic breast cancer (Nabholtz JM, etal, Breast Cancer Research and Treatment, Vol 37, Suppl 1996; Pg 45: #109).

INDEX OF COMPANIES & INSTITUTIONS

FUTURE ONCOLOGY

PUBLISHED BY **NEW MEDICINE, INC.**

PUBLISHER AND EDITOR:	**Katie Siafaca, MS**
RESEARCH ASSOCIATES:	**Sarah Nghiem and Fred Hall**
CIRCULATION MANAGER:	**Andrew Kim**
DESIGN & PRODUCTION:	**Jill Burch**

NEW MEDICINE, INC. MAILING ADDRESS:

P.O. Box 909
Lake Forest, California 92630
Tel: 714. 830. 0448 ■ Fax: 714. 830. 0887
e-mail: newmedinc@aol.com
www:http://www.wp.com/new_med/

SUBSCRIPTION INFORMATION:

- FUTURE ONCOLOGY (ISSN 1082-331X) is published as 10 issues (two double issues) per year, with a free annual index listing companies/institutions and subjects covered.
- A one-year subscription, (issues V1 #7 to V2 #6), sent first class to U.S. addresses is US $720. A one-year subscription, sent air mail to addresses outside the U.S., is US $780.
- One-year's subscription plus back issues (V1, #1-#6) is $1,000 (U.S.) and $1,100 (outside the U.S.).
- Additional subscriptions sent in the same envelope are $390 each.
- Back issues (V1, #1-#6) are $350.
- Payment must accompany your order; checks must be drawn on a U.S. bank. (A purchase order number is acceptable; however, the subscription will not begin until payment is received.) Make checks payable to New Medicine. Payment may also be made by AMERICAN EXPRESS, VISA or MASTERCARD and wire transfer; please call 714. 830. 0448.