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REVIEW ARTICLE

Treatment of Chronic Myelogenous Leukemia: Current Status and Investigational Options

By Hagop M. Kantarjian, Susan O'Brien, Paolo Anderlini, and Moshe Talpaz

O**VER THE PAST** few years, several important studies related to the treatment of Philadelphia chromosome (Ph)-positive chronic myelogenous leukemia (CML) have matured. These include single and multi-institutional programs with allogeneic bone marrow transplantation (BMT), interferon-α (IFN-A), autologous stem cell transplantation, and other investigational agents or modalities. As in other fields of research, these investigations have answered some questions, but have also raised additional ones. In this review, we will discuss the results of these studies and suggest therapeutic approaches in the community-based and investigational settings.

ALLOGENEIC BMT

Summary of Results

The long-term results from both the International and European Bone Marrow Transplantation Registries (IBMTR and EBMT) have reported event-free survival (EFS) rates of 40% to 45%.[1,2] Although these rates appear modest compared with the initial reports, several points should be considered.

(1) These registries have included the results from smaller transplant programs, in which patient outcome may be worse than in larger institutions with extensive transplant experience[3]; on the other hand, possible selective favorable data registration may also be occurring.

(2) These studies have included patients undergoing T-cell–depleted BMT. When the IBMTR selectively analyzed 450 patients (of 1,266) who were transplanted with non–T-cell–depleted marrow in chronic-phase CML, the 5-year EFS was about 50%.[4]

(3) EFS should not be equated with survival after allogeneic BMT, which is the point of comparison with other modalities. Many patients relapse in chronic-phase post-allogeneic BMT, have generally favorable survival, and can be reinduced into a cytogenetic remission with immunomodulatory approaches including IFN-A or donor lymphocyte reinfusion. In an analysis by Arcese et al,[5] the 6-year probability of survival among 130 patients who relapsed in chronic-phase post-allogeneic BMT was 36% after relapse. Twenty-nine patients underwent a second BMT with a projected 4-year survival rate of 28%. In a review of 189 patients transplanted in early chronic phase (ie, within 12 months

from diagnosis), the 4-year EFS rate was 60%, but the survival rate was about 80%.[6,7]

(4) Recent studies from single institutions show 2- to 5-year EFS rates of 60% or more, an improvement compared with previous results.[7-9] Improvement in allogeneic BMT outcome has also been reported in the EBMT. This can be attributed to (1) improved allogeneic BMT management, (2) different patient selection, or (3) short follow-up with early censoring. There is no doubt that outcome of patients post-allogeneic BMT has improved as a result of (1) better graft-versus-host disease (GVHD) prophylaxis and therapy (cyclosporin plus methotrexate, FK506),[10,11] (2) the use of ganciclovir with or without Ig therapy and prophylaxis against cytomegalovirus,[12,13] and (3) improved supportive care (antibiotics and colony-stimulating factors). Whether different preparative regimens have contributed to improved outcome remains doubtful[9,14,15]; in general, reductions in relapse rates with more intensive regimens have been counterbalanced by higher treatment-related mortality, with consequent similar EFS rates.[16]

As studies of allogeneic BMT mature, the indications and timing of the procedure vis-a-vis other modalities should be continuously reevaluated. Current results are summarized in Table 1.

Salvage Therapy Post-Allogeneic BMT Relapse

Patients who relapse post-allogeneic BMT do not have as poor a prognosis as previously expected and can be reinduced back into cytogenetic remission with several modalities.

The most exciting salvage approach is immunomodulation by donor lymphocyte reinfusion, which was initially reported by Kolb et al.[17] In an update of 84 CML patients treated post-BMT relapse, 54 (72%) of 75 evaluable patients achieved a

Table 1. Results of Allogeneic BMT in Chronic-Phase CML

Study Group (reference)	No. of Patients	EFS % (at x year)	Unfavorable Prognostic Factors for Disease-Free Survival (relative risk)
IBMTR (1)	1,426	45% (5)	T-cell depletion (5.4)
			Age >20 yr (2.6)
EBMT (2)	1,082	39% (5)	Age >20 yr (1.5)
			T-cell depletion (1.4)
			Male recipient/female donor (1.2)
Goldman; IBMTR (4)	450	No busulfan; 61% (3)	Prior busulfan therapy (1.5)
		Prior busulfan; 45% (3)	Time to BMT >1 yr (1.7)
Biggs (9)	62	58% (3)	Time to BMT >1 yr (2.7)
			Male recipient/female donor (2.5)
			Prior busulfan therapy (2.2)
Clift (15)	69	CY-TBI; 66% (3)	Not stated
	73	BU-CY; 70% (3)	
Snyder (8)	94	64% (5)	Older age (1.1)
			Longer time to BMT (1.48; ≥1 yr: 1.26)

Abbreviations: CY-TBI, cyclophosphamide with total body irradiation; BU-CY, busulfan with cyclophosphamide.

cytogenetic complete response (CR).[18] The cytogenetic CR rate was 82% among 17 patients treated in cytogenetic relapse and 78% among 50 evaluable patients treated in hematologic relapse in chronic phase, but only 12% among 8 patients treated in CML transformed phases. Forty-two of 44 patients tested in cytogenetic CR were also negative for the BCR-ABL RNA transcripts by polymerase chain reaction (PCR) analysis. The 3-year survival after lymphocyte reinfusions was 67%. The hypothesis behind this treatment is that donor T lymphocytes induce a graft-versus-leukemia (GVL) effect that suppresses the Ph-positive clones and allows the normal donor cells to re-expand.[19] As expected, marrow suppression (50% of patients treated for hematologic relapse) and acute GVHD (59% to 80%)[18,19] have been significant problems; the 1-year mortality rate was 18%. These complications may be reduced by earlier use of donor lymphocyte reinfusions at the time of cytogenetic relapse (myelosuppression rate, 13%)[18] or as prophylaxis among high-risk patients for relapse (accelerated or blastic phase). The presence of normal donor hematopoiesis at that time may minimize the problem of marrow hypoplasia. Modulation of the dose and subsets of T lymphocytes reinfused may also reduce GVHD while improving GVL.[20,21] Other immunomodulatory approaches may include interleukin-2, granulocyte colony-stimulating factor, linomide, or IFN-A.[22-25] The latter is capable of inducing cytogenetic remission in 20% to 40% of patients with cytogenetic relapse in chronic phase.[5,24] These approaches are less effective among patients who relapse in accelerated or blastic phase. A second allogeneic BMT, particularly among patients who are beyond 12 months from their first BMT, has been successful, but is associated with a high incidence of transplant-related complications and mortality.[23]

CML Transformed Phases

Treatment results in blastic-phase CML, defined by the presence of 30% or more blasts in the marrow or peripheral blood or extramedullary blastic disease, have been uniformly poor. The long-term EFS rates from the IBMTR and EBMT are 10% or less. This is primarily due to a high relapse rate of 60% to 80%.

Patient outcome in accelerated phase has been variable with EFS rates of 15% to 40%. Some studies have attributed their better results to improved preparative regimens (eg, busulfan-cyclophosphamide).[26] However, better results were more likely due to a less strict definition of accelerated-phase CML, which could have shifted a proportion of chronic-phase patients into the accelerated-phase category. This phenomenon of "population shift" of better-prognosis patients into a worse-prognosis group may falsely improve the EFS curves of both chronic and accelerated phase patients; the only feature that changes with such analyses is the ratio of chronic:accelerated phase patients. Thus, when analyzing the results of allogeneic BMT in CML, the selection criteria for accelerated-phase CML, and the ratio of chronic to accelerated phase patients should be considered. In the EBMTR study, the ratio was 4.3:1[2]; in two other studies, they were about 2.4:1[9] and 1:2.[27] Defining strict objective and reproducible accelerated phase criteria may help in the comparative analyses of such studies.[28]

Clonal evolution as the single criterion of accelerated-phase CML has also been associated with favorable outcome; the EFS rate among 58 such patients was 60%.[29] Clonal evolution does not bear a uniformly poor outcome with standard therapy, and prognosis may depend on the specific cytogenetic abnormality, its predominance in marrow metaphases, and time of its development.[30]

Breaking the Age Barrier

Investigators have advocated allogeneic BMT for older age groups, but few published data exist on the toxicities and outcome of BMT among patients more than 50 years of age. A recent study from Seattle[7] reported on 33 patients (23 aged 50 to 55 years and 10 aged 56 to 60 years) undergoing matched related allogeneic BMT. The estimated 2-year survival rate was 80%, which suggests significant selection of patients treated, but indicates the feasibility and success of

the procedure among such selected patients.[7] In the IBMTR studies, patients more than 50 years of age had a 5-year EFS rate of 30%.[1] In the EBMT studies, 71 patients more than 45 years old transplanted had a 47% treatment-related mortality and a 25% 5-year EFS rate.[2]

Timing of Allogeneic BMT in Chronic Phase

Although every patient with a matched (or 1 antigen mismatch) related donor should be offered allogeneic BMT before disease transformation, the timing of allogeneic BMT in chronic phase is controversial. Most groups advocate allogeneic BMT as early as possible based on the original Seattle and later IBMTR studies showing a significantly worse EFS with later transplant (within 1 year from diagnosis). This was because of a higher transplant-associated mortality and may be from other confounding variables increasing transplant mortality (prior busulfan therapy, older age, and others). In the EBMTR studies, patients transplanted within the first year, in the second year, or subsequently had similar 5-year EFS rates of about 35% to 40%.[2] An update of the Seattle data by Clift et al[6] indicates that patients transplanted within the first year or in the second year do equally well and that the critical prognostic cut-off time is for patients transplanted in the third year or later.

The timing of allogeneic BMT in chronic phase has to be considered in relation to the risk of the procedure as it relates to patient age, institutional experience, or other factors and to the current survival results in CML, particularly among good-risk groups and cytogenetic responders. As discussed later, about half of the patients in recent CML series have good-risk disease, and their median survival with IFN-A regimens is about 102 months.[31] Patients achieving major cytogenetic responses have excellent long-term survival rates (>80% at 5 to 7 years, mostly with major durable cytogenetic responses).[31]

In justifying the need for early allogeneic BMT, several arguments are brought up: (1) the worse outcome with delayed BMT (discussed above); (2) the unpredictable course of CML and sudden blastic transformation; and (3) the possible worse outcome of allogeneic BMT with IFN-A exposure (presumably from marrow fibrosis).

With IFN-A therapy, the incidence of blastic transformation is less than 5% yearly in the first 2 years and is most often heralded by disease resistance in chronic phase. Among 274 patients evaluated on our IFN-A studies, 11 (4%) had a blastic transformation in the first year; 6 of them has a lymphoid blastic transformation and all responded (5 CR and 1 partial response [PR]) to anti-acute lymphocytic leukemia therapy. Thus, the loss rate from unpredictable transformation is low.

Among 30 patients evaluated on IFN-A therapy over a period of 2 to 3 years, marrow reticulin fibrosis remained the same in 22, increased in 5, and decreased in 3 (unpublished data). The inaspirability of marrow samples among patients on IFN-A therapy is not due to marrow fibrosis, but perhaps to its antiproliferative or cytoadhesion-induced effect, which corrects one of the pathophysiologic defects of CML cells.[32]

In comparing the outcome after allogeneic BMT, Giralt et al[33] found no significant differences in the incidences of graft failure and GVHD, time to engraftment, and long-term prognosis by prior IFN-A exposure. This has also been confirmed by an Italian Study.[34,34a] However, Beelen et al[35] reported different results. Exposure to IFN-A for more than 12 months before allogeneic BMT was associated with a significantly worse outcome (5-year survival rate of 22% v 55%; P < .01). This was primarily due to a high incidence of graft failure in this group; 7 of 17 patients receiving related mismatched or unrelated BMT had a graft failure (49% incidence), which has not been seen in other studies. Factors contributing to this event (preparative regimen, stem cell infusion, CML phase, and marrow fibrosis) may have been present in these 7 patients. Other studies analyzing the impact of prior IFN-A therapy on allogeneic BMT outcome would resolve this controversy.

When Should Matched Unrelated Donor (MUD) Transplant Be Considered

The long-term follow-up results in MUD BMT indicate the procedure to be associated with high incidences of graft failure (16%), severe acute (54%) and extensive chronic (52%) GVHD, and 2-year mortality (above 50%). Still, MUD BMT is curative in selected patient subsets.[36,37] The estimated 2-year EFS rates among patients younger than 30 years were 43% with a matched donor and 31% with a 1-antigen mismatched donor. For older patients, the estimated 2-year EFS rates were 27% and 14%, respectively.[36] Based on these results, optimal candidates for MUD BMT are younger (<30 years) patients in chronic phase who have a matched donor and have exhibited resistance to IFN-A therapy. Older patients and those with ≥1 antigen mismatch donor may be offered the procedure if features of disease acceleration develop, because the outcome of such patients transplanted in chronic or accelerated phase are not much different.[36,37] However, this opinion is controversial, and many groups advocate MUD BMT in chronic phase to a broader selection of patients (older, 1 antigen mismatch) based on the potential curability of such patients and continued improvement of results in time regardless of the morbidity and mortality costs.

IFN-A THERAPY

In analyzing the comparative results of IFN-A studies in CML, uniform criteria for hematologic and cytogenetic responses, as proposed originally,[31,38] will be used when possible. A complete hematologic response (CHR) refers to a complete normalization of the peripheral counts (white blood cells [WBC], $<10 \times 10^3/\mu L$), platelets $<450 \times 10^3/\mu L$, no immature cells, and absence of all signs and symptoms of disease including palpable splenomegaly. Patients in CHR are further classified by the degree of Ph suppression (cytogenetic response): (1) complete cytogenetic response (Ph, 0%), partial cytogenetic response (Ph, 1% to 34%), and minor cytogenetic response (Ph, 35% to 90%). A major cytogenetic response includes complete and partial cytogenetic responses (Ph, <35%).

Summary of IFN-A Studies at M.D. Anderson Cancer Center

After the original discovery of the anti-CML efficacy of IFN-A, a series of studies were conducted in various CML phases and using different forms of IFN-A alone or in combinations.[38-40] The aims of these studies were to define the optimal dose schedules of IFN-A, identify subsets with different benefits, and improve on the incidence and durability of cytogenetic and major cytogenetic responses and on the toxicity profile.

The activity of single agent IFN-A was found to be modest in late chronic-phase CML (diagnosis to therapy, >12 months) and in the transformed phases (Table 2). These phases were then approached therapeutically with investigational programs. Combinations with IFN-A (eg, with cytosine arabinoside [ara-C]) yielded favorable results, as did novel agents (eg, homoharringtonine) or strategies (eg, purged autologous stem cell transplantation).

The long-term follow-up results in early chronic-phase CML were encouraging.[31] Among 274 patients treated from 1982 through 1990 with IFN-A programs using IFN-A at 5 million units (MU)/m² daily or the maximally tolerated lower dose schedule, 80% achieved CHR and 58% had a cytogenetic response (26% complete and 38% major). The median survival was 89 months (confidence interval, 66 to 102 months). Achieving a cytogenetic response after 12 months of therapy was associated with a statistically longer survival by landmark analysis; the 5-year survival rates dated from 12 months into therapy were 90% for complete cytogenetic response, 88% for partial cytogenetic response, 76% for minor cytogenetic response, and 38% for other response categories. A multivariate analysis incorporating major cytogenetic response as a time-dependent variable showed it to be an independent prognostic factor for survival; patients achieving a major cytogenetic response had a 0.21 risk of death per unit time compared with the total study group. Thus, the favorable outcome among patients achieving a cytogenetic response was not from identification of "an intrinsically more favorable group" that would live longer regardless of therapy, because the effect of cytogenetic response was observed after accounting for the prognostic effect of pretreatment variables by multivariate analysis. Confirming this finding is the observation of the favorable impact of cytoge-

Table 3. Survival by Cytogenetic Response Status at 12 Months Within CML Risk Groups

Prognostic Group*	Cytogenetic Response	No. of Patients	4-yr Survival (%) Dated From 12 Mo Into IFN-A Therapy	P Value
Good	Yes	73	79	<.01
	No	68	62	
Intermediate	Yes	25	82	<.01
	No	31	35	
Poor	Yes	9	83	<.01
	No	31	39	

* Prognostic risk group defined by synthesis model.[31]

netic response within prognostic risk groups by landmark analysis (Table 3).

Other Studies of Single-Agent IFN-A Therapy

Studies from single institutions and cooperative groups have confirmed the efficacy of IFN-A in CML. Patients treated in early chronic phase CML by Alimena et al[41] had a CHR rate of 46% and a cytogenetic response rate of 55% (12% major). The analysis of patients randomized to IFN-A 5 MU/m² or 2 MU/m² three times weekly showed a statistically better CHR rate with the higher dose schedule (57% v 38%) and led to subsequent use of IFN-A 5 MU/m² daily.[41]

In the Cancer and Leukemia Group B (CALGB) trial, Ozer et al[42] increased the dose schedule of IFN-A from 2 MU/m² 5 times weekly to 5 × 10⁶ U/m² daily, after observing poor responses among the first 16 patients on study (excluded from subsequent analysis). In their study, the hematologic response rate was 59% (22% complete and 36% partial), the cytogenetic response rate was 29% (18% complete among 78 evaluable patients and 13% complete among the total 107 study patients), and the median survival was 66 months. The median dose schedule of IFN-A delivered was 3.2 MU/m² daily; 38% of patients had their dose reduced by 50% or more. The investigators did not find a positive relationship between achieving a cytogenetic response and survival, but the number of patients with major (and complete) cytogenetic response was small.[42] In a study by Mahon et al,[43] 52 patients were treated in a single institution with IFN-A 5 MU/m² daily. The CHR rate was 81% and the major cytogenetic response rate was 44% (38% complete).

Randomized Trials of IFN-A Versus Conventional Therapy

Italian study. The Italian Cooperative Study Group on CML (ICSG-CML) randomized patients to receive IFN-A 5 MU/m² daily or conventional therapy with hydroxyurea or busulfan. The 218 patients randomized to IFN-A therapy had a significantly higher incidence of major cytogenetic response (19% v 1%; P < .01), although the complete cytogenetic response rate was only 8%.[44] They also had a significantly longer survival (median survival, 72 v 52 months; P < .01) and time to disease progression (median time, >72 v 45 months; P < .01). The median dose of IFN-A delivered was 4.3 MU/m² daily. Thirty-one percent of patients had IFN-A treatment discontinued, 16% had it discontinued for

Table 2. Response to IFN-A With or Without Ara-C in CML by Phase and Time From Diagnosis

Time From Diagnosis (mo)	No. of Patients	No. (%)	
		CHR	Major Cytogenetic Response
Chronic			
<12	274	219 (80)	104 (38)
12 to 24	74	55 (74)	18 (24)
25 to 36	27	16 (59)	3 (11)
>36	39	20 (51)	3 (8)
Accelerated	61	32 (52)	4 (7)
Blastic	5	1 (20)	0 (0)

IFN-A serious side effects, and 18% had IFN-A dose reduced by more than 50%. Both factors may have adversely affected the outcome of the IFN-A arm.[45] By landmark analysis, patients who had achieved at least a CHR after 8 months of therapy had a significantly better survival (5-year survival rate, 78% v 48%; $P < .001$), as did those who had a cytogenetic response after 24 months of therapy (5-year survival rate, 88% v 65% months; $P < .001$).

German study. The German randomized trial restricted patients to IFN-A monotherapy, unlike some trials that allowed IFN-A combinations. This assessed precisely the effect of IFN-A single agent therapy in achieving CHR and its durability. Patients treated with either IFN-A or hydroxyurea had significantly better survivals than did those receiving busulfan therapy. The median survivals were 66, 56, and 45 months, respectively ($P < .01$), but there was no survival difference between the IFN-A and hydroxyurea arms ($P = .44$). The median IFN-A dose delivered after the first 4 weeks was 2.0 MU/m² daily. Twenty-five percent of patients had IFN-A therapy discontinued. Only 84 (63%) of the 133 patients receiving IFN-A had any cytogenetic studies (the average number of studies, 2.3). Overall, 15 patients (7%) had a complete cytogenetic response. The estimated 3-year survival rates were 100% for cytogenetic responders versus 72% for nonresponders ($P = .20$).[46] The possible reasons behind the lack of significant survival difference between the IFN-A and hydroxyurea arms may be (1) a worse study group in this trial, (2) the low dose schedule of IFN-A therapy delivered, and (3) consequently, the low percentage of patients achieving a cytogenetic response (associated with survival benefit).

British study. The Medical Research Council (MRC) trial randomized 587 patients to Wellferon 3 to 9 MU daily versus hydroxyurea or busulfan after remission induction. Patients randomized to Wellferon had significantly better survival when compared with either hydroxyurea or busulfan (median survival times, 61 and 41 months, respectively; $P < .001$). Only 59 patients (22%) had any cytogenetic response (5% complete and 6% partial), and they had a significantly better survival compared with the other patients.[47] The 5-year survival rates were 100% with a complete cytogenetic response, 92% with a partial response, 59% with a minor response, and 47% with no cytogenetic response. The median daily dose of Wellferon was 3.2 MU or about 1.9 MU/m². Patients achieving CHR did significantly better than those who had lesser degrees of response ($P = .01$). Patients treated with IFN-A survived longer than those treated with conventional therapy even if they had not achieved a cytogenetic response. Of note is the shorter median survival of patients on the chemotherapy arm compared with that of the chemotherapy arms in the Italian and German trials (median, 41 v 45 to 56 months).[44,46]

Japanese trial. Ohnishi et al[48] randomized 170 patients to receive either IFN-A or busulfan. The major cytogenetic response rate was 16% with IFN-A versus 5% with busulfan ($P = .046$), and the projected 5-year survival rates were 54% and 32%, respectively ($P = .03$). Patients achieving any cytogenetic response with either IFN-A or busulfan therapy survived significantly longer than others. In this study, the median daily IFN-A dose delivered was about 7 MU (4 MU/m²).

Table 4 summarizes the results of IFN-A trials in relation to the study design, numbers of patients, IFN-A dose delivered, response profiles, and survival.

Combination Studies

Among various treatments combined with IFN-A, ara-C in low doses appears promising based on in vitro studies,[49] single-agent activity,[50] and early pilot trials of IFN-A and ara-C combinations.[51-53] Our study in late chronic-phase CML showed better CHR (56% v 38%; $P = .02$) and survival rates (3-year rate, 76% v 35%; $P < .01$) with the combination compared with IFN-A alone. Among 30 patients treated in early chronic-phase CML with IFN-A and low-dose ara-C, Arthur and Ma[52] reported a CHR rate of 93% and a cytogenetic response rate of 67%, which was major in 43% and complete in 30%. Guilhot et al[53] randomized patients in chronic-phase CML to IFN-A plus ara-C or IFN-A alone. The CHR rate was 80% versus 70%, the major cytogenetic response rate was 28% versus 20%, and the incidence of Ph suppression to less than 5% was 18% versus 7%. If the beneficial effect of ara-C in CML is confirmed, treatment with IFN-A and ara-C could be made easier with a new oral formulation of ara-C, YNK01.[54]

Prognostic Factors, Risk Groups, and Outcome With IFN-A Therapy

Prognostic factors for response to IFN-A therapy and for survival appear to be similar to those with conventional therapy. In multivariate analyses, the percentage of blasts and the degree of thrombocytosis have been correlated with response to IFN-A therapy; splenomegaly, marrow basophilia,[31] anemia, and percentage of blasts have been associated with survival.[44] The existing prognostic models segregate patients into different risk categories for response and survival (Table 5A) and could be useful in comparing results within risk groups. Patients with good-risk CML have an expected major cytogenetic response rate of about 50% and an expected median survival of 102 to 104 months. In contrast, those with poor-risk disease have an expected major cytogenetic response rate of 14% to 26% and an expected median survival of 47 to 62 months (Table 5A).

The in vivo response to IFN-A is a dominant treatment-associated prognostic factor. Achieving a CHR at 3 to 8 months,[43,44] a cytogenetic response at 12 months,[31] or a major cytogenetic response at 24 months[43] is associated with a statistically better outcome.

Combining the patient pretreatment features (risk group) with response to IFN-A may allow early selection of patients who benefit from continued IFN-A therapy, whereas others would be advised on alternative approaches. Currently, patients who do not achieve a CHR after 6 to 8 months or a cytogenetic response after 12 months of IFN-A therapy may be taken off IFN-A, if the aim of therapy is the achievement of a durable cytogenetic response and consequently im-

Table 4. Results of IFN-A Therapy in Early Chronic-Phase CML

Study	Therapy	No. of Patients	Median Daily Dose IFN-A (MU/m²)		CHR	CG Response (%)			Median Survival (mo)
			Planned	Delivered		Any	Major	Complete	
MDACC[31]	IFN-A	274	5	5	80	56	38	26	89
Mahon[43]	IFN-A	52	5	5	81	—	44	38	—
ICSG-CML[44]	IFN-A	218	5	4.3	62	55	19	8	72
	Chemotherapy	104	—	—	53	34	1	0	52
Ohnishi[48]	IFN-A	80	5	4.0	39	44	7.5	9	65+
	Busulfan	79	—	—	54	29	2.5	2.5	50
Alimena[41]	IFN-A	65	1 to 2.5	—	46	55	12	—	—
Ozer[42]	IFN-A	107	5	3.2	59	—	29	13	66
Allan[47]	Wellferon	293	3 to 12	2 (3.2)	68	22	11	6	61
	Busulfan or hydroxyurea	294	—	—	—	—	—	—	41
Hehlmann[46]	IFN-A	133	5	2	31	18	10	7	66
	Busulfan	186	—	—	23	4	1	0	45
	Hydroxyurea	194	—	—	39	5	1.5	1	56

proved survival. However, the MRC trial suggests that continued IFN-A therapy may still be the optimal approach for such patients, if allogeneic BMT is not a consideration.[47]

Cost and Toxicity With IFN-A Therapy

Therapy with IFN-A is significantly more expensive than conventional therapy with hydroxyurea or busulfan. Using

Table 5. Risk Group Distributions in Relation to Response and Survival With IFN-A Therapy in Different CML Trials

(A) Response and median survival ranges using different prognostic models in CML (M.D. Anderson Cancer Center)[31]

Risk Group	% Major Cytogenetic Response	Median Survival (mo)
Good	46-52	102-104
Intermediate	32-38	82-95
Poor	14-26	47-62

(B) Risk group distribution of patients in different CML trials

Study	% in Risk Group		
	Good	Intermediate	Poor
MDACC[31]	48-52	25-36	16-23
ICSG-CML[44]	43	33	24
Hehlmann[46]	27	35	38
Allan[47]	24	33	41

(C) Cytogenetic response within risk groups in different CML trials

Study	% Cytogenetic Response in Risk Group		
	Good	Intermediate	Poor
MDACC[31]	72	59	39
Allan[47]	34	31	7

(D) Survival within risk groups in different CML trials

Study	5-yr Survival (%)		
	Good	Intermediate	Poor
MDACC[31]	78	62	46
Allan[47]	66	63	34

the maximal tolerated dose of IFN-A results in an average yearly cost of $15,000 to $20,000, although the yearly charge in the United States has been capped at $8,000 to $10,000. This is compared with a yearly charge of $500 to $1,000 for hydroxyurea, considering an average dose of 1 g daily to maintain CHR. Cost-benefit analysis studies of IFN-A versus conventional therapy in CML are ongoing.

Side effects with IFN-A therapy are also significantly higher than with conventional therapy. Fifteen to twenty-five percent of patients had IFN-A therapy discontinued because of severe side-effects, whereas another 30% to 50% required dose reductions because of poor treatment tolerance. Common severe chronic side effects may include fatigue, weight loss, insomnia, depression, and neurotoxicity. Immune-mediated complications include hemolysis, thrombocytopenia, hypothyroidism, collagen vascular disorders, and occasional cardiac, renal, and other organ damage.[55]

Reasons for the Differences in Treatment Results With IFN-A Therapy in Different Trials

As shown in Table 4, the CHR rates among similar study groups (ie, early chronic-phase CML) have ranged from 31% to 80%. Some of variability in the CHR rates may be due to different response criteria or treatment designs. The use of IFN-A monotherapy in the German and CALGB studies, as opposed to allowing the addition of chemotherapy in others, may have produced a lower CHR rate. This would not explain the large differences in the cytogenetic (18% to 58%), major cytogenetic (10% to 38%), and complete cytogenetic (6% to 26%) response rates. Differences in cytogenetic response results may be due to (1) different risk group distributions, (2) patient and physician motivation, (3) the actual dose schedule delivery of IFN-A, and (4) the frequency of cytogenetic studies.

Our studies, by virtue of the referral patterns, include a higher percent of good-risk patients compared with the trials from Italy, Germany, and Britain (Table 5B). However, when patients were analyzed for response to IFN-A and for survival within risk groups (Table 5C and D), our studies still showed better results in each risk group, suggesting

the value of IFN-A dose-intensity to increase the quality of cytogenetic response and to prolong survival. As with any new modality, (eg, anthracyclines, cisplatin, and all-*trans* retinoic acid in acute promyelocytic leukemia), a learning curve may exist that improves the results as experience is gained. The complete cytogenetic response rate in our first IFN-A study was 14%, similar to current cooperative trials, and may have been due to unfamiliarity with toxicities and with the dose-response phenomenon.

Comparing the median dose of IFN-A delivered among responders versus nonresponders is misleading because many studies have, in the treatment design, built-in dose reductions after achieving a response and dose escalations with resistant disease.[44,46,47] Such an approach (higher dosages for resistant disease and lower dosages for responsive disease) would preclude meaningful analyses of the relationship of IFN-A dose-intensity with response within a particular study. However, comparison of the actual median dose of IFN-A delivered versus response rate among different studies may help demonstrating the dose-response phenomenon. Table 4 summarizes the response rates in different studies by the median actual dose of IFN-A delivered, suggesting the relationship between the schedule dose intensity delivery and the hematologic and cytogenetic response rates.

Finally, whether the frequency of cytogenetic studies would impact on the incidence of cytogenetic response remains to be elucidated.

Questions Raised by the IFN-A Trials

The studies (Table 4) raise several questions pertinent to IFN-A therapy. (1) What is the optimal dose schedule of IFN-A? (2) Is there an association between achievement of minimal residual disease (hematologic and cytogenetic) and survival prolongation? (3) Does IFN-A therapy prolong survival over conventional therapy?

Lower versus maximally tolerated dose schedules of IFN-A. A recent study of Schofield et al[56] argued that a lower dose schedule of IFN-A 2 MU/m² 3 times weekly was as effective as the higher dose schedules of 5 MU/m² daily recommended for CML (weekly dose 6 MU/m² v 35 MU/m²) and would certainly be less toxic and less expensive. This was based on the comparative analysis of 27 patients treated in early chronic-phase CML with the literature experience. Comparison of the 274 patients in our studies to theirs indicates that, although the overall hematologic response may be similar, the incidences and quality of cytogenetic responses is significantly better with the higher dose schedules (Table 6). This is an important issue if achievement of minimal residual disease at the cytogenetic level (as discussed later) is associated with a survival benefit. This is further supported by the initial CALGB experience with the lower IFN-A dose schedule,[42] by the comparative study of Alimena et al[41] with the 2 dose schedules of IFN-A, and by two additional studies of low-dose IFN-A schedules.[57,58] (Table 6). Another issue is the differential response to IFN-A by risk groups. The 27 patients studied by Schofield et al[56] may have belonged mostly to a good-risk subgroup, in whom the expected major cytogenetic response rate would be 46% to 52% (rather than the reported 22% rate) and the median survival 102 to

104 months (Table 5A). Although the current results in CML suggest a benefit from higher or maximally tolerated dose schedule of IFN-A, the optimal IFN-A dose schedule is controversial, and randomized studies of low-dose versus high-dose IFN-A schedules are currently ongoing.

Significance of minimal tumor burden and prognosis with IFN-A therapy. In solid tumors, achieving a minimal tumor burden had been the only means for prolonging survival and producing cures. The causal association between the Ph-related molecular events and development of CML encourages investigating approaches that reduce CML burden to the greatest extent possible. A minimal hematologic tumor burden, defined by achieving CHR, was associated with significant survival prolongation in all studies in which it was investigated[43-47] (Table 7). Achieving a minimal cytogenetic tumor burden was also associated with a significant survival advantage by landmark and/or multivariate analysis in 4 of 7 studies[31,43,44,47,48]; two studies included a small number of cytogenetic responses[42,46] and a positive trend was observed in one.[46] In the study of Ohnishi et al,[48] achieving any cytogenetic response was associated with a significantly better duration of chronic-phase CML (5-year rates, 79% v 22%; P = .0017) but only a trend for better survival (P = .10). Thus, the current data suggest that achieving minimal hematologic and cytogenetic disease burden would impact outcome favorably, and should be pursued as a therapeutic objective in future investigations.

Of the 4 randomized trials, 3 have shown a significant survival advantage with IFN-A versus conventional therapy[44,47,48]; the fourth showed the benefit compared with busulfan but not hydroxyurea.[46] Considering that (1) a cytogenetic response is independently associated with a survival advantage[31,44,47] and (2) a low cytogenetic response rate was observed in the German trial,[46] it is understandable that a survival advantage was noted with the modalities producing CHR (IFN-A or hydroxyurea versus busulfan), but that the additional survival advantage obtained by achieving a cytogenetic response (IFN-A therapy) was not observed in the German study,[46] because it occurred only in a minority of patients. However, this argument would not explain the survival benefit with IFN-A therapy in the MRC trial among patients not having a cytogenetic response.[47]

Direction of Investigational IFN-A–Based Programs in CML

Although the comparative trials of IFN-A versus conventional therapy were needed in the earlier investigations, the current dilemma, in view of the questions raised by the maturing experience, is whether further randomized trials are needed. Some investigators would argue that combination approaches (as for AML) would ultimately be the mainstay of therapy in CML (because the active agents have different mechanisms of action). Thus, investing expenses and patients into further randomized studies of single-agent IFN-A may not be the most fruitful investigational route. Rather, a series of pilot trials of IFN-A combinations should aim at improving the major and complete cytogenetic response rates to greater than 40% to 50% and ameliorating the treatment-related side-effects. If the survival advantage is most evident

Table 6. Response by the Dose Schedule of IFN-A Therapy in Early Chronic-Phase CML

Study	Schedule	No. of Patients	% CHR	% Cytogenetic Response		
				Any	Major	(Complete)
MDACC[31]	5 MU/m²/d	274	80	58	38	(26)
Schofield[56]	2 MU/m²/TIW	27	70	33	22	(7)
Alimena[41]	2 MU/m²/TIW	33	24	NS	NS	
	5 MU/m²/TIW	30	63	NS	NS	
Freund[57]	5 MU/TIW	10	33	0	0	
Anger[58]	3 MU/TIW	9	22	20	0	

Data for Schofield et al[56] included only early chronic phase CML.
Abbreviations: TIW, three times a week; NS, not stated.

with major cytogenetic response, increasing this response rate to significant levels (40% to 50%) would translate into a more evident survival benefit in the overall population, which would be difficult to show if the major cytogenetic response rate was lower (eg, <10%). Only when such cytogenetic response rates are achieved in cooperative (rather than single institution) trials with acceptable toxicity would further randomized studies be indicated.

Practical Guidelines for IFN-A Therapy and Management of Side Effects

The following guidelines may improve on patient tolerance, compliance, and side effects with IFN-A therapy in general.

(1) Initial tumor debulking can be achieved faster and less expensively with hydroxyurea at 1 to 5 g daily. Starting IFN-A with high WBC counts does not offer a therapeutic advantage, although it was required in the original trials to establish its anti-CML activity. It may, in fact, increase the early IFN-A toxicities related to leukocytosis (fever, chills, and bone and muscles aches) and result in early drop-outs. Once the WBC count is reduced to 10 to 20 × 10³/μL, IFN-A may be started and hydroxyurea gradually tapered.

(2) IFN-A therapy is initiated at a lower dose (eg, 3 MU daily for 3 to 7 days, then 5 to 6 MU daily for 3 to 7 days, and then 5 MU/m² or MTD) to induce tachyphylaxis to early

Table 7. Summary of Response and Survival Results With IFN-A Therapy

Design		Survival Advantage with		
		IFN-A Therapy	CHR	Cytogenetic Response
MDACC[31]	Single arm	NA	+*	+
Ozer[42]	Single arm	NA	ND	—
Mahon[43]	Single arm	NA	+	+
ICSG-CML[44]	Randomized	+	+	+
Hehlmann[46]	Randomized	+ v busulfan	+	Trend
		− v hydrea		
Allan[47]	Randomized	+	+	+
Ohnishi[48]	Randomized	+	ND	+

Abbreviations: NA, not applicable; ND, not done.
* Positive but not included in reported study.

IFN-A–related side-effects. These are almost never dose-limiting and may be managed by giving IFN-A at bedtime and by premedication with acetaminophen.

(3) Older patients (age ≥60 years) generally experience more serious side-effects and may not tolerate the full dose schedule as well as younger patients.

(4) Common chronic side effects include any or a combination of a triad of fatigue, depression, and insomnia. This has been managed empirically and successfully with a low dose of amitriptyline at bedtime (12.5 to 50 mg). A neuropsychiatric consultation and other antidepressants may benefit individual cases.

(5) Dose reductions of IFN-A, commonly practiced when the WBC count is reduced to 5 to 10 × 10³/μL are counterproductive for achievement of cytogenetic response. Dose reductions of 25% may be considered for chronic moderate side effects or if the WBC count decreases to less than 2 × 10³/μL or the platelet counts to less than 50 × 10³/μL. Serious (grade 3-4) toxicities necessitate interruption of IFN-A therapy and possible resumption at 50% of the previous dose with close monitoring.

(6) Patients achieving a cytogenetic response should continue IFN-A therapy. A complete cytogenetic response is not an indication for stopping therapy and observation. Patients should continue IFN-A therapy as long as a cytogenetic response (or CHR according to the MRC trial) persists or for at least 3 years beyond a documentation of a complete cytogenetic response. In such instances, IFN-A therapy may be gradually tapered with close (every 6 months) cytogenetic monitoring. The availability of better monitoring procedures of minimal cytogenetic disease burden, such as the hypermetaphase fluorescent in situ hybridization technique, will allow more rational treatment decisions at these particular periods.[59]

INVESTIGATIONAL MODALITIES

Investigational approaches have primarily focused on suppression of the Ph-positive clones. Intensive chemotherapy, new agents such as homoharringtonine, and autologous stem cell transplantation appear promising.

Intensive Chemotherapy

Treatment of CML with intensive chemotherapy using AML-like regimens was initiated in the seventies. Intensive

Table 8. Recovery of 100% Diploid Hematopoiesis in Peripheral Stem Cell Collections After Early Hematopoietic Recovery From Intensive Chemotherapy

Study	Therapy	CML Phase	No. of Patients	% With 100% Diploid Peripheral Collections
Carella[63]	ICE	Chronic	24	50
		Accelerated	22	23
MDACC[64]	Dauno-HDAC	Chronic	30	27
	FAM	Accelerated	17	18
		Blastic	8	0
Chalmers[65]	ICE	Chronic	25	44

Abbreviations: ICE, idarubicin, ara-C, etoposide; Dauno-HDAC, daunorubicin and high-dose ara-C; FAM, fludarabine, high-dose ara-C, and mitoxantrone.

chemotherapy induced cytogenetic remissions in 60% to 70% of patients, which was complete in 35% to 50%.[60] Its use in three initial intensive cycles followed by IFN-A maintenance did not increase the rate of long-term cytogenetic response compared with IFN-A alone.[61] Simonsson et al[62] treated 120 patients with CML with IFN-A for 6 months, followed by 3 different intensive chemotherapy regimens and autologous BMT using Ph-negative collected cells. The estimated 5-year survival rate of patients was 68%, and 11 of 26 autografted patients remain Ph-negative up to 48 months post-BMT.[62]

Intensive chemotherapy has been used recently with increasing frequency as a method for in vivo purging that allows collection of marrow or peripheral diploid-rich stem cells during early hematopoietic recovery. Carella et al[63] reported 50% of patients collected in chronic-phase CML to be 100% diploid in the peripheral stem cell collections. In our study, conducted in patients with longer chronic-phase duration and with IFN-A resistance, the Ph-negative collection rate was 27%, with 43% of patients having less than 35% Ph-positive cells; peripheral stem cell collections were cleaner than marrow collections in 23% of patients.[64] Similar findings were reported by others[65] (Table 8). The treatment-related mortality in chronic phase was 7%.[64,65]

Homoharringtonine (HHT)

HHT, a plant alkaloid, showed modest activity in AML with significant cardiovascular problems. The schedule was modified to a lower-dose longer-exposure schedule that almost eliminated the cardiovascular side effects and was associated with significant antiproliferation. HHT was then investigated in late chronic-phase CML at 2.5 mg/m² by continuous infusion for 14 days for remission induction and then for 7 days every month as maintenance. Among 71 patients treated (82% with prior IFN-A therapy and 58% with IFN-A resistance), 72% achieved CHR and 30% had a cytogenetic response, which was major in 15%.[66] These figures compared favorably with the results of IFN-A alone or with ara-C in late chronic-phase CML, albeit in different study groups as defined by prior IFN-A exposure and resistance.

Because of the encouraging results, the sequential combination of HHT for 6 cycles followed by IFN-A maintenance was investigated in early chronic-phase CML.[67] Among 90 patients treated, the CHR rate after 6 cycles of HHT was

92% and the cytogenetic response rate 68% (major, 27%). The longer-term follow-up results are also favorable with trends for higher hematologic and cytogenetic response rates at 3 years with the combination compared with IFN-A alone.

Autologous Stem Cell Transplantation (SCT)

Investigations of autologous SCT were initiated in CML-transformed phases and showed CHR or return of second chronic-phase rates of 30% to 70%, which were transient.[68] In chronic-phase CML, unpurged autologous SCT was associated with recovery with some Ph-negative cells, ie, cytogenetic response, in 30% to 77% of patients.[69,70] Occasional patients continue to maintain Ph-negative cells with long-term follow-up.[69] Three single arm studies (Table 9)[71-73] suggested a possible survival advantage with purged autologous SCT, with 4- to 5-year survival rates of 56% to 70% after transplantation. Our analysis of 22 patients undergoing SCT and compared with matched historical controls showed median survivals of 34 versus 49 months, respectively (P value not significant).[74] Our study groups consisted of patients in late chronic-phase CML (median time to transplant, 43 months) who had proven resistance to IFN-A therapy, whereas patients in other studies were transplanted in earlier chronic phase and had little or no IFN-A exposure. Thus, from the available data, unpurged autologous SCT cannot be recommended as a method to prolong survival in CML in current practice.

Purged autologous SCT is an exciting investigational approach in CML.[68] In vitro methods for purging have included long-term liquid (Dexter) cultures,[75] in vitro incubation with

Table 9. Autologous Stem Cell Transplant in Chronic-Phase CML

Study	No. of Patients	% Purged	% Major Cytogenetic Response	% Survival (x year)
McGlave[71]	142	NS	NS	60 (4)
Reiffers[72]	49	35	31	70 (3)
Hoyle[73]	21	0	52	56 (5)
Khouri[74]	22	0	NS	50 (3)
Simonsson[62]	26	100	NS	68 (6)
Carella[63]	11	100	45	NS
Talpaz[85]	10	100	40	90 (1)
Barnett[76]	16	100	68	80 (3)

Abbreviation: NS, not stated.

chemotherapy (eg, 4 hydroxycyclophosphamide),[76] biologic agents (eg, γ interferon),[77] negative selection for Ph-positive (CD34$^+$, HLA DR$^+$) cells, positive selection for normal (CD34$^+$, HLA DR$^-$) stem cells,[78] and purging with antisense oligodeoxynucleotides against different oncogenic products (eg, BCR-ABL and c-myb).[79-83] In vivo purging methods have included stem cell collections after α interferon or intensive chemotherapy, as discussed earlier.[61-65]

After their original observation of the growth advantage of normal over Ph-positive cells with long-term liquid cultures, the Vancouver group investigated such in vitro purging for autologous BMT. Of 87 patients screened, 36 (40%) exhibited this growth advantage pattern and 22 underwent purged autologous BMT. Marrows with 100% diploid cells were observed in 13 of 16 patients who had recovery, which lasted for a median of 12 months. Five patients maintained a Ph-negative status, 2 with IFN-A maintenance and 3 without maintenance. The 3-year survival rate was 75%.[75]

Gewirtz[84] used in vitro purging with c-myb antisense oligodeoxynucleotides. All 5 patients treated had later recovered with 100% Ph-positive cells after autologous BMT. Oligonucleotides against c-myb and BCR-ABL have shown survival prolongation in CML animal models.

In the study by Simonsson et al,[62] 26 of the 120 patients with CML treated with the sequence of IFN-A, intensive chemotherapy, and autologous BMT have undergone the BMT procedure. Eleven (46%; 9% of total) maintain a Ph-negative status. The 6-year actuarial survival rate of the total population is 68%.[62]

In the study of Carella et al,[63] 16 patients (11 chronic and 5 accelerated) have undergone autologous SCT using diploid stem cells collected during early hematopoietic recovery; 5 remain in cytogenetic CR on IFN-A maintenance at 5+ to 29+ months.

In our studies, patients with CML (10 chronic, 9 accelerated, and 3 blastic) underwent autologous SCT using stem cells collected during hematopoietic recovery from intensive chemotherapy. Five patients received 100% diploid SCT. There was a direct correlation between the percentage of Ph-positive cells infused and recovered. The median time to loss of cytogenetic response was 12 months for patients infused with less than 35% Ph-positive cells and 5 months for those infused with greater than 35% Ph-positive cells.[85]

The results of the above studies are summarized in Table 9. Because relapse post-BMT is contributed to partly by infused tumor cells,[86-88] improvement in purging methods remains an important investigational aim in the setting of autologous SCT in CML. Results of immunomodulation strategies after autologous SCT are encouraging. α Interferon, interleukin-2, and linomide are candidate approaches. Rowe et al[89] treated 12 patients who underwent unpurged autologous BMT with linomide up to 0.2 mg/kg orally twice weekly; 3 patients have maintained a Ph-negative status for 12+, 13+, and 16+ months.

TREATMENT OPTIONS

The majority of patients with CML (75% to 80%) are not candidates for related (match or 1 antigen mismatch)

allogeneic BMT. In this group, an initial trial of IFN-A therapy is indicated. Patients who achieve CHR by 6 to 8 months and a cytogenetic response by 12 months may continue IFN-A therapy as long as the cytogenetic response persists or for at least 3 years in cytogenetic CR. Patients who do not have a cytogenetic response after 12 months of therapy may either continue on IFN-A (based on MRC studies)[47] or may be offered investigational approaches aimed at suppressing Ph-positive disease (HHT, purged autologous SCT, or new agents) or MUD BMT in chronic or transformed phase depending on patient age and degree of donor-host matching. The median interval between the initiation of a preliminary search for a donor and MUD transplant is about 8 months[90] and is less likely to be successful among certain ethnic groups (eg, African-Americans and Orientals).[91] Hence, a preliminary MUD search soon after diagnosis among eligible patients is advisable.

Patients who have a related donor may be offered allogeneic BMT initially or after a trial of IFN-A therapy based on patient age, patient and physician preferences, and experience with allogeneic BMT and IFN-A. In general, younger patients may undergo allogeneic BMT as initial therapy if the risk of the procedure is low (<20% 2-year mortality) or if the experience with IFN-A in terms of achieving a cytogenetic response is poor. Patients who are older or with an expected transplantation associated mortality of more than 20% may undergo initial IFN-A therapy and would be offered related allogeneic BMT if no cytogenetic response is observed after 12 months or is lost later on.

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