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Intensive Treatment and Stem Cell Transplantation in Chronic Myelogenous Leukemia: Long-Term Follow-Up

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Key Words

Chemotherapy, intensive · Chronic myelogenous leukemia · Interferon · Stem cell transplantation, autologous and allogeneic

Abstract

In the present study we combined interferon (IFN) and hydroxyurea (HU) treatment, intensive chemotherapy and autologous stem cell transplantation (SCT) in newly diagnosed chronic myelogenous leukemia patients aged below 56 years, not eligible for allogeneic SCT. Patients who had an HLA-identical sibling donor and no contraindication went for an allogeneic SCT (related donor, RD). After diagnosis, patients not allotransplanted received HU and IFN to keep WBC and platelet counts low. After 6 months patients with Ph-positive cells still present in the bone marrow received 1–3 courses of intensive chemotherapy. Those who became Ph-negative after IFN + HU or after 1–3 chemotherapy courses underwent autologous SCT. Some patients with poor cytogenetic response were allotransplanted with an unrelated donor (URD). IFN + HU reduced the percentage of Ph-positive metaphases in 56% of patients, and 1 patient became Ph-negative. After one or two intensive cytotherapies 86 and 88% had a Ph reduction, and 34 and 40% became Ph-negative, respectively. In patients receiving a third intensive chemotherapy 92% achieved a Ph reduction and 8% became Ph-negative. The median survival after auto-SCT (n = 46) was 7.5 years. The chance of remaining Ph-negative for up to 10 years after autologous SCT was around 20%. The overall survival for allo-SCT RD (n = 91) and URD (n = 28) was almost the same, i.e. ≈60% at 10 years. The median survival for all 251 patients registered was 8 years (historical controls 3.5 years). The role of the treatment schedule presented in the imatinib era is discussed.

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Introduction

The poor prognosis of patients with chronic myelogenous leukemia (CML) on conventional symptomatic therapy is well documented [1, 2]. This treatment controls disease symptoms for some time, but does not prevent the transformation to a blastic crisis. There are reasons to believe that a significant reduction or elimination of the Ph-positive malignant clone in CML prolongs time to metamorphosis [3].

Allogeneic stem cell transplantation (SCT) results in a prolonged disease-free survival and is the only treatment that might cure the patients [4–8]. Autologous SCT is also an effective treatment in CML [9–12]. Its value compared to conventional therapy is, however, not known. Interferon (IFN) and intensive chemotherapy are treatments well known to reduce or eliminate the Ph-positive clone in CML [11, 13–19]. In the present study we used all these treatment modalities. Patients who had an HLA-identical sibling donor and no contraindication went for an allogeneic SCT (related donor, RD). The remaining patients received IFN + hydroxyurea (HU) followed by intensive chemotherapy. Some patients with poor cytogenetic response were allotransplanted with an unrelated donor (URD). Selected cases with therapy-induced major or complete cytogenetic responses were autotransplanted. We report long-term follow-up of this treatment schedule in Danish and Swedish CML patients below 56 years of age.

Imatinib (Gleevec®, Glivec®, Novartis) is at present the first choice of treatment of CML [20, 21]. It was introduced in the market after the last patient had been included in the present study. This paper could, therefore, be seen as a summary of treatments before the imatinib era. We discuss these treatments as alternatives for imatinib-resistant patients.

Methods

Patients

All newly diagnosed Ph-positive CML patients in the chronic phase below 56 years of age in Denmark and Sweden (except one University Hospital region) were eligible for the study. Patient inclusion started on September 1, 1989 and ended on September 30, 1997. The median follow-up time is 5.2 years (censored 7.1). All patients gave informed consent to participate in the study. The study was approved by regional ethics committees in Denmark and Sweden.

Study Design

The patients were treated according to the study design shown in figure 1 and table 1. Exclusion criteria from intensive treatment (but not from follow-up) were pregnancy, severe other diseases, and noncompliance.

Cytogenetic responses were measured as the percentage of Ph-positive metaphases in the bone marrow cells. Usually 20–25 metaphases were examined. All patients were 100% Ph-positive at inclusion.

The aim of the study was to give the patients intensive treatment and thus by achieving a major reduction or an elimination of the

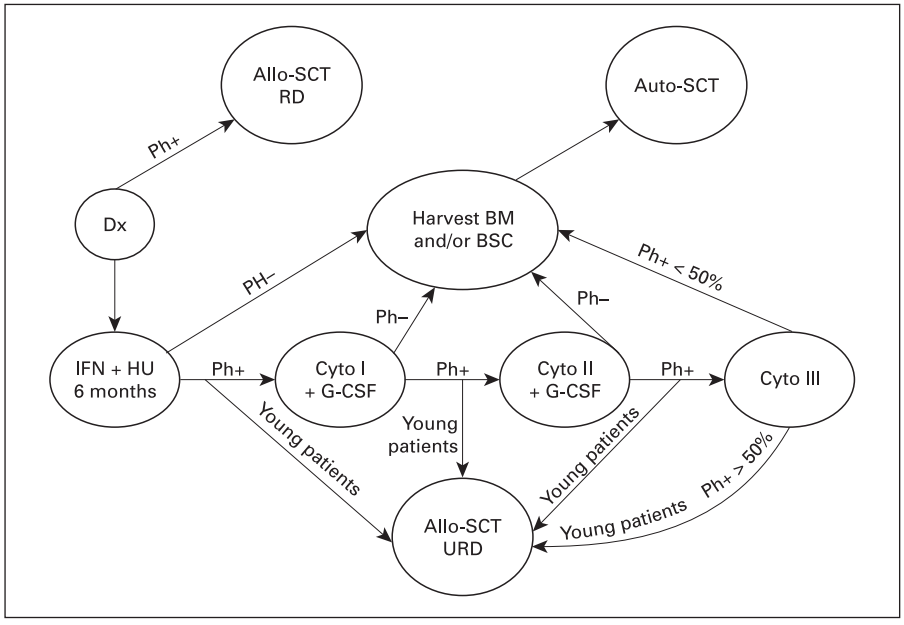

Fig. 1. Study design.

malignant clone hopefully reduce the risk of the development to a blastic crisis. If possible the patients went for an allogeneic SCT (RD) (if they had an HLA-identical sibling) or autologous SCT (if they had enough Ph reduction in the bone marrow). Patients not primarily allotransplanted were treated (table 1) with HU and IFN (Introna®, Schering-Plough) for 6 months. The treatment aim was to keep WBC and platelet counts in the range of 2–4 and 100–150 $\times$ 10^9/l, respectively. If the patients did not become cytogenetically normal (i.e. Ph-negative) in the bone marrow after IFN + HU treatment, they received 1–3 courses of intensive chemotherapy. G-CSF (lenograstim, Chugai-Rhone-Poulenc, France, 1,052 µg $\times$ 1 s.c., from day 8 → leukapheresis completed) was from 1994 onwards added to the intensive chemotherapy with the intention to harvest Ph-negative blood stem cells (BSC) [12]. If Ph negativity occurred bone marrow and/or BSC were harvested and the patient went for an autologous SCT. Patients with less than 50% Ph-positive metaphases in the bone marrow after the third chemotherapy course were also offered BSC harvest and an autologous SCT. For young patients with no cytogenetic response (or <50% after third chemotherapy) and eligible for SCT we searched for a well-matched URD. With time we tended to accept patients for allo-SCT URD earlier in the course of the disease than we did at the start of the study. This was due to improved tissue typing and supportive care.

Endpoints

The primary endpoint of the study was overall survival for the registered patients by the intention to treat principle, i.e. including also those who could not get, or who refused, intensive treatment. Secondary endpoints were side effects of treatment, outcome of the different forms of SCT and cytogenetic response.

Table 1. Treatment details

IFN + HU	HU 1–3 g daily and IFN (Introna, Schering-Plough) 5–10 $\times$ 10^6 IU/m^2 s.c. daily in order to keep WBC <2–4 $\times$ 10^9/l and/or platelets 100–150 $\times$ 10^9/l; in case of pronounced side effects the IFN dose was reduced to 3 $\times$ 10^6 IU/m^2
Cyto I	Daunorubicin days 1–3, 50 mg/m^2, 1 h; Ara-C days 1–7, 200 mg/m^2
Cyto II	Mitoxantrone days 1–4, 12 mg/m^2, 1 h; etoposide days 1–4, 100 mg/m^2; Ara-C twice daily days 1–4, 1 g/m^2, 2 h
Cyto III	Amsacrine days 1–4, 75 mg/m^2 and Ara-C twice daily days 1–4, 1 g/m^2, 2 h

Results

From September 1, 1989 to September 30, 1997, 251 patients were registered in the study. They represented 80% of the estimated number of CML patients in this age group in Denmark and Sweden. The male/female ratio was 163/88 and median age was 42 years (15–55).

The treatments patients had received at their latest follow-up are shown in the flow sheet (fig. 2). The majority of the patients underwent SCT (n = 165; 91 RD, 28 URD, 46 autotransplanted). The ages and the median times from diagnosis for the allotransplanted patients are shown in table 2.

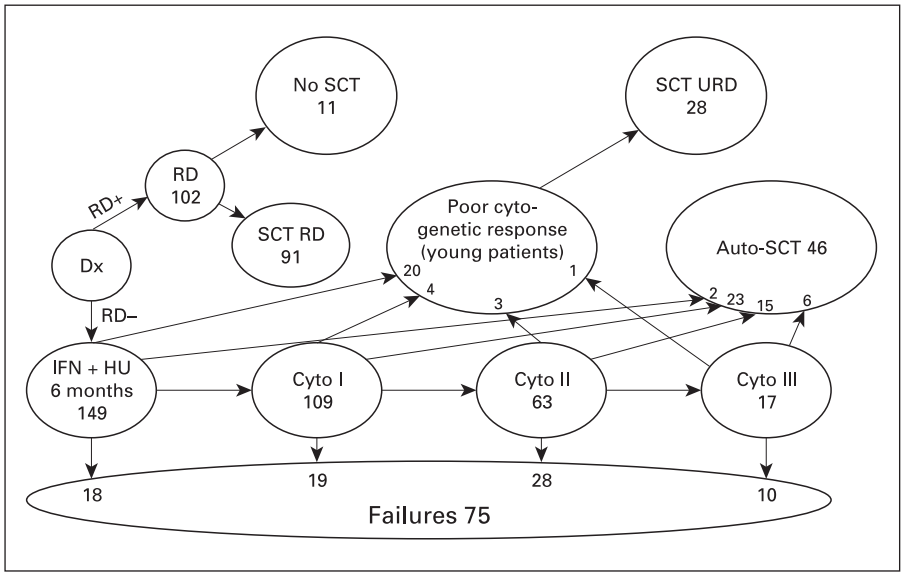

Fig. 2. The treatment the patients received. Numbers indicate number of patients.

Allo-SCT with RD

Figure 3 shows the outcome for allogeneic SCT with RD. Long-term survival seems to be around 60%. Eleven patients with a donor were not allotransplanted since they were considered to have a high risk for complications to this treatment or developed a blastic crisis. Four of these patients underwent intensive chemotherapy (2 underwent 1 course, 1 had 2 courses, 1 had 3 courses). The outcome for all 102 patients with RD (= intention to treat) is also shown in figure 3.

IFN + HU and Intensive Chemotherapy

The cytogenetic outcome of IFN + HU treatment and of the intensive chemotherapies is shown in table 3. Fifteen percent had a major or complete cytogenetic response after 6 months' IFN + HU. Fifty-nine and 72%, respectively, were the corresponding figures for chemotherapy I and chemotherapy II, while 30% of the patients had this response after chemotherapy III. Figure 2 shows that 18 of the patients who started could not fulfil IFN + HU treatment and therefore were characterized as failures. One of these patients died, 4 had a blastic crisis, 2 had an accelerated phase and 11 developed very severe side effects or refused therapy. Due to no cytogenetic response, 20 young patients went to an allogeneic SCT with URD (fig. 2). The 2 complete cytogenetic responders went to autologous SCT with bone marrow stem cells. Side effects during IFN + HU treatment were the same as usually found with IFN treatment. The IFN dose during the IFN + HU period was due to side effects reduced in around 50% of the patients.

Table 2. Patients who underwent allo-SCT

	SCT RD (n = 91)	SCT URD (n = 28)
Age at diagnosis, years		
Median	39	39
Range	17–55	25–51
Time from diagnosis to transplantation, months		
Median	7.1	18
Range	3–46	6–91

Table 3. Cytogenetic response to the different treatments

Ph-positive metaphases %	IFN + HU 6 months, %	Cyto I %	Cyto II %	Cyto III %
0	2	34	40	8
1–35	13	25	32	22
36–90	35	21	10	54
91–99	6	3	6	8
100	44	15	12	8
Patients analyzed	130	89	48	13
Patients not analyzed	19	20	15	4

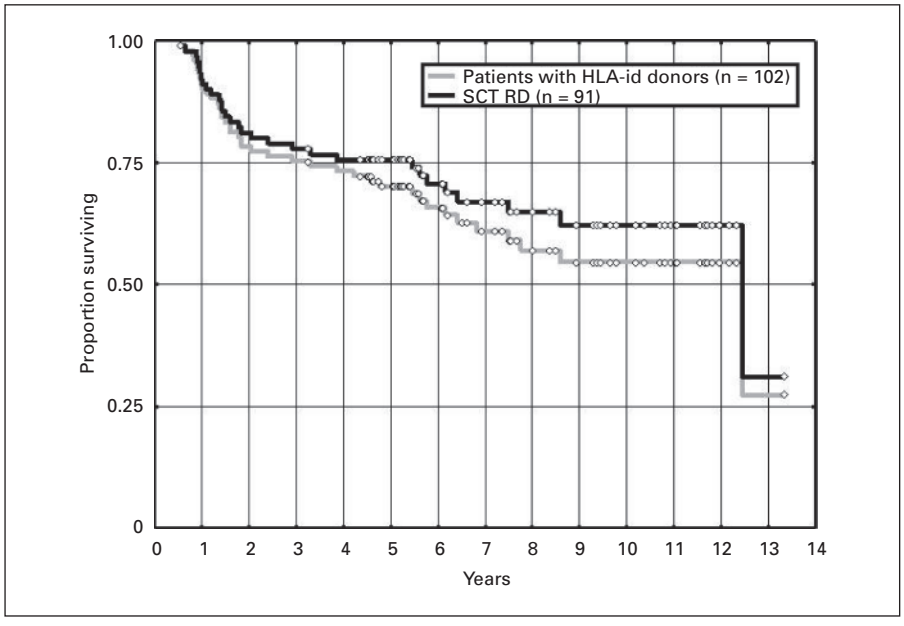

Fig. 3. Survival (from diagnosis) in patients with HLA-identical (HLA-id) donors and SCT RD.

The side effects of the intensive chemotherapy were cytopenia, fever and bleeding. Five patients died of complications due to the first, 2 due to the second, and none due to the third course. Among the failures of these three intensive chemotherapy treatments were blastic transformation (n = 8), accelerated phase (n = 4) and patients who were considered too weak to receive further heavy treatment (n = 38). The majority of the patients receiving chemotherapy I and II had a major or a complete cytogenetic response. These 2 courses, therefore, recruited the great majority of patients for autologous SCT (23 and 15, respectively). Only 17 patients received chemotherapy III and 6 of these went to autologous SCT regardless of not having achieved a major or a complete cytogenetic response.

Allogeneic SCT with URD

Figure 4 shows overall survival for 28 patients who underwent allogeneic SCT with URD. Patients selected for this transplantation had no cytogenetic response to IFN + HU or to the intensive cytocourses. In table 2 characteristics of patients undergoing SCT RD or SCT URD are shown. Median age and range were the same in the two groups, while median time from diagnosis to transplantation was much longer in the SCT URD group.

It seems that the outcome after SCT URD is not less good than after SCT RD. It should be pointed out that the URD group probably represents more high-risk patients, since they responded very poorly to IFN.

Autologous SCT

In 29/37 (80%) of the patients the stem cell product was Ph-negative. Forty-six patients underwent autologous SCT (fig. 4). The number of CD34+ cells given was >2 × 10^6/kg. The curve in figure 4 is censored for allogeneic SCT performed in patients after cytogenetic relapse (n = 9). We have so far not registered treatments other than allo-SCT after the cytogenetic relapse. Figure 5 shows the chance of remaining Ph-negative after autologous SCT. Around 20% of the patients remain Ph-negative 10 years after autologous SCT (however, few patients at risk). One of these Ph-negative patients also was negative for BCR/ABL as measured with quantitative PCR. The cytogenetic outcome after SCT was not influenced by the Ph positivity (up to 20%) in the graft. Patients who were incomplete cytogenetic responders in bone marrow and were autotransplanted seemed to have a less favorable cytogenetic outcome compared to those autotransplanted in complete cytogenetic remission. Figure 5 also shows that around 35% of patients had a cytogenetic relapse already at the first analysis after autologous SCT. There was no procedure-related mortality after autologous SCT. Recovery of platelets to >20 × 10^9/l and hemoglobin to >90 g/l was faster after BSC-transplantation compared to bone marrow transplantation (data not shown).

Overall Survival for All Registered Patients

No secondary leukemias or other malignancies were reported in any of the patients surviving long-term. As shown

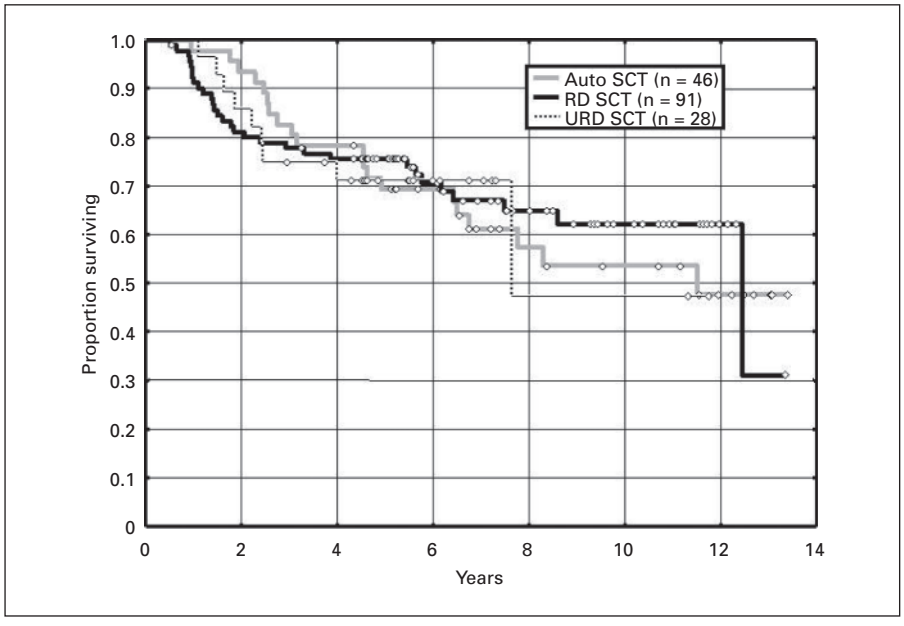

Fig. 4. Survival (from diagnosis) after auto-SCT, SCT RD and SCT URD.

in figure 6, the median overall survival for all patients included is around 8 years. In figure 6 the outcome for the same age group of patients in a previous Swedish CML study comparing busulfan with HU is also shown. In that study, age-matched patients had a median survival of 3.5 years (sibling donor transplants were included). Comparing nontransplanted patients from the two time periods also shows a better outcome for the intensively treated group (data not shown). Thus, the outcome for the CML patients might have improved in the present study compared to the outcome in the historic busulfan-HU study. The influence of prognostic factors could not be studied.

Discussion

There are several treatment possibilities for CML. Palliative treatment only gives symptom relief but practically no prolongation of time to blastic crisis [1, 2]. IFN prolongs overall survival [13–17] but has pronounced side effects. Autologous SCT also reduces tumor mass substantially for a long time. Its clinical value is, however, not known. The only way known at present to cure CML is allogeneic SCT [4–8].

The rationale for the present study was that a treatment leading to a significant reduction of the malignant

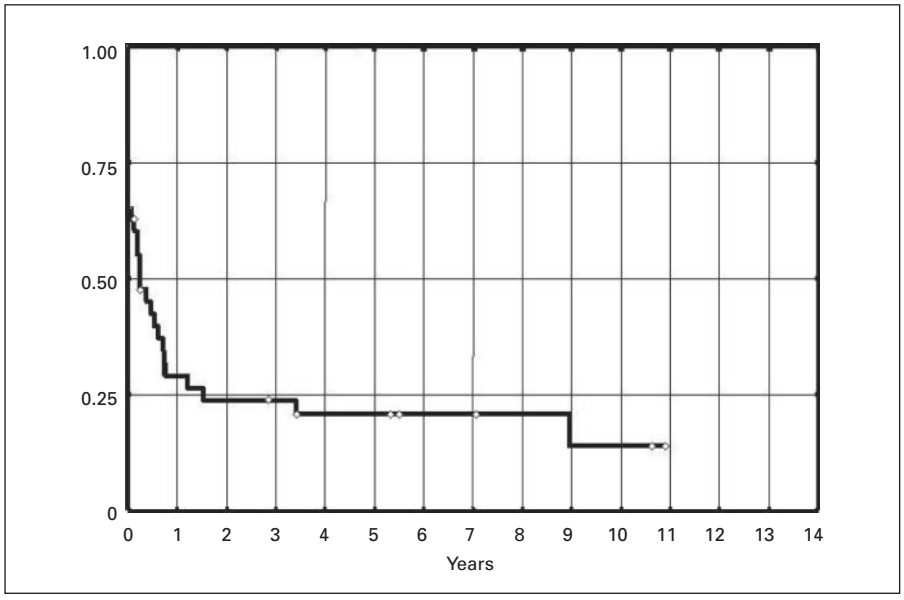

Fig. 5. Chance to remain Ph-negative after auto-SCT.

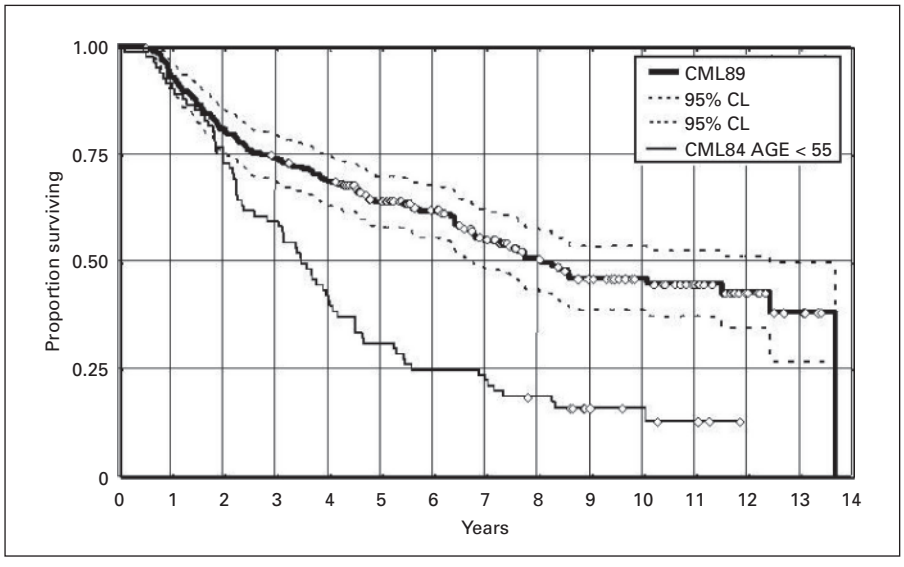

Fig. 6. Overall survival of all 251 patients included compared to 80 patients of corresponding age treated with busulfan or HU (CML 84). CL = Confidence limit.

clone in CML might prolong the time to blastic crisis and thereby also prolong overall survival.

We decided in 1989 to select relatively young (<56 years) CML patients for a more aggressive therapy to achieve a significant tumor reduction. Patients with an identical sibling donor had if possible an allotransplantation soon after diagnosis. The remaining patients received intensive chemotherapy. A cytogenetic response after 6 months IFN + HU was found in 56% of patients. This is comparable to the outcome of IFN treatment in other studies [13–17]. A dose reduction of IFN because of side effects had to be done in about half of the patients. Some of the patients responding poorly to IFN + HU or the 1–3 intensive courses were selected for allo-SCT URD. Patients becoming Ph-negative on IFN + HU or on any of the chemotherapy courses were autotransplanted.

The outcome for allo-SCT seems to be similar for transplantation with RD or URD. It should be stressed that the URD-transplanted patients might represent a worse-prognosis group (due to poor IFN response). The chance for a long-time survival was around 60%. Only 46 of 132 patients who were not allotransplanted were autotransplanted. Eleven of these patients had a RD but were not allotransplanted due to a high risk of complications or to a blastic transformation. None of them had autotransplantation. The remaining 75 patients were treatment failures (not enough Ph reduction, death due to complications of intensive chemotherapy, metamorphosis or other severe side effects of treatment). The survival in the auto-SCT group seems to be the same as reported earlier [10], but it should be recognized that patients in this treatment group were highly selected, precluding any solid conclusion about the clinical value of this treatment.

The overall survival for the patients in the present study is better than for age-matched historical control patients, who (except for a few allotransplanted patients) received HU or busulfan as symptomatic treatment [20]. A substantial number of these patients also received acute leukemia treatment in blast crisis [21]. It seems that survival in CML has improved with the more intensive treatment approach. Median survival has increased from 3.5 to 8 years. No comparison between prognostic indices was included. This survival advantage is in part due to the outcome from allogeneic SCT and to a minor part to autologous SCT. Compared to palliative treatment the intensive regimen in the present study gives considerable more side effects (IFN, intensive chemotherapy, SCT). It might be argued that these side effects may be a price well worth paying to achieve a better survival. We have, however, not measured the quality of life of our patients, so this is just speculation.

What then is the treatment of choice for CML? Imatinib (Gleevec, Glivec, Novartis, Switzerland) has recently shown impressive responses in the chronic phase [22, 23]. This drug might improve the treatment algorithm of CML. Since not all patients respond to imatinib and since some develop a resistance to this drug, there is still room for other therapies. For this reason it is of value to know that intensive chemotherapy seems to give better survival than palliative treatment, at least in the younger patients.

Several studies [24–26] have shown that it is possible to perform BSC harvest (G-CSF mobilization) in imatinib-treated patients. The success rate is 40–90%. The outcome is even better if the harvest is performed during imatinib withhold. The experience of autologous SCT with BSC harvested during imatinib treatment has so far been limited. Meng et al. [27] have, however, reported in 2 patients a successful take with BSC harvested after intense cytotherapy (as in the present paper) and G-CSF.

A plausible treatment algorithm for patients not eligible for allo-SCT thus could be imatinib (or imatinib combined with IFN or Ara-C), with BSC harvest at complete cytogenetic response (or best cytogenetic response) to be used for auto-SCT in case of imatinib treatment failure. Obviously either intensive chemotherapy and/or G-CSF could be used for the mobilization procedure.

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