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ANTI-TUMOUR TREATMENT

Autologous stem cell transplantation in chronic myeloid leukaemia: A meta-analysis of six randomized trials

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KEYWORDS
Autologous stem cell transplantation; Chronic myeloid leukaemia; Randomized meta-analysis

Summary *Rationale:* A number of collaborative trial groups developed prospective randomized trials to compare autologous stem cell transplantation (ASCT) with non-transplant therapy (interferon-α alone or in combination) for chronic myeloid leukaemia (CML) with the aim of obtaining reliable evidence on the possible benefit of ASCT. With the arrival of tyrosine kinase inhibitors, notably imatinib, these trials closed early without reaching their recruitment targets and no trial was able to address its objectives. Following discussions with the principal investigators, it was agreed that a meta-analysis be performed to attempt to determine the effect of ASCT on the main outcomes.
Objectives: To establish the effect of ASCT followed by interferon-αcompared with interferon-α only.
Findings: There was no evidence of a difference in survival; odds ratio = 0.99 (95% confidence intervals = 0.67—1.46). Nor were there statistically significant differences between treatment groups in best haematological or cytogenetic response achieved in the first year. It was not possible to analyse whether autografting with predominantly Philadelphia negative cells early on in the disease resulted in a better outcome.
Conclusions: The results do not suggest a role for ASCT in initial treatment for CML, but it may still merit investigation in patients resistant to tyrosine kinase inhibitors.

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Introduction

Autologous stem cell transplantation (ASCT) has been evaluated in a number of phase I studies for the treatment of chronic myeloid leukaemia (CML). Initially it was used for patients who had transformed to blast crisis and was sometimes successful in establishing a short-lived second chronic phase.[1] Subsequently, it was postulated that an autologous transplant could be a strategy to decrease the leukaemic cell mass and possibly restore sensitivity to biological response modifiers such as interferon-α (IFN). IFN was the first drug shown to produce sustained reductions in the numbers of cells with the Philadelphia chromosome abnormality which characterizes chronic myeloid leukaemia (CML), and was subsequently shown to prolong the survival of patients with CML and became the standard treatment.[2] In the 1990s a number of series were reported of autologous stem cell transplantation using protocols which attempted to mobilise Philadelphia chromosome (Ph) negative stem cells following a variety of chemotherapeutic regimens.[3,4] Subsequently, it was shown that when mobilisation was carried out in patients early after diagnosis up to 75% of patients would achieve a major or complete cytogenetically negative harvest. In a proportion of patients polyclonal Ph negative haematopoiesis was observed following transplantation using these cells and transplant mortality was low.[5] Other purging approaches include that piloted by the Vancouver group using bone marrow cultures although only 30% of newly diagnosed patients were suitable for this procedure.[6]

Retrospective registry analyses in Europe and America show that overall 60—70% of CML patients receiving autologous transplants are alive at 5 years.[7,8] In the registry analyses the survival of patients is not influenced by the source of cells (bone marrow versus blood), purging, conditioning regimen or the presence of cytogenetic conversion before ASCT.

In the absence of any clear cut evidence for the efficacy of this approach, a number of European and US collaborative trial groups were motivated to develop prospective randomised trials to explore further the role of ASCT. In general these studies attempted to compare ASCT with the best non-transplant therapy, either IFN alone or IFN and cytosine arabinoside (ara-C). (A randomized trial from the French collaborative group including 721 patients demonstrated that adding low dose ara-C to IFN increased both haematological and cytogenetic response rates, and suggested an improvement in survival.[9] However, the survival benefit has not been confirmed by other trials.)[10—13] Some of these studies of ASCT also evaluated the role of in vivo purging strategies. However, with the advent of tyrosine kinase inhibitors (TKI), and imatinib in particular, and the finding that it produced much higher rates of cytogenetic response than had been achieved with any other treatment, these trials closed prematurely due to falling recruitment rates. Hence no single trial would be able to answer the question as to the role for ASCT in the treatment of CML. However following discussions with the principal investigators of each study, it was agreed that a meta-analysis be performed to attempt to determine the effect of autograft on the main outcomes, as had been successfully done previously for interferon by the CML Trialists' collaborative group.[2] It was also hoped that the analysis might give useful information on the effect of imatinib given post ASCT.

Materials and methods

To ensure a complete picture was obtained, avoiding possible bias due to selection of particular trials, electronic searches of medical literature and trial registration databases and hand searches of international meeting abstracts were carried out.

For each study, data were centrally collected on each patient, including:

(a) Allocated treatment, (b) characteristics and main outcomes (gender, dates of birth, diagnosis, randomization, and death or last follow-up, best haematological status and best cytogenetic response achieved in the first year from randomization, and disease status at 12 months), (c) clinical details at diagnosis (white blood count (WBC), haemoglobin, percent blasts, basophils and eosinophils in the blood, platelets and spleen size), (d) autograft treatment details (date of transplant, type of autograft done, number of cells reinfused, dates of neutrophil and platelet recovery, and whether interferon was given), (e) control arm treatment details (maximum interferon dose and dose of ara-C if given), (f) other treatment given (whether imatinib was given, and date started, and dates of any non-protocol transplant of any sort). Information on each trial was also collected, including copies of the protocols.

Data were checked for possible imbalances between treatment arms in randomization or follow-up, for internal consistency, and against any reports available. Tables were produced and sent to trialists for checking, along with queries, and problems were sorted out by discussion.

Statistical analysis

Logrank analyses by allocated treatment were done separately for each trial and the resulting observed minus expected ($O - E$) and variance (V) were added and used to obtain an overall death rate ratio, or odds ratio, by the one-step approximation $\exp[(O - E)/V]$.[12,15] For the main outcome, death, time to event analyses were done. Descriptive curves were drawn using $O - E$ and V calculated for periods of a year and the average survival.[14] Best haematological and cytogenetic responses in the first year were analysed as the binary variables complete haematological response, any haematological response (complete of partial), complete cytogenetic response, and major cytogenetic response (including complete response).

Details of trials

The following prospective randomised trials were included in the analysis:

1. Societe Francaise de Gree de Moelle (SFGM): Protocole LMC 94.
2. Societe Francaise de Gree de Moelle (SFGM): Protocole LMC 97.
3. Medical Research Council (MRC) and Eastern Co-operative Oncology Group (ECOG) Joint Trial (CML IV, E7995).

4. Süddeutsche Hämoblastosegruppe (SHG) CML Study IIIA.[16]
5. European Group for Blood and Marrow Transplantation (EBMT)-MRC-ECOG Joint Trial (CML 2000).
6. Grupo Espanol de Transplante Hemopoyético (GETH) LMC-001 Study.

Table 1 summarises the trials in terms of initial therapy administered, the comparator arms (with doses of IFN given), mobilisation and conditioning regimens. Table 2 summarises the primary end points, frequency of monitoring and response criteria used.

Two trials used IFN alone as the control arm, one used IFN plus ara-C, and in three ara-C was optional. Most trials randomized early after diagnosis, but the MRC-ECOG trial included a three month period of IFN before randomization, and patients who had a major cytogenetic response were not eligible for randomization. As regards source of stem cells, in the French SFGM studies unmobilised stem cells were used, but in the remaining four studies (MRC-ECOG, SHG CML IIIA, EBMT-MRC-ECOG, GETH LMC-001) attempted mobilisation of Ph negative stem cells was evaluated. This was optional in the two (EBMT-)MRC-ECOG collaborative trials.

The GETH trial randomised using a list held in the principal investigator's centre. All other trials randomized through a central office. All trials aimed at balance between treatment allocations by using stratified randomisation, either by centre, or by trial group (MRC, ECOG or EBMT). In addition, the German trial used balanced blocks, SFGM stratified by Sokal risk, and the (EBMT-)MRC-ECOG trials used minimization over several prognostic factors.

Cytogenetic responses analysed were all based on the examination of at least 10 metaphases, and for the GETH and SFGM trials at least 20.

Results

Table 3 summarises the patient characteristics and median period of follow up within each trial.

A total of 416 patients were randomized with a median follow-up of 4.4 years (Table 1). Sokal status was unknown for 27 patients. For the remainder, 38% were low risk, 35% intermediate risk, and 27% high risk.

There was no evidence of an effect on survival, with an odds ratio of 0.99 (95% confidence interval (CI) = 0.67—1.46) (Figs. 1 and 2), and a survival difference at 4 years of 2.1% (standard deviation (SD) = 4.7%). There was no evidence for any different effect in any particular trial, nor for age or gender subgroups. The most favourable effect was in the high risk group, but a formal test for trend over Sokal risk groups was not statistically significant ($p = 0.1$). No evidence of a trend was seen for haematological or cytogenetic responses.

Compliance

All transplants were assumed to be in chronic phase unless there was a date of accelerated phase or blast crisis before the date of transplant. 156 (72%) of those randomised to autograft received it, while 14 (7%) of those randomised to the control arm crossed over and were also autografted in chronic phase. Of the 64 remaining patients randomised to autograft, 3 received a transplant from a related donor (MRD), and 14 from a matched unrelated donor (MUD), while still in chronic phase. In the control arm, 4 patients had a MRD, and 14 a MUD. In addition, a small number of patients in the autograft arm who received an autologous transplant, later had an allogeneic transplant while apparently still in

Table 1 Trial details: protocol treatments

Trial identifier	Pre-randomisation treatment	Control arm	Transplant arm	
			Mobilisation	Conditioning
SFGM LMC94	IFN	IFN max 5 MU/m^2/d	None	HBuMel
MRC-ECOG	IFN for 3 mths, then must be >35% Ph + ve	IFN 5 MU/m^2/d or IFN 3 MU 5 d/wk (randomised in MRC patients)	None or IdAC	HBu
SFGM LMC97	Hu	Hu until WBC < 10, then IFN 5 MU/m^2/d + AraC from d15, 10 d/mth	None	HBuMel
German CMLIIIA	Hu or IFN	Hu until WBC < 20, then IFN 5 MU/m^2/d; AraC (optional) from d15, 10 d/mth	Mini-ICE or HHu	HBu
EBMT-MRC-ECOG	Hu recommended, IFN allowed	IFN 3MU 3 d/wk, escalating to 5 MU/m^2/d; AraC (optional) from d15, 10 d/mth	Mini-ICE or HHu or Ara-C or none	HBu
GETH LMC-001	Hu	IFN 1MU/d escalating to 5 MU/m^2/d; AraC (optional) from d15, 10 d/mth	Mini-ICE or HHu	HBu

d = day, wk = week, mth = month Hu = hydroxyurea; IFN = interferon; AraC = cytosine arabinoside, Ida = idarubicin, Bu = busulphan.
Mobilization: IdAC = Ida 8 mg/m^2 iv days 1—2, AraC 200 mg/m^2 iv days 1—5.
Mini-ICE = Ida 8 mg/m^2 iv days 1—3, AraC 800 mg/m^2 iv days 1—3, Etoposide 150 mg/m^2 iv days 1—3.
HHu = Hu 2 g/m^2 oral days 1—14 increased by 1 g/m^2 daily days 15—28 to neutrophils <1.0 × 10^9/l or platelets <20 × 10^9/l.
Conditioning: HBu = Bu 5 mg/kg days 1-4; HBuMel = Bu 4 mg/kg days 1—4, melphalan 140 mg/m^2 day5.

Table 2 Trial details: Response criteria and frequency of assessments

Trial	1° End point	Frequency of assessments in 1st year			Response criteria (cytogenetic)		Other
		Haematological	Cytogenetic				
MRC-ECOG	Overall survival (OS)	(1) At Dx (2) As required for adjustment of dosage of HU and α-INF (3) At three months from registration (4) As for cytogenetic assessment (5) If receiving autograft, FBC at 1 and 3 months post-auto	(1) At Dx (2) 3 mths from registration If α-IFN (3) 6 and 9 mths (4) 12 mths (5) 18 and 24 mths then yearly from registration	If autograft (3) 1 month post auto (4) 3 mths post auto then as per α-IFN	Not defined		
EBMT-MRC-ECOG	(1) OS (2) Time to BC and/or AP	(1) Dx (2) As (2) Above (3) Every 3 months from registration for 1st year and every 6 months thereafter If autograft- monitor for haemopoietic response with each step of IFNα dose escalation post-auto, then as above in (3)	(1) Dx (2) Every 3 months from registration for 1st year (3) Six monthly thereafter If autograft − 3 months post autograft for 1 year and then 6 months thereafter		0 ph-ve 1—32% Ph-ve 33—65% Ph-ve 66—99% Ph-ve 100% Ph-ve <10 metaphases	No response Minimal resp Minor resp Major resp Complete resp Not evaluable	BCR-ABL mRNA transcript levels monitored centrally
German CML IIIa	OS	(1) Study entry (2) 3 months until 3 years post-diagnosis (3) 6 months from 3 years after diagnosis (4) IFNα antibody assay if no response to IFN Rx or increasing WBC on IFN Rx (5) If CHR achieved, additional Haem assessment	(1) Same as haem but additional BM cytogenetics if achieve CHR before planned follow up (2) Following allo or auto BMT − 3 monthly (3) Additional BM histology every 12 months (see p. 27, version October 1997)		0—4% Ph-ve 5—34% Ph-ve 35—65% Ph-ve 66—99% Ph-ve 100% Ph-ve	Failure Minimal resp Minor resp Partial resp Complete resp	(1) Southern Blot for BCR-ABL translocation prior to treatment and every 3 months until 3 years post-diagnosis, then every 6 months (2) Multiplex PCR prior to Rx (3) Additional PCR for responders to Rx
SFGM LMC'94	(1) Cytogenetic response (2) Overall survival	(1) At Dx (2) Monthly	(1) At Dx (2) 3 months for 1st year, then 6 months thereafter If autograft as above but also immediately pre-transplant		0 ph-ve 1—64% Ph-ve 65—99% Ph-ve ⩾65% Ph-ve 100% Ph-ve	No response Minimal resp Partial resp Major resp Complete resp	All patients receive interferon. Those patients achieving CHR at 3 months stay on α-IFN. If not, randomised to autograft or not with cells collected at diagnosis. Interferon restarted post auto

SFGM LMC97	Cytogenetic response	(1) At Dx (2) Monthly	(1) At Dx (2) 3 months (3) 6 months (4) 15 months(Every 3 months if possible, at 6 and 15 months obligatory)	post randomisation	O ph-ve 1—64% Ph-ve 65—99% Ph-ve 100% Ph-ve >65% Ph-ve	No response Minimal resp Partial resp Complete resp Major resp
GETH CML 001	(1) Overall Survival (2) Time to develop blast crisis	(1) As required for monitoring of HU therapy/ cytoreduction (2) As required for each phase of IFNα dose escalation (3) Every 3 months post therapy	(1) At Dx (2) 3 monthly in 1st year (3) 6 months thereafter (both arms)		''Houston criteria'' (Ref. *Br J Haematol* 1986;**64**(1):87—95) Essentially the same as that in the SFGM trials	

Table 3 Trial start dates, numbers randomised and main patient characteristics

Trial identifier	Year started	Total randomised	Males (%)	Median age (range)	Sokal group				Median follow-up (years) (range)
					Low	Int.	High	Unknown	
SFGM LMC94	1995	26	16 (61%)	47 (26—64)	5	12	9	0	5.8 (1.3—8.0)
MRC-ECOG	1996	81[a]	50 (62%)	48 (24—60)	31	25	22	3	5.5 (0.2—8.3)
SFGM LMC97	1997	128[b]	77 (60%)	47 (20—65)	57	47	24	0	3.5 (0.3—5.6)
German CMLIIIA	1997	86	59 (69%)	50 (18—65)	32	25	17	12	5.3 (0.9—7.9)
EBMT-MRC-ECOG	1999	71	42 (59%)	49 (19—65)	22	23	26	0	3.5 (0.1—5.6)
GETH LMC-001	1999	24[b]	16 (67%)	49 (21—62)	3	3	6	12	4.6 (2.6—6.5)
Total		416	260 (62%)	49 (18—65)	150	135	104	27	4.4 (0.1—8.3)

[a] 1 (autograft) patient in the MRC-ECOG trial had diagnostic data but no follow-up, and so contributes only to the denominators.
[b] 5 (3 autograft, 2 control), 7 (4 autograft, 3 control) patients in SFGM LMC97 and GETH LMC-001, respectively, were excluded.

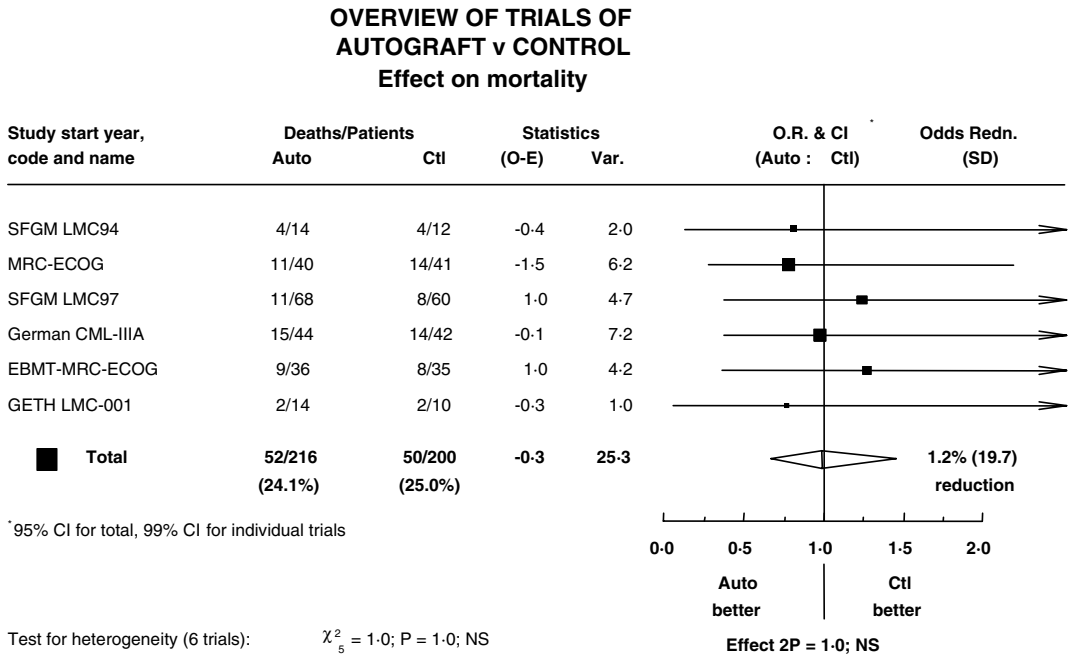

Figure 1 Effect on mortality of autograft versus control. The numbers and the odds ratio of autograft versus control with confidence intervals are shown for each trial, and overall. $O - E$ = observed minus expected; OR = odds ratio; CI = confidence interval.

chronic phase, 3 MRD and 8 MUD. Censoring at allogeneic transplant in chronic phase did not make any material difference to the result: odds ratio = 0.98 (95% CI = 0.64—1.52).

When imatinib became available, some patients were taken off protocol and treated with this. As this was naturally not foreseen, data collection forms did not ask for information on imatinib and this was collected retrospectively and so may be somewhat incomplete. 111, 121 patients in the autograft, control arms, respectively, are known to have received imatinib. For 105, 113, respectively, the date of starting imatinib is known, and 84, 89 of these received it while still in chronic phase. The median time (and range) from randomisation to receipt of imatinib in chronic phase was 2yrs 3mths (2mths—6yrs 8mths) for the autograft arm, and 1yrs 9mths (3mths—5yrs 7mths). Censoring at imatinib given in chronic phase did not make any material difference to the results: odds ratio = 0.85 (95% CI = 0.56—1.29).

Autograft details

Among the 156 patients randomised to autograft who received it in chronic phase, all had IFN pre-transplant in MRC-ECOG & SFGM LMC94, 2 in EBMT-MRC-ECOG, 5 in SHG CML IIIA, and none in SFGM LMC97 & GETH LMC-001, giving a total of 41/156 given IFN pre-transplant. 135 patients received interferon at some time after their transplant. 71 transplants were mobilised, 79 not, and 6 combined. Of the 77 mobilised or combined transplants, the mobilisation used was 44 Mini-ICE, 10 hydroxyurea, 21 IdAC, and 2 unknown. The median number of mononuclear cells reinfused was 5×10^8/kg (range = 1—323), and of CD34 cells reinfused was 6.8×10^6/kg (range = 0.1—510.0). Neutrophil recovery to 0.5×10^9/l took a median of 14 days (range = 2—149).

Responses

There were more complete haematological responses in the first year in the autograft arm (66% versus 60% in 201, 183 evaluable patients, respectively), but this was not statistically significant ($p = 0.2$), nor was the effect of autograft on response in any particular trial or subgroup different from the overall average.

Thirty-four Patients achieved a complete cytogenetic response during the first year from randomisation, and another 62 had a major response. Among 180, 158 patients evaluable for cytogenetic response, there were somewhat more patients with a complete or major response in the autograft arms (31% versus 25%), but this difference was not statistically significant (odds ratio = 0.75; 95% CI = 0.47—1.20; $p = 0.2$), nor were there significantly different effects from the average in particular trials.

Discussion

This meta-analysis shows that patients receiving an autograft achieved haematological remissions more frequently, and a greater number achieved a major or complete cytogenetic response than those treated in the control arm. However, neither of these observations achieved statistical significance, and in terms of the primary end point of survival, no benefit was apparent. The trend in cytogenetic response is in keeping with previous observations that autografting, even with unpurged bone marrow, could lead to Ph negative haematopoiesis.[8,17] Unfortunately it was not possible from the available data to evaluate whether autotransplantation improved the degree of cytogenetic response in the patients receiving this therapy, nor was it

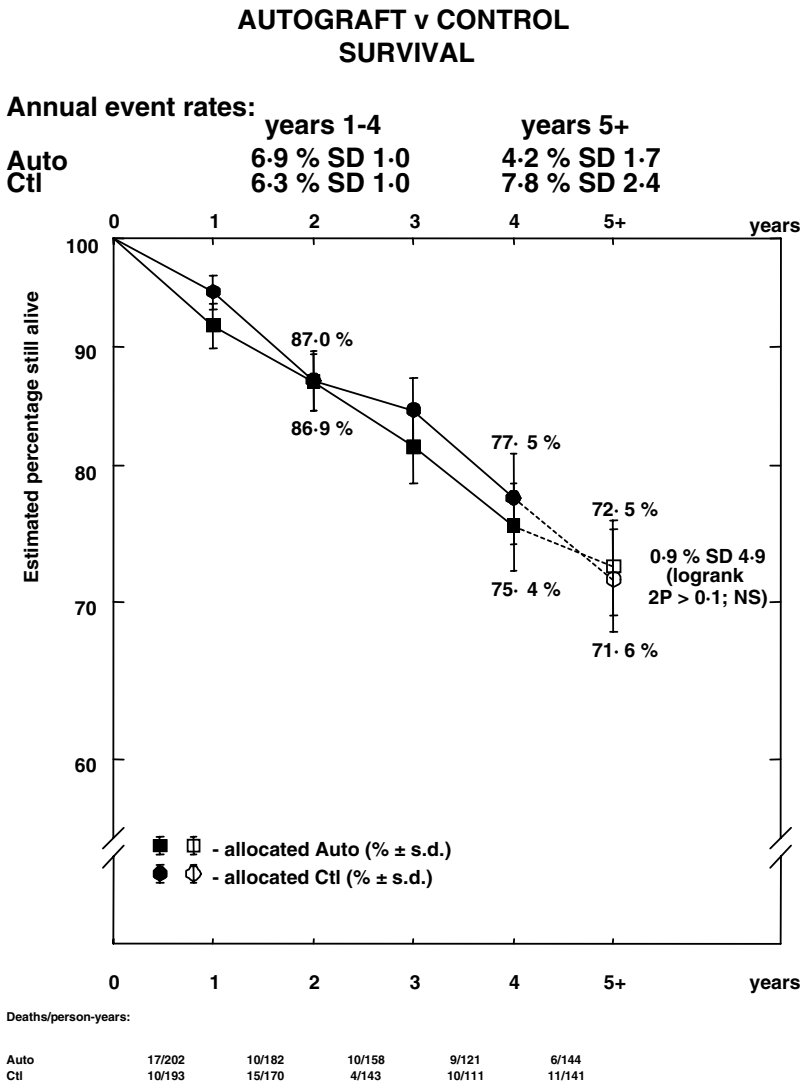

Figure 2 Descriptive survival curve of the effect of autograft on mortality. Descriptive curves based on annual observed and expected event rates and their variance show the effect of autograft on survival out to 5 years.

clear what proportion of patients achieving these better cytogenetic responses had undergone transplantation with mobilised stem cells, and if they had, whether the re-infused cells were predominantly Ph negative. In the absence of this information, this analysis does not shed any further light on whether the re-infusion of mobilised Ph negative stem cells produces better responses than unmanipulated autografts, as the evidence from Genoa would suggest. A more clear cut benefit for autotransplantation might have been apparent if it had been possible to analyse the outcome for patients transplanted early in their disease with predominantly Ph negative cells, as reported by Carella et al.[5] Equally the effect of in vivo purging with pre-harvest IFN on transplant outcome could not be evaluated.

In considering autologous transplantation, the evidence suggests that the selection and engraftment of a 'benign' progenitor population from the re-infused cells is unlikely by itself to establish durable haematological or cytogenetic remissions without 'ongoing biologic, pharmacologic or immunologic therapy' to actively suppress expansion of malignant clones.[18] There is some evidence that IFN given post autograft to patients achieving a complete cytogenetic response may have a role in maintaining response,[18] and there are anecdotal reports of patients improving their response to IFN therapy over that achieved when the drug was given pre-transplant. Although nearly 50% of the ASCT patients in this study received IFN post transplant, there was not enough data to explore this premise further.

The emergence of TKI therapy, notably with imatinib, has revolutionised the treatment of CML. In newly diagnosed patients one can expect event free survival (EFS) rates of 83% at 60 months, overall survival (OS) of 89% and an 87% probability of achieving a complete cytogenetic response.[19] Although rates of progression are small, a significant minority of patients display either primary resistance, or develop resistance due to the acquisition of bcr-abl kinase mutations. Various strategies have been proposed for overcoming resistance, including cytoreductive therapy. It is interesting to note that no difference in survival was noted between the control arm and autografted

patients who subsequently received imatinib. However, it is likely that there would be a selection bias in choosing patients with more advanced disease for early evaluation of imatinib therapy in the time period covered by this analysis and hence no firm conclusions can be made. Increasingly, patients achieving a complete cytogenetic response on imatinib are asking whether they should have a stem cell harvest of their Ph negative stem cells. Several studies have reported that this can be successfully carried out with G-CSF mobilisation, achieving adequate numbers of CD 34+ cells in 50–70% of patients.[20,21] The ability of such TKI in vivo purged cells to successfully engraft following myelosupressive therapy is not clearly established, with only one case in the literature of successful re-establishment of Ph negative haematopoiesis in a patient autografted after entering blast crisis having previously achieved a complete cytogenetic response (CCyR) on imatinib.[22]

In conclusion, in the absence of clear evidence of benefit in terms of survival, cytogenetic response or improved response to IFN, this meta-analysis does not demonstrate any benefit for performing auto SCT in the initial treatment of CML. The fact that many control arm patients will have received imatinib may of course have masked any benefit. However, the role of auto SCT in the management of patients resistant to current first line therapy with a TKI is unknown and worthy of further evaluation in suitably designed clinical trials.

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