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Systematic review of high dose chemotherapy and autologous haematopoietic stem cell transplantation for chronic lymphocytic leukaemia: what is the published evidence?

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Summary

Despite improved responses, chronic lymphocytic leukaemia (CLL) remains incurable with conventional chemotherapy. Patients with poor-risk factors or who fail conventional chemoimmunotherapy are offered autografts, preferably after achieving remission. This report presents the totality of evidence through a systematic review that assessed the efficacy of autografts in CLL. A search of MEDLINE databases from 1966–2006 and hand-search of references identified 82 prospective-randomized, non-randomized comparisons or single-arm trials, of which only nine met our inclusion criteria: two trials were funded by public/government, one by private foundations, one jointly by private/public, and was unclear in five. No randomized controlled trials comparing autografts *versus* conventional chemotherapy (or chemoimmunotherapy) were found. Six studies were single-arm and three were non-randomized with a control-arm (autologous *versus* allogeneic). Overall, 361 patients were enrolled, but only 292 were transplanted. Transplant-related mortality ranged from 0% to 9%. Complete responses ranged from 74% to 100% and molecular responses ranged from 57% to 88%. Overall survival ranged from 68% at 3 years to 58% at 6 years. It is uncertain whether autograft is superior to conventional therapy. The high incidence of myelodysplastic syndrome (9–12%) is particularly concerning in CLL, where median survival is 9 years.

Keywords: systematic review, chronic lymphocytic leukaemia, autologous haematopoietic cell transplantation, outcome, response rates.

B-cell chronic lymphocytic leukaemia (B-CLL) is the most common leukaemia diagnosed in the Western hemisphere (Jemal *et al*, 2006). In the majority of cases, the disease is characterized by an indolent course that requires no immediate treatment, while in others CLL progresses rapidly even with aggressive therapy (Rai *et al*, 1975; Binet *et al*, 1981). The availability of modern prognostic factors, and more effective chemotherapy and immunotherapy, are challenging the 'watchful-waiting' approach that has characterized the treatment of CLL. The prognosis of CLL is poor in the presence of chromosomal aberrations, such as 17p- and 11q-, unmutated status of the variable region of the immunoglobulin heavy chain gene (*IGHV@*), or increased expression of zeta-associated protein 70 (ZAP-70) or CD38 (Fais *et al*, 1998; Dohner *et al*, 2000; Ibrahim *et al*, 2001; Rassenti *et al*, 2004; Chiorazzi *et al*, 2005). Despite significant progress in our understanding of the disease biology, and development of more targeted pharmacological therapies, CLL remains incurable with standard treatments (Cheson, 2006; Yee & O'Brien, 2006).

High-dose chemotherapy (HDCT) and autologous haematopoietic stem cell transplantation (auto-HCT) has been utilized to treat patients with CLL across various stages of the disease. Encouraging clinical and molecular remissions (MR) have been reported after auto-HCT, even in patients with poor prognostic features (Ritgen *et al*, 2003; Dreger *et al*, 2004; Gribben *et al*, 2005). A risk-matched comparison of auto-HCT *versus* conventional chemotherapy showed a survival benefit for poor-risk CLL patients treated with HDCT

and auto-HCT (Dreger *et al*, 2004). However, conclusive evidence related to using, or not using, auto-HCT in CLL patients has not been presented before. Therefore, the objective of this study was to present the totality of the evidence by conducting a systematic review to assess the efficacy of auto-HCT in the treatment of CLL, and accordingly, key questions were formulated.

Material and methods

A systematic and comprehensive search of the literature was performed using MEDLINE databases from 1966 to September 12, 2006 and a hand search of references. The following terms were used to identify potential studies: ['Leukaemia, Lymphocytic, Chronic' (Medical Subject Headings, MeSH) OR 'Leukaemia, B-Cell, Chronic' (MeSH)] AND ['Clinical Trial' (Publication Type) OR 'Clinical Trials' (MeSH) OR 'Controlled Clinical Trial' (Publication Type) OR 'Clinical Trial, Phase III' (Publication Type) OR 'Clinical Trial, Phase II' (Publication Type) OR 'Clinical Trial, Phase I' (Publication Type) OR 'Meta-Analysis' (MeSH)] AND ['Transplantation' (MeSH) OR 'transplantation' (Subheading) OR 'haematopoietic Stem Cell Transplantation' (MeSH) OR 'Bone Marrow Transplantation' (MeSH) OR 'Peripheral Blood Stem Cell Transplantation' (MeSH) OR 'Stem Cell Transplantation' (MeSH)].

Studies were included if they were prospective-randomized, non-randomized or single-arm trials. To minimize bias in the results, we restricted our eligibility criteria to prospective studies available as full publications only. We did not include trials published in abstract form because the quality of the trial cannot be judged from the abstract, and have limited data compared with the papers published in full (von Elm *et al*, 2003; Eisen *et al*, 2004). Our search was also limited to using publications in the English language only. Data were extracted on primary outcomes [e.g. response rates (clinical and/or molecular), survival (overall survival, disease-free survival, event-free survival, etc.)].

Results

Our search identified 82 publications, of which only nine publications met our predetermined inclusion criteria (Fig 1): two trials were funded by public/government sources, one by private foundations, one was funded jointly by private and public resources and in the remaining five studies the sources of funding were unclear. We did not find any randomized controlled trial evaluating auto-HCT in CLL. We formulated four key questions related to auto-HCT in CLL. It is important to note that, because of heterogeneity in the design of studies discussed herein, the differences in eligibility criteria, and the inconsistency in data reporting among the various trials, we could not perform a meta-analysis.

Is auto-HCT effective in the relapsed/salvage setting?

We found four prospective single-arm studies that evaluated the efficacy of auto-HCT in patients with relapsed/refractory CLL. Pavletic *et al* (1998) evaluated auto-HCT in 16 previously treated patients with CLL with a median age of 49 years (range: 44–60) years and a median number of two (range: 1–3) prior chemotherapy regimens. Twelve (75%) patients received a preparative regimen of total body irradiation and cyclophosphamide (TBI/CY) (CY 60 mg/kg/d for 2 d followed by TBI of 200 cGy twice per day for 3 d). Three patients received a chemotherapy regimen with BEAC (carmustine 300 mg/m^2 on 1 d, etoposide 200 mg/m^2 for 4 d, cytarabine 200 mg/m^2 for 4 d and cyclophosphamide 35 mg/kg for 4 d) and one patient received TBI/CY plus cytarabine. Thirteen (81%) patients received autologous mobilized peripheral blood stem cells (PBSC) and three patients received autologous bone marrow (BM) cells. All patients (100%) achieved complete

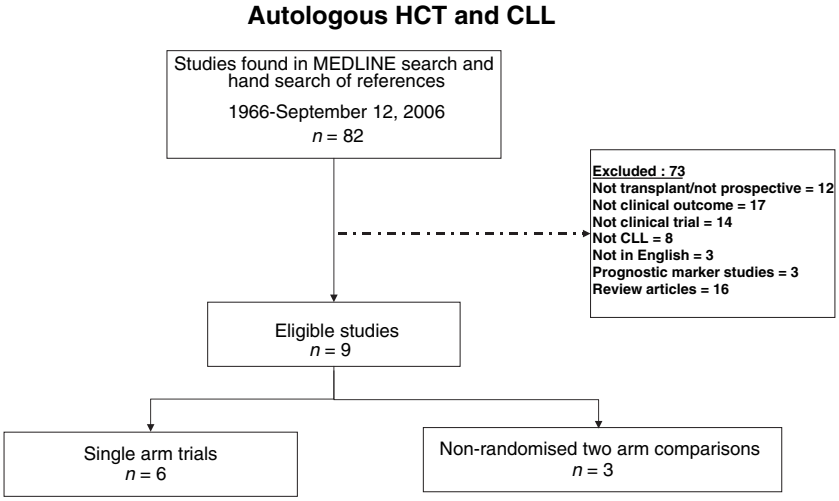

Fig 1. Flow diagram depicting the selection of studies.

remissions (CR) post-transplantation. Ten (63%) patients were alive at a median of 41 months. Five of 10 patients were alive and disease-free at a median of 37 months, while five patients had evidence of relapse. The projected 3-year overall survival (OS) and failure-free survival (FFS) were 68% and 37% respectively. Six (37%) patients died at a median of 13·5 months as a result of the following: disease progression ($n = 3$), acute respiratory distress syndrome during the first month post-transplant ($n = 1$), cerebral haemorrhage ($n = 1$), and secondary marrow failure three years after transplantation ($n = 1$). The investigators suggested that auto-HCT may be more effective when used earlier in the course of disease because drug resistance is less likely to develop, and raised questions about the value of auto-HCT in those who are beyond CR1 even when disease is chemosensitive.

Dreger *et al* (1998) evaluated a sequential treatment strategy consisting of 1–2 cycles of Dexa-BEAM (dexamethasone, carmustine, etoposide, cytarabine and melphalan), mobilization of peripheral PBSC with granulocyte colony-stimulating-factor (G-CSF) at a dose of 5–10 μg/kg s.c./d (from day 8 after starting Dexa-BEAM until last day of collection) and stem cell harvest in 18 patients. The median age of patients was 49 (range: 29–61) years with disease-stages as follows: Binet A = 6 (33%), B = 9 (50%) and C = 3 (17%). The majority, 14 (78%) of 18 patients, were previously treated (median of one prior regimen). After Dexa-BEAM, 16 (89%) patients achieved responses [CR or very good partial responses (very good PR)]. Haematopoietic cell harvests were successful in 14 (PBSC: 11; BM: 3) patients at a median of 2 (range: 1–4) leukaphereses. PBSC grafts were purged by immunomagnetic B-cell depletion using CD19, CD20, CD23 and CD37 monoclonal antibodies (MoAbs) with the MaxSep (Baxter Biotech Division, Munich, Germany). BM grafts were purged by immunomagnetic $CD34^+$ selection via the Isolex 300 system (Baxter immunotherapy Division, Irvine, CA, USA). Thirteen patients received auto-HCT (BM = 3, PBSC = 10) following a preparative regimen of TBI/CY. There were no transplant-related deaths. Ten (77%) of 13 patients were in MR [by polymerase chain reaction (PCR) amplification of CDRIII rearrangements], whereas 12 (92%) patients were in CR at a maximum follow-up of 48 months. The authors concluded that the sequential approach of Dexa-BEAM and auto-HCT is highly effective for treatment of CLL, but longer follow-up is needed to determine if cure is possible with this approach.

A third study by Sutton *et al* (1998) evaluated a sequential salvage approach of ESHAP (etoposide, methylprednisone, high-dose cytarabine and cisplatinum) chemotherapy, a conditioning regimen of TBI/CY and auto-HCT. Twenty patients with relapsed/refractory disease, who had at least two prior regimens including a purine nucleoside analogue-based regimen (mean: 5·6 cycles) were enrolled (male: 15; female: 5) at a median of 4·5 (range: 0·7–9) years from initial diagnosis. Response rates after a median of 4 (range: 3–6) cycles of ESHAP were as follows: CR: 50%, PR: 15%. Sufficient stem cells to undergo autografting were harvested only in eight patients. Six (75%) of eight patients who underwent auto-HCT were alive and in CR at a median of 30 months post-transplant. This study raised concern about the inability to harvest sufficient stem cells in heavily pretreated patients and argued for harvesting stem cells as early as a significant remission is achieved. This study also showed that auto-HCT is capable of inducing clinical remissions even in heavily pretreated patients.

Schey *et al* (1999) evaluated auto-HCT in 10 patients with relapsed ($n = 4$) or previously untreated CLL ($n = 6$). Patients received fludarabine as cytoreductive therapy followed by TBI/CY and $CD34^+$-selected PBSC. Two patients (previously untreated: 1 and relapsed CLL: 1) did not respond to fludarabine and received salvage chemotherapy with FMD (fludarabine, mitoxantrone and dexamethasone) or CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) respectively. Four (67%) of six previously untreated, and two (50%) of four with relapsed CLL achieved a CR after a median of four (range: 2–7) cycles of fludarabine. The remaining two (33%) of six untreated, and two with relapsed CLL achieved a good PR. Two patients did not harvest sufficient cells for CD34 selection and, therefore, received unmanipulated grafts. All patients had molecular evidence of persistent disease by PCR after CD34 selection. CR and MR were achieved, at 3 months post-auto-HCT, in 10 (100%) of 10 patients and seven (88%) of eight patients respectively. However, MR was not long-sustained and relapses were seen at 6–24 months of follow-up. The findings suggested that auto-HCT is capable of inducing MR in patients with CLL, but those responses are not sustained in the majority of cases and relapses are anticipated; these findings have been validated in other non-systematic reviews (Dreger & Montserrat, 2002; Jabbour *et al*, 2004).

Studies analysed herein demonstrated that auto-HCT is feasible in patients with relapsed/refractory CLL and that the procedure is capable of inducing encouraging clinical and molecular responses, *albeit* not long lasting, with a low transplant-related mortality (TRM) (0–6·3%). Selection of patients with advanced disease and extensive pretreatment may have partly contributed to the high TRM observed in some studies. Importantly, success of auto-HCT requires that patients preferably achieve CR prior to initiation of HDCT (Montserrat *et al*, 2006). These studies (Pavletic *et al*, 1998; Dreger *et al*, 1998; Sutton *et al*, 1998; Schey *et al*, 1999) do not take into account the effect of modern adverse prognostic risk factors, such as 17p- and 11q- chromosomal aberrations, unmutated *IGHV@*, and increased expression of ZAP-70 or CD38.

Also, auto-HCT needs to be offered at an earlier stage of disease to avoid cumulative toxicity from chemotherapies that may impede harvesting sufficient haematopoietic cells. Purine analogues, such as fludarabine, have been shown to detrimentally affect stem cell mobilization in patients with lymphoproliferative neoplasms (Ketterer *et al*, 1998). Therefore, early stem cell mobilization, once significant CLL debulking is

achieved, may be a reasonable strategy to consider for optimizing stem cell collection and graft quality. Patients should be made aware of the increased risk of developing secondary myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML), which ranges from 9% (at median of 3 years) up to 12% after 8 years from autografting (Gribben *et al*, 2005).

Should auto-HCT be considered for first-line consolidative therapy in patients with CLL?

Two published studies evaluate the efficacy of auto-HCT as first line therapy for patients with CLL. In the first study, Dreger *et al* (2000) evaluated 20 consecutive patients with poor risk CLL defined as advanced clinical stages (Binet B or C) or Binet A with short lymphocyte doubling time and diffuse marrow infiltration pattern plus elevated serum thymidine kinase and B-2 microglobulin respectively. Following pretreatment with conventional chemotherapy, such as CHOP or fludarabine, patients received 1–2 cycles of Dexa-BEAM for additional debulking of disease prior to undergoing mobilization with G-CSF. Harvested PBSC were purged with double B-cell depletion using immunomagnetic $CD34^+$ selection (Isolex 300i; Nexell, Irvine, CA, USA) followed by a negative step with anti-CD19/20/23/37-labelled immunomagnetic beads. Myeloablative therapy consisted of TBI/CY. Seventeen (85%) of 20 patients were alive and in CR at a median follow-up of 20 (range: 6–29) months.

A second study (Milligan *et al*, 2005) enrolled 117 previously untreated patients with CLL from 31 centres in the United Kingdom and New Zealand. Induction chemotherapy consisted of fludarabine for 5 d, with further courses repeated every 28 d to induce major responses before proceeding to PBSC mobilization. Responses were seen in 94 (82%) of 115 evaluable patients. However, only 65 (56%) of 115 patients proceeded with conditioning chemo- or chemo-radiotherapy (TBI/CY: 49; BEAM: 11; busulfan/CY (BUCY): 1; Unspecified: 4). TRM was 1·5%. CR rates increased from 37% to 74% after autografts. Of those patients not in CR, 63% entered CR after transplantation. Sixteen (80%) of 20 evaluable patients achieved MR on PCR for *IGHV@* rearrangements within 6 months of transplantation. The 5-year OS and disease-free survival (DFS) rates, from transplantation, were 77·5% and 51·5% respectively. Five (8%) patients who received TBI-based regimens developed MDS at 20–70 months after transplantation.

These findings demonstrated that auto-HCT is feasible as first-line therapy for patients with CLL with minimal TRM. Auto-HCT is capable of inducing significant clinical and MR, but is by no means curative. One may argue that the definition of poor-risk in the study by Dreger *et al* (2000) did not account for the effect of adverse cytogenetic aberrations, such as 17p- and 11q-, or the unmutated status of *IGHV@*. Also, the increased incidence of MDS (8%) seen with TBI-based regimens (Milligan *et al*, 2005) raises concerns about the risks of developing secondary malignancies.

Is allogeneic-HCT superior to auto-HCT in patients with relapsed/refractory disease?

There are no randomized controlled studies that address this specific question. We found three non-randomized comparisons that evaluate autologous *versus* allogeneic stem cell transplantation. Rabinowe *et al* (1993) evaluated the role of T-cell depleted allogeneic BM transplantation (BMT) and auto-BMT as a consolidative therapy in CLL patients with poor prognostic features, defined by diffuse pattern on BM biopsy, abnormal cytogenetics and rapid doubling time (in BM or lymph nodes) within 6–12 months. Eight patients with human leucocyte antigen (HLA)-matched siblings received allogeneic BM cells, whereas 12 patients received an autograft. TBI/CY was the preparative regimen in all patients. Allogeneic recipients received T-cell depleted grafts with anti-T12 (CD6) MoAbs and complement. Recipients of autografts received *in vitro*-purged BM with multiple anti-B cell MoAbs and complement. CR was observed in six (86%) of seven evaluable allo-HCT recipients and 10 (82%) of 12 recipients of auto-HCT. There were two TRM (one recipient of auto-BMT died of diffuse alveolar haemorrhage and one allo-BMT recipient died of pneumocystis pneumonia). This study did not intend to compare the efficacy of auto-HCT *versus* allo-HCT, but to demonstrate feasibility of either approach in patients with poor risk CLL. The definition of poor-risk was based entirely on clinical parameters, not accounting for the adverse effect of modern prognostic markers.

A single institution study by the MD Anderson transplant group evaluated the efficacy (non-randomized) of auto-HCT and allo-HCT in patients with CLL relapsing after fludarabine (Khouri *et al*, 1994). Eleven patients received *ex vivo* purged BM cells (with anti-CD19 and immunomagnetic separation). Allo-HCT was administered in 11 patients {HLA-sibling matched: 9; HLA-mismatched [1 Antigen (HLA-A)]; Syngeneic: 1}. All patients received a preparative regimen of TBI/CY. Graft-versus-host disease prophylaxis consisted of methotrexate and cyclosporine in 82% of allo-HCT recipients. TRM was 9% for the auto-HCT recipients and 9% for the allograft recipients. CR [and nodular CR (nCR)] was 91% in recipients of auto-HCT at 2 to >29 months after transplant. The response rate (CR and nCR) in allo-HCT recipients was 82% at 2 to >36 months after allograft. This study demonstrated that transplantation, autologous or allogeneic, is feasible and capable of inducing CR in patients resistant to fludarabine chemotherapy. These single institution studies were limited by the small sample size (Rabinowe *et al*, 1993; Khouri *et al*, 1994).

A larger study reported long-term follow-up on patients with poor-risk CLL who underwent T-cell depleted allogeneic ($n = 25$) or *ex vivo* purged auto-HCT ($n = 137$) at a single institution (Gribben *et al*, 2005). Ninety-five percent of auto-HCT recipients and 92% of allograft patients had received prior fludarabine-based therapy. TRM at 100 d was 4% for patients who underwent auto-HCT and 4% for allo-HCT

Table I. Summary of clinical characteristics and patient/disease-oriented outcomes of patients with chronic lymphocytic leukaemia undergoing autologous haematopoietic stem cell transplantation.

Studies	Rabinowe *et al* (1993)	Khouri *et al* (1994)	Dreger *et al* (1998)	Pavletic *et al* (1998)	Sutton *et al* (1998)	Schey *et al* (1999)	Dreger *et al* (2000)	Gribben *et al* (2005)	Milligan *et al* (2005)
Summary of findings									
No. participants (*N*) actual transplanted (*n*) *versus* total enrolled (*N*)	12 (12)	11 (11)	13 (18)	16 (16)	8 (20)	10 (10)	20 (20)	137 (137)	65 (117)
Median age, years (range)	45 (27–54)	59 (37–63)	49 (29–61)	49 (34–60)	54 (38–66)	51 (41–63)	51 (39–60)	51 (19–66)	49 (27–60)
Median no. prior therapies (range)	3 (1–4)	3 (1–6)	No prior regimens: 4 patients 1–3 regimens: 14 patients	2 (1–3)	At least 2 regimens	2 (1–3)	1 (1–4)	–	–
Median interval (months) from time of diagnosis to transplant (range)	28 (12–115)	48 (13–198)	–	11 (5–58)	54 (8·4–108)	–	–	46 (7–212)	–
Study design	Non-RCT	Non-RCT	Single arm	Single arm	Single arm	Single arm	Single arm	Non-RCT	Single arm
Conditioning regimens	TBI/CY *ex vivo* purging	TBI/CY *ex vivo* purging	TBI/CY	TBI/CY: $n = 12$; BEAC: $n = 3$; TBI/CY + ARAC: $n = 1$	ESHAP → TBI/CY	TBI/CY	TBI/CY	TBI/CY *ex vivo* purging	Fludarabine based → TBI/CY: $n = 49$; BEAM: $n = 11$; BUCY: $n = 1$; unspecified: $n = 4$
Patient-oriented outcomes									
Overall survival	–	–	–	68% at 3 years (projected)	–	Median survival 22 months (range 6–45 months)	–	58% (at 6 years)	78% (at 5 years)
Disease-free survival	–	–	–	32% at 3 years (projected)	75% (at median of 30 months)	–	–	–	52% (at 5 years)
Progression-free survival	–	55% (2–29 months)	92%*	–	–	–	–	30% (at 6 years)	–
TRM	8%	9%	0%	6% (at 30 d)	0%	0%	5% (at 5 months)	4% (at 100 d)	2%
Disease-oriented outcomes									

CR	83%†	91%‡	–	–	100%	100%	89% (median of 20 months)	–	74%
PR	–	9%	–	–	–	–	–	–	–
Molecular response	–	–	77%*	–	57%	88%	–	–	80%§
Relapse rate	–	–	–	56% (at 3 years)	25% (in two patients at 8 and 19 months)	40% (molecular relapse at 24 months)	–	–	–
Secondary malignancies (MDS/AML)	–	–	–	–	–	–	–	9%	8%

*Maximum follow-up at 48 months
†Assessed at ≤3 months post-transplant.
‡Includes patients with complete response (55%) and nodular response (36%).
§16 of 20 evaluable patients.
RCT, randomized controlled trials; TBI/CY, total body irradiation and cyclophosphamide; BEAC, carmustine, etoposide, cytarabine and cyclophosphamide; ESHAP, etoposide, methylprednisolone high dose cytarabine and cisplatinum; BEAM, carmustine, etoposide, cytarabine and melphalan; BUCY, busulfan and cyclophosphamide; TRM, transplant-related mortality; CR, complete response; PR, partial response; MDS, myelodysplastic syndromes; AML, acute myeloid leukaemia; (-), not reported/not available.

recipients. OS at 6 years was statistically similar for auto-HCT and allo-HCT patients (58% vs. 55%, $P = 0{\cdot}96$). Forty (29%) patients who underwent auto-HCT and six (24%) allo-recipients died from CLL recurrence. It is likely that use of T-cell-depleted grafts in the allo-group, by eliminating the *bona fide* graft-versus-leukaemia (GVL) effect, was responsible for the relatively high relapse rate after allografting. Reduced intensity conditioning (RIC) regimens have been shown to be associated with lower TRM while reasonably preserving the beneficial GVL effect (Schetelig *et al*, 2003; Dreger *et al*, 2005; Sorror *et al*, 2005; Brown *et al*, 2006); but RIC allo-HCT have not been directly compared with auto-HCT to date. MDS/AML developed in 9% and 12% of the auto-HCT recipients at 3 and 8 years respectively. Although TRM was relatively low, the development of MDS/AML is seriously concerning. Auto-HCT again failed to show a plateau in survival curves. Results of these and other studies are summarized in Table I.

Is ex vivo *stem cell purging feasible and does it affect outcome?*

There is no standardized approach for purging haematopoietic cells. *Ex vivo* purging techniques described in various studies include combination of MoAbs (anti CD20, anti-CD10 and B5) and complement (Rabinowe *et al*, 1993; Gribben *et al*, 2005), or anti-CD19 and immunomagnetic separation (Khouri *et al*, 1994), or double B-cell depletion using immunomagnetic B-cell depletion using immunomagnetic $CD34^+$ selection via the Isolex 300 system followed by a negative step with anti-CD19, CD20, CD23 and CD37 MoAbs with the MaxSep (Dreger *et al*, 2000). Montillo *et al* (2006) showed that *in vivo* purging with subcutaneous alemtuzumab is feasible and effective in purging minimal residual disease after induction with fludarabine-based regimens; however, the study did not evaluate the direct effect of purging on post-auto-HCT outcomes. There are no randomized studies that compare clinical outcome in patients receiving different purging modalities [*ex vivo* (MoAbs and complement, immunomagnetic, etc.) *versus in vivo* alemtuzumab] or that compare purged *versus* unpurged haematopoietic cells. However, the applicability of purging in heavily pretreated cases may be limited by the inability to harvest sufficient haematopoietic progenitor cells, especially in those patients who were heavily pretreated with chemotherapies, such as fludarabine (Milligan *et al*, 2005).

Conclusions

Despite the paucity of data, it is important to note that this article represents the first systematic review of the entire body of available prospective evidence on the effects of auto-HCT on CLL in the English language. The following conclusions could be derived from the studies analysed in this review: (i) in the absence of randomized controlled studies, it is uncertain whether auto-HCT is superior to conventional

chemotherapy (or chemo-immunotherapy) combinations as first-line consolidation therapy in CLL patients regardless of disease risk, or as a salvage strategy in patients with relapsed disease. One may argue that the definition of poor-risk (when applicable) used in some of the reviewed studies, do not take into account modern adverse prognostic markers such as chromosomal aberrations (17p-, 11q-), unmutated *IGHV@* and ZAP-70, among others. Whether there is any benefit of HDCT and auto-HCT in patients with poor-risk disease, as defined by modern prognostic risk factors, compared with novel chemoimmunotherapy combinations of fludarabine plus alemtuzumab (Montillo *et al*, 2006), among others, remains to be determined in a randomized trial. Also, patients undergoing HCT represent a highly selected group of patients and selection bias is always a concern; in fact, the median age of patients who received auto-HCT in this review ranged from 45 to 59 years of age, younger than the median age of CLL patients in general; (ii) auto-HCT in patients with CLL is associated with a relatively low TRM (0–9%); (iii) auto-HCT can deliver impressive clinical responses (CR: 74–100%), and MR (57–88%); but success of auto-HCT requires that patients preferably achieve CR prior to initiation of HDCT. Unfortunately, MR is generally short-lived, and relapses are anticipated. MR are also achieved nowadays with alemtuzumab as consolidative therapy after fludarabine-based regimens (Montillo *et al*, 2006); and this may present a potential argument against performing auto-HCT in patients with CLL. However, comparing molecular responses among different trials is not recommended because of the lack of standardization between various methodologies used to measure such responses, and different patient and disease characteristics among studies; and (iv) the high incidence of MDS is particularly concerning in a disease like CLL, where the median survival is 9 years. Interestingly, secondary MDS/AML has also been reported with an incidence of 2·8%, outside the setting of auto-HCT, in patients with CLL after treatment with fludarabine, particularly when combined with alkylating agents (Wierda *et al*, 2005). There are no randomized studies that compare clinical outcome in patients receiving different purging modalities; and it remains unclear whether purging improves DFS or OS.

In addition to these findings, we identified a newsletter report from the Center for International Blood and Marrow Transplant Research (CIBMTR) that presented survival data on 342 patients with CLL who received auto-HCT (Pasquini *et al*, 2006). The 3-year probability of survival for these patients is 77 ± 3%; however, it is unclear if some of these patients have already been reported as part of the prospective studies discussed herein. This report did not show up in our search of MEDLINE database as it was not reported in a peer-reviewed journal. Also, a retrospective multicentre survey (Jantunen *et al*, 2006) reported clinical outcome in 72 patients with CLL treated with auto-HCT at five transplant centres across Finland. The median age of patients, median time from initial diagnosis and the median number of prior therapies were 57 (range: 38–69) years, 32 (range: 6–181) months, and one (range: 1–4) prior therapy respectively. Sixty-two (86%) patients achieved (or maintained) CR, eight (11%) achieved PR, and two did not show a response. MDS was observed in two (2·8%) patients. The projected 5-year OS was 80% and the median survival was 95 months. At a median follow-up of 28 (range: from 5 to >120) months, relapse or progression was seen in 27 (37%) patients. The projected median progression-free survival was 48 months (95% CI 30–66) from transplantation. This study showed that auto-HCT is feasible without TRM, but is not curative in CLL.

The data presented in this systematic review summarizes what is currently known (and not known) about HDCT and auto-HCT in CLL. This is a considered important scientific and ethical prerequisite for any future study aiming to test the role of auto-HCT in CLL patients (Chalmers, 2001; Egger & Altman, 2001). Failure to examine existing evidence in a systematic way has resulted in lethal consequences for patients volunteering to take part in research (Chalmers, 2001; Clarke, 2004; Djulbegovic & Lyman, 2006). Currently, prerequisites for human research in several countries demand conducting, or referencing, a systematic review prior to approving new clinical trials to provide the background rationale for the study (Egger & Altman, 2001). We hope that our study will serve such a purpose for future studies of auto-HCT in CLL.

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