Infectious toxicity using alemtuzumab

Alemtuzumab is a humanized monoclonal antibody directed against CD52, a non-modulating glycosylated peptide antigen that is highly expressed on B-cell in chronic lymphocytic leukemia (CLL) and on normal lymphocytes. CD52 is expressed on virtually all lymphocytes at various stages of differentiation, as well as on monocytes, macrophages and eosinophils; it is not expressed on granulocytes (<5%) or hematopoietic $CD34^+$ stem cells.[1] The highest levels seem to be expressed on T-prolymphocytic leukemia (PLL) cells, followed by B-cell CLL, with the lowest levels on normal B cells.[2] After binding to target cells alemtuzumab may cause cell death through host-effector mechanisms, such as antibody-dependent cellular cytotoxicity, complement-mediated cytolysis and induction of apoptosis and it may also sensitize tumor cells to chemotherapy.[3]

Alemtuzumab has been extensively used to prevent graft-versus-host disease in allogeneic stem cell transplantation. It has been employed in CLL, and promising results were obtained in refractory/relapsed patients.[4-6] More recently alemtuzumab has been used as first-line therapy for CLL,[7] obtaining results similar to those provided by fludarabine or cladribine, with a pronounced effect on bone marrow and long-lasting remissions. The profound and long-lasting lymphocytolysis caused by alemtuzumab is also responsible for severe and prolonged immunodepression which produces a major predisposition to infectious complications. Obviously, the risk and the type of infection differ according to the indications for using this antibody and its doses; its association with chemotherapy, the use as conditioning regimen, in myeloablative and non-myeloablative transplantation, the concomitant administration of immunosuppressive drugs, and the characteristics of CLL itself can greatly change the severity of immunodepression, favoring those particular opportunistic infections associated with a low CD4 cell level ($<50\times10^9$/L). However, because the number of treated patients has so far been low, and above all perspective studies have not been performed, it is difficult to correctly define the profile of infectious toxicity although this complication is beginning to emerge clearly.

Infections in patients with B and T lymphoproliferative disorders treated with alemtuzumab

The importance of correct prophylaxis of infections appeared early and is clearly demonstrated by a comparison of the results of the first studies with subsequent studies that included prophylaxis for *Pneumocystis carinii* and *Herpes viruses.*

Cytomegalovirus (CMV) infection

Viral reactivation, especially that of CMV, is an emerging problem. When assessing the toxicity caused by alemtuzumab, it is important to note that the majority of patients treated with this drug had previously received alkylating and fludarabine-based therapy. It was demonstrated that infectious morbidity and mortality is high in both previously treated and fludarabine-refractory CLL.[8,9]

In the pivotal study[5] anti-infectious prophylaxis with sulphamethoxazole-trimethoprim and famcyclovir (or an equivalent antiviral regimen) was used. However, it is now evident that famcyclovir does not prevent CMV reactivation, although most patients respond rapidly to intravenous ganciclovir.[5,10,11] This recently completed pivotal trial included 93 patients treated at 21 centers in USA and Europe[5] who had received alkylating agents and in whom fludarabine treatment failed. Infections occurred in 51 (55%) patients during the study, being mild to moderate in 26 and grade III to IV in 25 cases. Septicemia occurred in 14 patients (15%), and two cases led to death. Herpes simplex was present in 6 cases. CMV reactivation in 7 patients caused concern. Eleven patients, all of whom with advanced disease, developed opportunistic infections (OI) during treatment and a further 7 did so in the follow-up period (1 *Pneumocystis carinii* pneumonia, 3 aspergillosis, 1 mucormycosis, 1 cryptococcal pneumonia, 1 *Listeria meningitis*, 4 Herpes zoster and 7 CMV reactivation). Six of 9 deaths were due to infections. Responders seemed to experience fewer infections than non-responders. In a compassionate-use protocol[11] which included 152 B-CLL heavily pretreated fludarabine-refractory patients, CMV infection occurred in 4 patients (1.8%) and was fatal in one. Five patients died from infection (4 from pneumonia, 1 from gas gangrene). The incidence of CMV viremia during alemtuzumab therapy was evaluated[10] in patients with relapsed/refractory disease receiving famcyclovir prophylaxis (250 mg PO bid or equivalent); despite this prophylaxis, 15% of cases had CMV viremia at a median of 28 days after the first dose of alemtuzumab, but there was no clinical evidence of CMV organ disease. Gancyclovir treatment resulted in prompt resolution of fever. No risk factors for CMV viremia were identified by univariate regression analysis although there was a trend towards prior rituximab therapy being significant (p=0.07).

Only recently, some papers have reported induction with alemtuzumab, in association with fludarabine or

not, in previously untreated patients.[7,12] In 41 patientstreated only with alemtuzumab by the subcutaneous route, infections were rare, but 10% of the patients developed CMV reactivation which rapidly responded to i.v. ganciclovir.[7] One patient, allergic to cotrimoxazole prophylaxis, developed *Pneumocystis carinii* pneumonia. CMV reactivation seemed to increase when alemtuzumab was administered after fludarabine as consolidation therapy in patients with minimal residual disease.[13] Despite the administration of reduced doses (10 mg) of alemtuzumab, three patients showed CMV reactivation (20%) at the end of treatment, but only two were treated with ganciclovir, one because of symptoms (fever, nausea) and the other because of a high number of CMV positive cells. In this study, the weekly monitoring of CMV antigenemia could explain the higher percentage of CMV reactivation than that found in previous studies, because CMV reactivation can be asymptomatic in a certain number of patients. A recent phase III study[12] evaluating efficacy and safety of front-line therapy with alemtuzumab at a dosage of 30 mg i.v. 3 times a week for a maximum of 12 weeks reported PCR-detected CMV reactivation in 53% of cases; among these 31 patients, only 6 were symptomatic and they were successfully treated with ganciclovir (5 patients) and foscarnet (1 patient). These results have been very recently confirmed for alemtuzumab used as consolidation therapy.[14,15] In these studies the rates of infectious episodes seemed clearly lower than those observed in previously treated patients, and only sporadic opportunistic infections were reported. However, CMV reactivation was also found in these patients, albeit in a smaller percentage, highlighting how this reactivation is strictly related to alemtuzumab administration and to the particular immunodepression caused by this antibody therapy. In patients with B-CLL the absolute number of T cells is increased and there are large numbers of tetramer-binding CMV-specific $CD8^+$ T cells.[16] These data suggest that in B-CLL the composition of T cells is shifted toward a $CD8^+$ cytotoxic cell type in an effort to control infections with persistent viruses such as CMV. The data offer an explanation for the high incidence of CMV reactivation in CLL patients treated with T cell-depleting agents, such as alemtuzumab, in whom the $CD8^+$ cell control is very reduced.

T-cell malignancies may be particularly responsive to therapy with alemtuzumab. The experience of the MD Anderson Cancer Center[17] in B and T chronic lymphoproliferative disorders suggests that the same infectious complications occur in B-CLL and T-cell malignancies. Recently, a phase 2 study of alemtuzumab in 22 patients with advanced mycosis fungoides[18] showed symptomatic CMV reactivation in 4 (18%) patients, 1 aspergillosis, 3 generalized Herpes simplex infections, and 1 fatal *Mycobacterium* pneumonia (Table 1). The frequency of CMV pneumonia following alemtuzumab treatment was retrospectively determined from pooled safety data on 1538 patients with lymphoid malignancies.[19] The incidence of symptomatic CMV infection and/or reactivation was 3.6%. Nine (0.6%) patients had CMV pneumonia and 3 died. In these studies specific prophylactic therapy was not given.

Other viruses

Sporadic cases of fatal infections caused by virus es other than CMV and Herpes viruses were described in heavily pretreated patients. Adenovirus infections, in particular, need to be considered in B-CLL patients as a possible cause of fever of unknown origin while on alemtuzumab treatment.[20]

Combination therapy rituximab + alemtuzumab

The combination of two antibodies, rituximab plus alemtuzumab, has been studied by several groups.[21,22] In the M.D. Anderson series[22] of the 48 evaluable patients, all receiving antinfectious prophylaxis with cotrimoxazole and valacyclovir, 25 (52%) experienced at least 1 infectious episode; fever of unknown origin was seen in 6 (13%), pneumonia in 5 (10%), CMV reactivation in 13 cases (27%), but only 15% were symptomatic and required therapy. The combination regimen was feasible with an acceptable safety profile in patients with poor prognosis.

Infections in bone marrow transplantation utilizing alemtuzumab in conditioning regimens

CMV infection

Although the adoption of reduced intensity conditioning regimens has been associated with fewer bacterial, fungal and viral infections following transplants, alemtuzumab administration has been associated with slower immune reconstitution and an increased incidence of viral infections. Chakrabarti *et al.*[23] showed a 50% incidence of CMV infection following a non-myeloablative conditioning regimen containing alemtuzumab 100 mg. Fifty-one patients developed CMV infection at a median of 27 days post-transplant. The rate of infection in patients at risk (donor or recipient CMV positive) was 84.8%. Infection was more common in unrelated donor transplant recipients. CMV reactivation was independent of type and number of transplant (unrelated or related; first or second transplant procedure) and of GVHD, which was present in a severe form in only 4% of cases. The probability of CMV infection recurring was high (71.3%) despite prophylactic therapy. Reactivation was present as a *late infection* at a median of 122 days (range 100-240) after transplantation in 46.6% of patients. CMV disease was

Table 1. Severe infections in patients with lymphoproliferative disorders treated with alentuzumab.

Authors	*N. of pts.*	*Diagnosis*	*Treatment*	*Prophylaxis*	*Dose*	*Fungi*	*CMV infections*	*Pts with infections (%)*
Keating[5] 2002	93	B-CLL	salvage	cotrimoxazole valacyclovir	30 mg i.v. 3/week (12 wks)	1 candida 4 aspergillus 1 mucor 1 cryptococcus	7 symptomatic	51 (55%)
Rai[11] 2002	223	B-CLL	salvage	NA*	30 mg i.v. 3/week (12 wks)	NA*	4 symptomatic	NA*
Lundin[7] 2002	41	B-CLL	induction	cotrimoxazole valacyclovir fluconazole	30 mg s.c. 3/week (18 weeks)	no	4 reactivations 3 symptomatic	5 (12%)
Skotnicki[12] 2003	60	B-CLL	induction	cotrimoxazole famcyclovir	30 mg i.v. 3/week (12 weeks)	no	31 reactivation 6 symptomatic	7 (12%)
Montillo[13] 2002	9	B-CLL	consolidation	cotrimoxazole acyclovir	10 mg s.c. 3/week (6 weeks)	no	3 reactivations 1 symptomatic	1 (11%)
Wendtner[15] 2004	11	B-CLL	consolidation	cotrimoxazole famcyclovir	30 mg i.v. 3/week (12 weeks)	1 aspergillus	4 symptomatic	7 (63%)
O'Brien[16] 2003	41	B-CLL	consolidation	cotrimoxazole acyclovir	10-30 mg iv 3/week (12 weeks)	no	9 symptomatic	15 (37%)
Ferrajoli[18] 2003	50	B-CLL T-malignancies	salvage	cotrimoxazole valacyclovir	30 mg i.v. 3/week (12 weeks)	2 aspergillus, 1 mucor	15 symptomatic	36 (46%)
Lundin[19] 2003	22	Mycosis fungoides	salvage	cotrimoxazole valacyclovir	30 mg i.v. 3/week (12 weeks)	1 aspergillus	4 symptomatic	11 (50%)

NA: not available.

diagnosed in only 5 patients, in whom it was fatal. Survival was similar in patients infected or not with CMV. In a subsequent study Bainton *et al.*[24] reported their experience of 69 transplanted patients who received conditioning with alemtuzumab at a reduced dose of 50 mg; overall, 77.8% of patients at risk developed CMV infection. One of the significant risk factors for CMV infections was the use of fludarabine in the conditioning regimen (p=0.41); the authors suggested that the combination of fludarabine and alemtuzumab was responsible for a higher risk of CMV infection and its earlier appearance (median 4.3 vs 7.8 weeks).

A recent comparison between different conditioning regimens in non-myeloablative allogeneic transplant including alemtuzumab or anti-thymocyte globulin (ATG) showed lower levels of T cells 180 days after transplantation in alemtuzumab-conditioned patients and more frequent infectious complications; 2-year survival was better in ATG-conditioned patients.[25] In patients with lymphoproliferative diseases in whom the autologous transplantation had failed, subsequent allotransplantation with a non-myeloablative fludarabine, melphalan and alentuzumab (FMC) conditioning regimen[26] was associated with low transplant-related mortality (7.9% at 100 days, 20% at 14 months) with 10.5% of infectious deaths. CMV reactivation was present in 75% of cases, but only one patient suffered CMV disease, probably due to early antiviral therapy started on the basis of CMV detection by PCR testing. Despite the rate of CMV reactivation being very high (50-80%) in non-myeloablative transplants utilizing alemtuzumab,[27,28] and reaching 100% in mismatched, unrelated stem cell transplants (compared with 47% in patients conditioned with ATG),[27] infectious mortality

remains low and it does not seem to have a negative effect on patients' outcome. Moreover, when antiviral treatment of CMV disease fails, adoptive transfer of CMV-specific CD8 cytotoxic T lymphocytes from the donor can be used as alternative immunotherapy.[29]

Other viruses

The risk of other infections, especially from respiratory viruses such as parainfluenza virus (PIV) and respiratory syncytial virus (RSV) may also be increased in patients who receive conditioning regimens with alemtuzumab. Chakrabarti described 35 episodes of respiratory virus infections in 25 of 83 transplant recipients conditioned with FMC; of these, 80% received early antiviral therapy. PIV 3 was the commonest isolate (45.7%) and RSV was the second most common (37%). Patients with myeloma were more susceptible to these infections. Although more than half of the episodes progressed to lower respiratory infection, mortality was only 8%.[30]

Finally, the risk of Epstein-Barr virus (EBV) triggered lymphoproliferative diseases is strongly associated with T-cell depletion, particularly with protocols which retain B-cell populations, and is lowest when the techniques used (e.g. alemtuzumab) also eliminate donor B cells. The risk of EBV-triggered lymphoproliferative diseases is 1.3% with alemtuzumab compared with 29% using the E-rosette depletion method.[31] Circulating antigen-specific T-cell immunity to EBV recovers later in patients submitted to non-myeloablative transplantation with alemtuzumab than in those receiving myeloablative bone marrow transplants; in fact, following myeloablative transplantation, a detectable EBV-specific response is present in 75% of patients at six months and in all patients at one year, the non-myeloablative conditioning regimen with FMC caused a delay in EBV-specific T-cell recovery, with this being present in 10% of patients at six months and in 70% at one year.[32]

Conclusions

Alemtuzumab is a useful tool in lymphoproliferative diseases and in the transplant setting. Its use must be accompanied by careful monitoring and prophylaxis against viruses. The bacterial and fungal infections that occur in alemtuzumab-treated patients are the same as those that develop in T-cell-depleted patients. Prevention of *Pneumocystis carinii* pneumonia is mandatory during and after alemtuzumab therapy despite the lack of placebo-controlled studies in this patient population. Sulfamethoxazole-trimethoprim (one double-strength tablet three times a week) has become the prophylaxis of choice in these patients and is given at least until 2 months after discontinuation of fludarabine treatment[4] and for at least 4 months after completion of alemtuzumab treatment, or until the CD4 count is > 200 μL. Invasive fungal infections are sporadically diagnosed above all in heavily treated patients who experienced neutropenic phases. Acyclovir is active against Herpes viruses which are very frequent in CLL patients and it is usually performed as prophylaxis in patients treated with fludarabine and/or monoclonal antibodies (400 mg twice daily), particularly in those with previous Herpes infections (800 mg twice daily). Alemtuzumab determines CMV reactivation in 10-40% of CLL patients and in up to 80% in patients who undergo allogeneic myeloablative and non-myeloablative bone marrow transplants, but CMV disease develops more rarely; this evolution can be prevented by monitoring levels of antigenemia frequently.[15] CMV infection should be suspected in all patients with febrile episodes with negative cultures; prompt therapy for symptomatic CMV infection is crucially important to cure these patients. Famcyclovir (or equivalent antiviral regimen) seems not to prevent CMV reactivation, although most patients respond rapidly to intravenous gancyclovir.[5,10,11] Finally, respiratory virus infections are possible and often recurrent in patients with severe $CD4^+$ T lymphopenia. However, reported mortality is low, perhaps because of reduced inflammatory damage to the lungs due to severe lymphopenia and early institution of antiviral treatment.[30]

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References

1. Gilleece MH, Dexter TM. Effect of campath-1H antibody on human hematopoietic progenitors in vitro. Blood 1993;82:807-12.
2. Ginaldi L, De Martinis M, Matutes E, Farahat N. Morilla R, Dyer MJ, et al. Levels of expression of CD52 in normal and leukemic B and T cells: correlation with in vivo therapeutic responses to Campath-1H. Leuk Res 1998;22:185-91.
3. Kennedy B, Rawstron A, Carter C, Ryan M, Speed K, Lucas G, et al. Campath-1H and fludarabine combination are highly active in refractory chronic lymphocytic leukaemia. Blood 2002;99:2245-7
4. Osterborg A, Dyer MJS, Bunjes D, Pangalis GA, Bastion Y, Catovsky D, et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. The European Study Group of campath-1H treatment in CLL. J Clin Oncol 1997; 15:1567-74.
5. Keating MJ, Flinn I, Vinay J, Binet JL, Hillmen P, Byrd J, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. Blood 2002;99:3554-61.
6. Rai KR, Freter CE, Mercier RJ, Cooper MR, Mitchell BS, Stadtmauer EA, et al. Alemtuzumab in previously treated chronic lymphocytic leukaemia who also had received fludarabine. J Clin Oncol 2002; 20:3891-7.
7. Lundin J, Kimby E, Bjorkholm M, Broliden PA, Celsing F, Hjalmar V, et al. Phase II trial of subcutaneous anti-CD52 monoclonal anti-

body alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood 2002;100:768-73.
8. Anaissie EJ, Kontoiyannis DP, O'Brien S, Kantarjian H, Robertson L, Lerner S, et al. Infections in patients with chronic lymphocytic leukemia treated with fludarabine. Ann Int Med 1998; 129:559-60.
9. Byrd JC, Houde-McGrail LL, Hospental DR, Howard RS, Dow NA, Dihel LF. Herpes virus infections occur frequently following treatment with fludarabine: results of a prospective natural history study. Br J Haematol 1999;105:445-7.
10. Nguyen DD, Cao TM, Dugan K, Starcher SA, Fechter RL, Coutre SE. CMV viremia during campath-1H therapy for relapsed/refractory CLL and PLL. Clin Lymph 2002;3:105-10.
11. Rai KR, Keating MJ, Coutre S, Rizzieri DA. Patients with refractory B-CLL and T-PLL on a compassionate basis. A report on efficacy and safety of CAM 511 trial. On behalf of the campath-1H Study Group. Blood 2002;100:802[abstract].
12. Skotnicki AB, Robak T, Mayer J, Craig A,Weitman S. Phase III study to evaluate the efficacy and safety of front-line therapy with alemtuzumab vs chlorambucil in patients with progressive B-cell chronic lymphocytic leukemia. Blood 2003;102:439[abstract].
13. Montillo M, Cafro AM, Tedeschi A, Brando B, Oreste P, Veronese S, et al. Safety and efficacy of subcutaneous campath-1H for treating residual disease in patients with chronic lymphocytic leukemia responding to fludarabine. Haematologica 2002;87:695-700.
14. Wendtner CM, Ritgen M, Schweighofer CD, Fingerle-Rowson G, Campe H, Jaeger J, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia in first remission. Experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). Leukemia 2004;18:1093-101.
15. O'Brien SM, Kantarjian HM, Thomas DA, Cortes J, Giles FJ, Wierda WG, et al. Alemtuzumab as treatment for residual disease after chemotherapy in patients with CLL. Cancer 2003;98:2657-63.
16. Mackus WJ, Frakking FN, Grummels A, Gamadia LE, De Bree GJ, Hamann D, et al. Expansion of CMV-specific $Cd8^{+}CD45RA^{+}CD27^{-}$ T cells in B-cell chronic lymphocytic leukaemia. Blood 2003; 102:1057-63.
17. Ferrajoli A, O'Brien SM, Cortes JE, Giles FJ, Thomas DA, Faderl S, et al. Phase II study of alentuzumab in chronic lymphoproliferative disorders. Cancer 2003;98:773-8.
18. Lundin J, Hagberg H, Repp R, Cavallin-Stahal E, Freden S, Jiuliusson G, et al. A phase II study of alentuzumab in patients with advanced mycosis fungoides/ Sézary syndrome. Blood 2003; 101:4267-72
19. Williams TE, Roach J, Rugg T, Brettman L. Frequency of CMV pneumonia following alemtuzumab treatment in lymphoid malignancies: review of 1538 patients. Blood 2002;100:294.
20. Cavalli-Bjorkman N, Osby E, Lundin J, Kalin M, Osterborg A, Gruber A. Fatal adenovirus infection during alemtuzumab treatment of a patient with fludarabine-refractory B-cell chronic lymphocytic leukaemia. Med Oncol 2002;19:277-80.
21. Nabhan C, Tallman MS, Riley MB, Fitzpatrick J, Gordon LI, Gartenhaus R, et al. Phase I study of rituximab and campath-1H in patients with relapsed and refractory chronic lymphocytic malignancies. Blood 2001;98:365[abstract].
22. Faderl S, Tomas D, O'Brirn S, Wierda W, Kantarjian HM, Garcia-Manero G, et al. Combined use of alemtuzumab and rituximab in patients with relapsed/refractory chronic lymphoid malignancies. An update of M. D. Anderson experience. Blood 2003;101:3413-5.
23. Chakrabarti S, Mackinnon S, Chopra R, Kottaridis PD, O' Gorman P, Chakaverti R, et al. High incidence of cytomegalovirus infection after nonmyeloablative stem cell transplantation: potential role of Campath-1H in delaying immune reconstitution. Blood 2002; 99:4357-63.
24. Bainton RD, Byme JL, Davy B, Russel N. CMV infection following nonmyeloablative allogeneic stem cell transplantation using Campath. Blood 2002;100:3843-4.
25. Juliusson G, Karlsson K, Frodin U, Backstrom G, Malm C. Subcutaneous Campath-1H instead of thymoglobulin in nonmyeloablative allogeneic peripheral blood stem cell transplantation: reduced toxicity but delayed lymphocyte recovery leading to more mixed chimerism, more fatal infections and impaired long-term survival: a single center study of 56 patients. Blood 2002;100 Suppl 1:430[abstract].
26. Kroger N, Thomson K, Zabelina T, Peggs K, Chopra R, Shimoni A, et al. Comparison between anti-thymocyte globulin and alemtuzumab in melphalan/fludarabine dose-reduced conditioning following by HLA-matched and mismatched unrelated stem cell transplantation in patients with lymphoid malignancies. Blood 2003; 102:484[abstract].
27. Koh LP, Rizzieri DA, Long GD, Vredemburg JJ, Gasparetto C, Morris A, et al. Campath-1H T cell depleted non-myeloablative peripheral blood stem cell transplantation from 3-6/6 HLA matched family members. Blood 2002;100 Suppl 1:638[abstract].
28. Smith SM, Stock V, Sher D,Wickrema A, Odenike T, Zimmermann T, et al. Engraftment and early-treatment- related complications after fludarabine-melphalan-campath conditioning in patients with advanced hematologic malignancies. Blood 2002;100 Suppl 2:430b[abstract].
29. Cobbold M, Khan N, Tauro S, Mc Donald D, Osman H, Assenmacher M, et al. Adoptive transfer of tetramer selected cytomegalovirus-specific cytotoxic cells after allogeneic stem cell transplantation. Blood 2002;100:215[abstract].
30. Chakrabarti S, Collingham KE, Marshall T, Holder K, Gentle T, Hale G, et al. Respiratory virus infections in adult T cell-depleted transplant recipients: the role of cellular immunity. Transplantation 2001;72:1460-3.
31. Hale G, Waldmann H. Risks of developing Epstein-Barr virus-related lymphoproliferative disorders after T-cell depleted marrow transplants in campath users. Blood 1998;91:3079-83.
32. Chakrabarti S, Milligan DW, Pillay D, Mackinnon S, Holder K, Kaur N, et al. Reconstitution of Epstein-Barr virus-specific cytotoxic T-lymphocyte response following T-cell-depleted myeloablative and nonmyeloablative allogeneic stem cell transplantation. Blood 2003; 102:839-42.

Alemtuzumab for treatment of lymphoproliferative disorders

Two papers in this issue of the journal regard alemtuzumab and its potential use in lymphoproliferative disorders. Golay and co-workers (page 1476) have investigated its mechanism of action *in vitro* against different neoplastic B cells. Their findings show that complement-mediated lysis is likely to be an important mechanism of action in B-cell chronic lymphocytic leukemia (CLL). In a perspective article, Nosari (page 1415) examines the infectious complications of using alemtuzumab in lymphoproliferative disorders and in the transplant setting. She concludes that alemtuzumab is a very useful drug, but requires strict monitoring and prophylaxis against infection.

In the last few years, there have been major advances in defining the risk of the individual patient with CLL and attempts to develop risk-adapted strategies. The reader may be interested in a number of articles on this topic that have been recently published in this journal[1–16] and that can be downloaded for free at our website (*www.haematologica.org*). Alemtuzumab has considerable potential in the treatment of CLL, and appears already to have a place in a risk-adapted strategy. Its inclusion in combination therapies may allow the intent of therapy to be shifted from palliation towards cure. As any other effective drug it does, however, have side effects and must be employed with particular care.

References

1. Morabito F, Mangiola M, Stelitano C, Deaglio S, Callea V, Malavasi F. Peripheral blood CD38 expression predicts time to progression in B-cell chronic lymphocytic leukemia after first-line therapy