Cancer Immunol Immunother (1992) 34: 337–342

Cancer Immunology Immunotherapy

© Springer-Verlag 1992

Continuous intravenous infusion of high-dose recombinant interleukin-2 for acute myeloid leukaemia – a phase II study

S. H. Lim[1], A. C. Newland[2], S. Kelsey[2], A. Bell[3], E. Offerman[4], C. Rist[5], D. Gozzard[6], D. Bareford[7], M. P. Smith[1], and A. H. Goldstone[1]

Departments of Haematology at [1] University College Hospital, London; [2] The Royal London Hospital, London; [3] Royal Victoria Hospital, Bournemouth; [4] Queen Mary Hospital, Sidcup; [5] Worthing Hospital, Worthing; [6] Glen Clwyd Hospital, Clwyd; and [7] Dudley Road Hospital, Birmingham, UK

Received 10 September 1991/Accepted 26 November 1991

Summary. A group of 13 patients with acute myeloid leukaemia of differing disease status were treated with continuous intravenous infusion of high-dose recombinant interleukin-2 (rIL-2). There was up-regulation of the cellular cytotoxic functions in all these patients following the rIL-2 therapy, with increase in the natural killer (NK) activity, lectin-dependent cellular cytotoxicity, induction of cytotoxicity-linked cytoplasmic serine esterase and lymphocyte activation. However, the clinical response to rIL-2 in these patients was disappointing, especially in patients treated in frank relapse. Although 1 patient treated in early second relapse achieved a third complete remission, the duration of the remission was brief and lasted only 6 months. Adverse reactions among these patients were common. Whether or not lymphokine-activated killer cells are needed to improve the response rate over rIL-2 alone in these patients deserves further investigation.

Key words: Acute myeloid leukaemia – Recombinant interleukin-2

Introduction

Using conventional combination chemotherapy, complete remission rates in the region of 70% have been reported in young adult acute myeloid leukemia (AML) patients [21]. However, the long-term prognosis of these patients remains poor, with a 3-year disease-free survival in young adults of only 25%–30%. Although the use of allogeneic bone marrow transplantation has been shown to improve the prognosis in these patients [4, 19], only a proportion of AML patients can be treated by this modality because of the age limitation and availability of histocompatibility-locus-antigen(HLA)-matched sibling donors. Therefore other forms of treatment modality to prolong the remission are needed.

The demonstration that recombinant interleukin-2 (rIL-2) and lymphokine-activated killer (LAK) cells were capable of eradicating or reducing metastatic tumours in several animal models [11, 18, 24] opened the way towards a new era in the use of immunotherapy in the treatment of malignant diseases. Some successes have been reported in patients with advanced and resistant solid tumours using LAK cells and rIL-2 [22, 23] or rIL-2 alone [25]. These results suggest that rIL-2 may be suitable candidate agent for use in patients with AML.

The rationale behind this form of treatment includes the stimulation of cytotoxic T lymphocytes and natural killer (NK) cells, induction of LAK cells and secretion of secondary cytokines like tumour necrosis factor (TNF) and interferon γ, all of which are potentially cytotoxic to tumour cells [5, 8–10]. There is also a large body of in vitro and animal data to suggest the possible beneficial effect of rIL-2 as an immunotherapeutic agent in AML. Previous studies showed that it was feasible to generate LAK cells from patients with AML, whether in complete remission or with active disease, and that the LAK cells were cytolytic for the autologous leukaemia blast cells [1]. Both NK and LAK cells also inhibit the clonogenic growth of fresh leukaemia cells [3, 16]. Besides direct cellular cytotoxicity, both TNF and interferon γ, produced as a result of infusion of high-dose rIL-2, have been shown also to have a direct cytotoxic effect on leukaemia blast cells [20].

We have therefore carried out a phase II study of rIL-2 in AML patients of differing disease status. The purpose of this study was to evaluate continuous intravenous high-dose rIL-2 alone without LAK cells to determine its feasibility and toxicity in this group of patients. This will expand our knowledge about the activity of rIL-2 in AML and assess its potential role in future use, possibly in minimal residual disease following autologous bone marrow transplantation.

Offprint requests to: S. H. Lim, Department of Haematology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK

Table 1. Detailed characteristics of all the patients entered into the study

Patient no.	Sex	Age (years)	FAB type	Previous therapy[a]	Status at entry[b]
001	M	49	Unknown	3+10 DAT ×2	1st PR, marrow blast 9%
002	M	46	M2	3+10 DAT ×2, Mit/AraC/VP16, HD-AraC	2nd CR
003	M	29	M1	1+5 DAT, 3+10 DAT ×2, MACE, MIDAC	2nd CR
004	M	29	M3	2+7 DAT ×2, MACE, MIDAC ×2	1st relapse, marrow blast 38%
005	M	42	M3	3+10 DAT ×2, 2+7 DAT ×2, Bu/Cy ABMT, AraC ×5	2nd PR, marrow blast 17%
006	M	63	M2	2+7 DAT ×2, 1+5 Mit/AraC, 3+7 DAT, VP16/AMSA	2nd relapse, marrow blast 40%
007	F	52	M2	3+10+5 DAE ×2, MACE, MIDAC	1st CR
008	M	21	M5	3+10 DAT ×2, UCH ABMT	1st relapse after ABMT, marrow blast 95%
009	M	45	M7	3+10 DAT, 3+8 DAT, MACE	1st CR
010	F	34	M4	3+10 DAT, 2+7 DAT ×2, Bu/Cy ABMT, 2+7 DAT ×2	Early 2nd relapse, marrow blast 10%
011	F	31	M4	3+10 DAT ×2, MACE, Cy/AraC ABMT, MIDAC ×2	2nd CR
012	F	40	M4	3+10 DAT, 3+8 DAT, MACE, Mit/VP16 ×2	1st CR
013	M	25	M1	3+10 DAT ×2, MACE ×1, Cy/TBI ABMT, MIDAC ×2	2nd CR

[a] DAT, daunorubicin, cytosine arabinoside (AraC) and 6-thioguanine; Mit/AraC/VP16, mitoxantrone, AraC and etoposide; HD-AraC, high-dose AraC; MACE, amsacrine, AraC and etoposide; MIDAC, mitoxantrone, intermediate-dose AraC; Bu/Cy ABMT, busulphan + cyclophosphamide followed by autologous bone marrow transplant; VP16/AMSA, etoposide and amsacrine; DAE, daunorubicin, AraC and etoposide; UCH ABMT, *N,N'*-bis(2-chloroethyl)-*N*-nitrosourea, cyclophosphamide, Adriamycin, AraC and 6-thioguanine followed by autologous bone marrow transplant; Cy/AraC ABMT, cyclophosphamide and AraC followed by autologous bone marrow transplant

[b] PR, partial remission; CR, complete remission

Materials and methods

Patients. With the approval of the Hospital Ethical Practices Committees, 13 patients with acute myeloid leukaemia were entered into this study. The diagnoses of these patients were: M1 (2), M2 (3), M3 (2), M4 (3), M5 (1), M7 (1) and unknown (1). Their disease status at entry into the study was: AML first complete remission (CR) (3), AML second CR (4), AML early relapse/partial remission (3) and AML frank relapse (3). Two of the patients treated in their second CR, 2 in early relapse/partial remission and 1 in frank disease relapse had relapsed after autologous bone marrow transplant in the first CR. There were 9 men and 4 women. The median age of these patients was 40 years (range 21–63 years). No patient had received any antileukaemic therapy within 4 weeks of study entry. The detailed patient profile, disease status and previous therapy given to these patients are listed in Table 1.

Interleukin-2. Recombinant IL-2 (Proleukin, EuroCetus, Amsterdam) was reconstituted with 5% dextrose and made up to 1.5% final concentration of human albumin. This was given on an in-patient basis as a continuous intravenous infusion via a Hickman catheter at a dose of 3×10^6 Cetus units m^{-2} day^{-1}. The treatment schedule consisted of two priming cycles and two maintenance cycles. During the 2 to 6-week priming cycle, rIL-2 was administered on days 1–5 for 120 h continuously and on days 13–17.5 for 108 h continuously, while during the maintenance cycles, rIL-2 was given on days 1–5 for 120 h continuously of each 4-week cycle. rIL-2 therapy was continued in the absence of serious toxicity or evidence of disease progression. No patient received any steroids or non-steroidal anti-inflammatory drugs while on therapy.

Clinical and laboratory monitoring. All patients were monitored before treatment and then daily during the course of the study by physical examination and by measurements of the pulse, temperature, blood pressure, weight and fluid balance. Toxicity was recorded and graded using the WHO grading system. Full blood counts including differential and full biochemistry analyses were also undertaken daily. The immunological status of these patients was also monitored before starting and after finishing each course of rIL-2 therapy. The various methods have been described previously [14]. Briefly, natural killer activity and lectin-dependent cellular cytotoxicity were measured using the standard 4-h radioisotope-release assay using ^{51}Cr-labelled K562 cells, and the percentage of specific cytotoxicity was calculated from the following formula:

$$\frac{\text{experimental release} - \text{spontaneous release}}{\text{maximum release} - \text{spontaneous release}} \times 100$$

Serum levels of tumour necrosis factor (TNF), soluble IL-2 receptors (sIL-2R), soluble CD4 (sCD4) and CD8 (sCD8) were measured using the standard double-antibody sandwich technique using cell-free enzyme-linked immunosorbent assay (ELISA) kits (T cell Sciences, Cambridge, Mass.). Immunophenotyping of the mononuclear cells in the peripheral blood was performed using the standard alkaline-phosphatase/anti-alkaline-phosphatase technique and employing the following monoclonal antibodies: CD3 (UCHT1, provided by Professor P. C. L. Beverley), CD4 (Dakopatts, Dako, Denmark), CD8 (Dakopatts, Dako, Denmark) and CD56 (Becton Dickinson).

Supportive care. All patients received paracetamol 500 mg orally every 4 h to control fever. Rigors were treated with intravenous pethidine (25–50 mg) and any fluid retention relieved by diuretics ± human albumin infusion. The infusion of rIL-2 was temporarily stopped in cases of hypotension not controlled by infusion of human albumin or vasopressor.

Assessment of response. Response was evaluated by using standard WHO criteria. Stable disease (SD) followed the definition of "no change", i.e. no significant change for at least 4 weeks, an estimated decrease of less than 50%, and the lesion with an estimated increase of less than 25% [17]; partial remission (PR) was defined as a reduction of the marrow blast count to less than 30% but more than 5%, and complete remission (CR) the restoration of normal haemopoiesis with less than 5% blast cells in the bone marrow.

Statistical methods. All the laboratory measurements were expressed as means ±SD and the difference evaluated using Student's *t*-test.

Results

Response

All 13 patients were evaluated for response (in the case of patients in their first CR, the response related to where they remained in the first CR). The response of these patients to

Table 2. Response and current status of all the patients entered into the study

Patient no.	Time of rIL-2 therapy (days)	Status following rIL-2 therapy[a]	Present status
001	18	SD for 8 weeks	Dead after disease progression
002	18	Remained in 2nd CR for 5 months 3 months after initiation of rIL-2 therapy	Dead after relapse
003	23	Remained in 2nd CR for 6 months 4 months after initiation of rIL-2 therapy	Dead after relapse
004	13.5	SD for 8 weeks	Dead after disease progression
005	4	SD for 8 weeks	Dead after disease progression
006	9.5	SD for 6 weeks	Dead after disease progression
007	27	Remains in 1st CR	Alive in 1st CR for 22+ months, 16 months after starting rIL-2 and 13 months after stopping rIL-2 therapy
008	4	Disease progression	Dead after disease progression
009	28	Remains in 1st CR	Alive in 1st CR for 13+ months, 11 months after starting rIL-2 and 8 months after stopping rIL-2 therapy
010	28	Achieved 3rd CR for 6 months	Alive in 4th relapse
011	14.5	Remains in 2nd CR	Alive in 2nd CR for 12+ months, 10 months after starting rIL-2 and 8 months after stopping therapy
012	5	Remains in 1st CR	Alive in 1st CR for 13+ months, 8 months after starting rIL-2 and 7 months after stopping therapy
013	14.5	Remains in 2nd CR	Alive in 2nd CR for 7+ months, 5 months after starting rIL-2 and 3 months after stopping therapy

[a] rIL-2, Recombinant interleukin-2; SD, stable disease; CR, complete remission

Table 3. Changes in the peripheral blood haematology in acute myeloid leukaemia (AML) patients following each course of recombinant interleukin-2 (rIL-2) infusion

Parameter	Pre	During	Post	P
Hb (g/dl)	11.5 ± 1.2	10.0 ± 1.4	–	<0.001
Neutrophils $\times 10^9$/l	4.87 ± 4.04	8.49 ± 5.32	–	<0.001
Eosinophils $\times 10^9$/l	0.39 ± 0.50	1.04 ± 1.12	–	<0.02
Lymphocytes $\times 10^9$/l	2.16 ± 1.25	0.87 ± 0.83		<0.0001
			5.45 ± 2.90	<0.0001
Platelets $\times 10^9$/l	131 ±94	67 ±56	–	<0.001

rIL-2 infusion is shown in Table 2. All the patients treated in the first CR of AML have remained in CR (13+ months, 13+ months and 22+ months respectively). Of the 4 patients treated in the second CR, 2 have relapsed, 5 and 6 months after achieving the second CR and 3 and 4 months after initiation of rIL-2 therapy respectively. The other 2 patients have remained in the second CR (7+ months and 12+ months respectively). Of the 3 patients treated in frank relapse of their disease, 2 had periods of 6 and 8 weeks, respectively, of stable disease but they eventually died as a result of disease progression. One of the patients treated in early second relapse achieved CR and remained in the third CR for 6 months before relapsing. The other 2 patients treated in PR had periods of 8 weeks each of stable disease but both died subsequently as a result of disease progression.

Haematological parameters

The changes in the haematological parameters caused by the rIL-2 infusion are shown in Table 3. There were significant drops in the haemoglobin levels and the platelet counts during each course of rIL-2 infusion. Blood transfusion was needed in 9 patients. Platelet transfusion was needed in 5 patients, 3 patients treated in relapse and 2 in their second remission. The absolute eosinophil counts increased steadily during the rIL-2 infusion ($P < 0.02$). Absolute lymphocyte counts decreased significantly ($P < 0.0001$) during each course of infusion and reached a nadir between days 2 and 3. However, rebound lymphocytoses occurred ($P < 0.0001$) and reached a peak 48–72 h after completion of the infusion. The degrees of rebound lymphocytosis varied among the courses of rIL-2 infusion patients received and did not predict the response of the patients to the therapy.

Biochemical parameters

There were consistent falls in the serum sodium, potassium and albumin during the period of rIL-2 infusion (Table 4). Whilst all patients were asymptomatic with the biochemical changes, severe hypokalaemia needing potassium replacement occurred initially in most patients. Such severe potassium loss was later prevented by the routine use of spironolactone. There were also increments in the serum urea, creatinine, bilirubin, and alkaline phosphatase with drops in the serum albumin. All these changes were transient and reverted to normal within a week of stopping the rIL-2.

Table 4. Changes in the blood biochemistry in AML patients following each course of rIL-2 infusion

Parameter	Pre	Post	*P*
Sodium (mmol/l)	136.1 ± 4.5	131.7 ± 5.3	<0.01
Potassium (mmol/l)	3.84 ± 0.26	3.35 ± 0.62	<0.01
Urea (mmol/l)	5.16 ± 2.00	7.24 ± 5.45	<0.05
Creatinine (μmol/l)	74.6 ± 13.1	89.9 ± 27.0	<0.02
Albumin (g/l)	36.3 ± 6.1	31.1 ± 4.9	<0.001
Bilirubin (μmol/l)	8.88 ± 4.28	17.17 ± 10.14	<0.001
Alkaline phosphatase (IU/l)	220.3 ± 181.3	257.7 ± 174.5	<0.01
Aspartate transaminase (IU/l)	30.9 ± 12.9	34.0 ± 18.2	NS

Table 5. Adverse reactions observed in this study, graded according to the WHO grading system

Adverse reaction	WHO grading system for severity				
	0	1	2	3	4
Fever					13
Hypotension		4	3	6	
Diarrhoea	5	6	2		
Nausea/vomiting	4	5	3	1	
Breathlessness	9	2	2		
Mucositis	5	4	4		
Cutaneous	6	5	2		

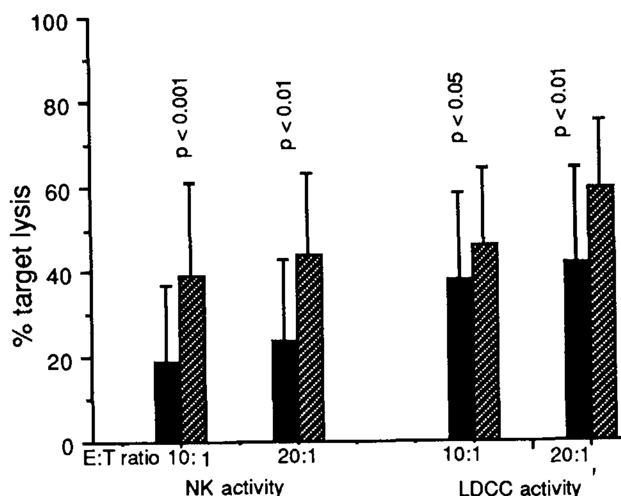

Fig. 1. Changes in the cytotoxic functions in acute myeloid leukaemia patients following each course of recombinant interleukin-2 (*rIL-2*) infusion. *NK*, natural killer; *LDCC*, lectin-dependent cellular cytotoxicity. ■ pre rIL-2; ▨ post rIL-2

Thyroid function tests were checked before and after the rIL-2 therapy in 3 patients. As reported previously [12], 1 patient developed severe hypothyroidism needing thyroxine replacement. This occurred within 2 months of starting the rIL-2 infusion. Another patient, although developing thyroglobulin and microsomal autoantibodies, remained euthyroid clinically and biochemically for 3 months but was later lost for follow-up when he returned to Greece.

Immunological parameters

In accord with a previous study [13], all patients with AML, whether in CR or in the leukaemic phase, had subnormal NK and lectin-dependent cellular cytotoxicity activities before any rIL-2 therapy. There were increases in the cellular cytotoxic functions in terms of target lysis after each course of rIL-2 (Fig. 1). There were also concomitant increases in the mononuclear cells expressing the cytotoxicity-linked cytoplasmic serine esterase ($CD3^+$ pre: $0.39 \pm 0.41 \times 10^9/l$ to post: $2.71 \pm 3.33 \times 10^9/l$ ($P < 0.05$); $CD4^+$ pre: $0.17 \pm 0.19 \times 10^9/l$ to post: $1.13 \pm 0.78 \times 10^9/l$ ($P < 0.01$); $CD8^+$ pre: $0.18 \pm 0.23 \times 10^9/l$ to post: $2.02 \pm 2.55 \times 10^9/l$ ($P < 0.05$); $CD56^+$ $0.25 \pm 0.35 \times 10^9/l$ to post: $1.04 \pm 0.92 \times 10^9/l$ ($P < 0.02$)), sIL-2R levels (pre: 1762 ± 2174 U/ml to post: 9747 ± 3883 U/ml) ($P < 0.0005$) and sCD8 levels (pre: 766 ± 418 U/ml to post: 1067 ± 692 U/ml) ($P < 0.05$). However, the TNF levels (pre: 17 ± 23 pg/ml to post: 17 ± 27 pg/ml) (NS) and the sCD4 levels (pre: 36.5 ± 26.4 U/ml to post: 81.6 ± 92.0 U/ml) (NS) did not change significantly.

Tolerability of rIL-2 infusion

Although adverse reactions were common, these patients received on average between 80% and 85% of the intended dose per treatment day of rIL-2. Nausea, vomiting, hypotension, fluid retention, diarrhoea and fever were very common, occurring in nearly all the patients. The severity of the adverse reactions experienced by these patients is shown in Table 5. Other toxic effects of rIL-2 observed included breathlessness and mucositis. Depression/anxiety was encountered in 4 patients. Only 2 patients received the total scheduled treatment of rIL-2. rIL-2 was discontinued because of disease progression in 5 patients and adverse reactions in 6 patients.

Discussion

There have only been very few AML patients treated with rIL-2 [2, 6] and therefore it was the aim of this study to assess the feasibility and clinical response of AML patients differing in disease status to this form of immunotherapy; in particular, to assess whether the clinical response matches the in vitro results reported so far.

Owing to the small number of patients treated in complete remission, no firm conclusion can be drawn from AML patients in their first or second CR. Nevertheless, in contrast to a previous study involving 8 patients in which 4 patients relapsed after a median remission duration of 8 months [2], all first-remission patients in this study have remained in first remission. Of the 4 patients treated in the second complete remission, 2 have also remained in second remission. Only by a controlled randomised trial involving more patients in complete remission can the question of the role of rIL-2 in these patients be answered.

The preliminary clinical results of patients treated in partial remission or early relapse with rIL-2 are slightly encouraging. Whilst 2 patients only had brief periods of stable disease, 1 patient achieved a complete remission. Similar results have been reported in which one patient achieved a durable fourth remission and one a third remission lasting for 7 months after being treated with rIL-2 alone in early relapse [6]. A point worth noting is that all 3 patients who achieved complete remission on rIL-2 alone (2 treated by Foa et al. and 1 in this study) had myelomonocytic leukaemia (M4). Such results support the in vitro findings that rIL-2 does not enhance the proliferation of malignant leukaemic blast cells, even those expressing monocytoid features [7].

The results of patients treated in frank relapse remain very disappointing. All patients eventually died of disease progression after only very brief periods of stable disease, a similar finding to that observed in patients treated by Foa et al. [6]. Whether or not these patients benefited from the rIL-2 therapy is unknown since the very brief periods of the stable disease may only be reflections of the slow tempo of disease progression in these patients.

It is, however, clear that rIL-2 infusion resulted in immune activation and up-regulation of the cytotoxic functions. This was observed in all the patients treated in this study, irrespective of whether the patients were in complete remission or with active disease. Other evidence for the intense immune activation in these patients is the development of autoimmune antibodies and autoimmune thyroiditis with resultant hypothyroidism observed in some of these patients.

Therefore the rather disappointing clinical results occurred in the face of immune activation, which may be cytotoxic to the leukaemic blast cells. This failure of immunotherapy with rIL-2 to produce results matching those observed in in vitro studies may be a reflection of the high tumour load in patients with frank AML. Hence, the in vitro effector: target ratio was effectively very low. A further possibility is the presence of tumour-derived suppressor factor [15], which inhibits the effector mechanism and tilts the balance between immune effector mechanisms generated by the immunotherapeutic agent and tumour escape from the effector mechanisms towards leukaemia progression.

Adverse reactions among these patients were common. Fever and hypotension were universal. These adverse reactions and the need for close monitoring of these patients would indicate that rIL-2 at the dose given to these patients has to be administered on an in-patient basis. Infusion of the rIL-2 was discontinued temporarily in most cases and resulted in only around 80% of the intended dose per day of rIL-2 being received by these patients.

In conclusion, we have shown in this study that it is feasible to administer high-dose continuous intravenous infusion of rIL-2 to AML patients, whether in remission or with active disease. Although there was immune activation, the preliminary clinical responses observed have not matched those obtained in in vitro studies. Whether or not LAK cells are needed to improve the response rate over rIL-2 alone in these patients deserves further investigations.

References

1. Adler A, Chervenick IA, Whiteside T, Lotzova E, Herberman RB (1988) Interleukin 2 induction of lymphokine-activated killer (LAK) activity in the peripheral blood and bone marrow of acute leukemia patients: I. Feasibility of LAK generation in adult patients with active disease and in remission. Blood 71: 709–716
2. Barrett AJ (1989) IL-2 in treatment of haematological malignancies. Presented at the Grantholder's meeting, Leukaemia Research Fund, London, November 1989
3. Beran M, Hansson M, Kiessling R (1983) Human natural killer cells can inhibit clonogenic growth of fresh leukemic cells. Blood 61: 596–599
4. Champlin RE, Ho WG, Gale RP, et al (1985) Treatment of acute myelogenous leukemia: a prospective controlled trial of bone marrow transplantation versus consolidation chemotherapy. Ann Intern Med 102: 285–291
5. Fletcher M, Goldstone AL (1987) Recent advances in the understanding of the biochemistry and clinical pharmacology of interleukin-2. Lymphokine Res 6: 45–57
6. Foa R, Meloni G, Tosti S, et al (1990) Treatment of residual disease in acute leukemia patients with recombinant interleukin-2 (IL-2): clinical and biological findings. Bone Marrow Transplant 6 [Suppl 1]: 98–102
7. Foa R, Caretto P, Fierro MT, et al (1990) Interleukin 2 does not promote the in vitro and in vivo proliferation and growth of human acute leukaemia cells of myeloid and lymphoid origin. Br J Haematol 75: 34–40
8. Gillis S, Smith KA (1977) Long-term culture of tumour-specific cytotoxic T-cells. Nature 268: 154–156
9. Grimm EA, Mazumder A, Zhang HZ, Rosenberg SA (1982) Lymphokine-activated killer cell phenomenon. Lysis of natural killer-resistant fresh solid tumour cells by interleukin 2-activated autologous human peripheral blood. J Exp Med 155: 1823–1841
10. Henney CS, Kurybayashi K, Kern DE, Gillis S (1981) Interleukin-2 augments natural killer cell activity. Nature 291: 335–338
11. Lafreniere R, Rosenberg SA (1985) Successful immunotherapy of murine experimental hepatic metastases with lymphokine-activated killer cells and recombinant interleukin-2. Cancer Res 45: 3735–3741
12. Lim SH, Callaghan T, Goldstone AH (1991) Thyroid disorders in two cases of AML following treatment with recombinant interleukin-2. Acta Hematol (Basel) 85: 49–50
13. Lim SH, Worman CP, Jewell AP, Goldstone AH (1991) Cellular cytotoxic function and potential in acute myelogenous leukaemia. Leuk Res 15: 6411–6444
14. Lim SH, Worman CP, Jewell A, Tsakona C, Giles FJ, Goldstone AH (1991) Lymphocytes activation and serine esterase induction following recombinant interleukin-2 infusion for lymphoma and acute leukaemias. Cancer Immunol Immunother 33: 133–137
15. Lim SH, Worman CP, Jewell AP, Goldstone AH (1991) Production of tumour-derived suppressor factor in patients with acute myeloid leukaemia. Leuk Res 15: 263–268
16. Lista P, Fierro MT, Liao XS, et al (1989) Lymphokine-activated killer (LAK) cells inhibit the clonogenic growth of human leukaemia stem cells. Eur J Haematol 42: 425–430
17. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207–214
18. Mule JJ, Shu S, Schwarz SL, Rosenberg SA (1984) Adoptive immunotherapy of established pulmonary metastases with LAK cells and recombinant interleukin-2. Science 255: 1487–1489
19. Powles RL, Morgenstern G, Clink HM (1980) The place of bone marrow transplantation in acute myelogenous leukaemia. Lancet 1: 1047–1050
20. Price G, Brenner MK, Prentice HG, Hoffbrand AV, Newland AC (1987) Cytotoxic effects of tumour necrosis factor and gamma-interferon on acute myeloid leukemia blasts. Cancer 55: 287–290
21. Rees JKH, Gray RG, Swirsky E, Hayhoe FGJ (1986) Principal results of the Medical Research Council's 8th acute myeloid leukaemia trial. Lancet 2: 1236–1241

22. Rosenberg SA, Lotze MT, Muul LM, et al (1985) Observation on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. N Engl J Med 313: 1485–1492
23. Rosenberg SA, Lotze MT, Muul LM, et al (1987) A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high dose interleukin-2 alone. N Engl J Med 316: 889–897
24. Rosenstein M, Yron I, Kaufmann Y, Rosenberg SA (1984) Lymphokine-activated killer cells: lysis of fresh syngeneic natural killer-resistant murine lymphocytes cultured in interleukin-2. Cancer Res 44: 1946–1953
25. West WH, Tauer KW, Yanelli JR, et al (1987) Constant infusion recombinant interleukin-2 in adoptive immunotherapy of advanced cancer. N Engl J Med 316: 898–905