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High-Dose Systemic Interleukin-2 Therapy in Stage IV Neuroblastoma for One Year After Autologous Bone Marrow Transplantation: Pilot Study

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Despite intensified chemotherapy protocols, including autologous bone marrow transplantation (ABMT), stage IV neuroblastoma has a poor prognosis, and modern therapeutic trends are aimed at the eradication of minimal residual disease, which is thought to be the main factor leading to relapse. In this pilot study, we report the systemic administration of high doses of interleukin-2 after ABMT in four patients. Five-day cycles of IL-2 at a dose of 18×10^6 IU/m^2/day were administered at variable time intervals as frequent as it was necessary to maintain the levels of natural killer (NK) cytotoxic activity higher than the median control value (40 LU/ml blood) throughout 1 year from the start of first IL-2 treatment. After Il-2 infusion, NK and LAK activities increased significantly (median 742×10^{-3} LU/ml blood and 186.8×10^{-3} LU/ml blood, respectively). Toxicities were transient and no life-threatening complications were observed. Fever, anorexia, skin rash and enlarged liver were always present. Anaemia, thrombocytopenia, leukocytosis, lymphocytosis and and eosinophilia occurred following most of the IL-2 courses. Although the small number of patients does not allow an estimation of the immunomodulatory-antineoplasic effects of IL-2, the results seem promising for the management of neuroblastoma patients.

Key words: interleukin-2, natural killer, neuroblastoma, autologous bone marrow transplantation

INTRODUCTION

Neuroblastoma is one of the most common and characteristic childhood neoplasms. At diagnosis, around 60% of patients have disseminated disease (stage IV), with a poor prognosis [1]. Despite intensified chemotherapy protocols, including autologous bone marrow transplantation (ABMT), long-term survival for high risk neuroblastoma in children is still below 30% [2,3]. Presumably chemotherapy-resistant tumor cells survive the conditioning regimen, and this minimal residual disease, as well as tumor cells persisting in the marrow used to rescue the patients, could be the origin of the high relapse rate [4]. Neuroblastoma is a nonimmunogenic tumor [5,6]. Therefore, its interaction with the immunological system would be mediated by MHC-unrelated cytotoxic natural killer (NK) and lymphokine-activated killer (LAK) activities.

It has been shown that neuroblastoma cells can effectively be killed in vitro by interleukin-2 (Il-2)-activated mononuclear effector cells, and several reports have shown that NK cells are the main effectors implicated in the mechanism of neuroblastoma cell killing [7]. The first report of IL-2 treatment in active metastasic neuroblastoma was published by Favrot et al. in 1989 [8]; they reported partial responses and disappearance of bone metastases during treatment in two children, with disease progression after cessation of therapy. In our opinion the optimal effect of IL-2 could be obtained when there is minimal residual neoplasia, but not in the setting of progressive disease.

We report the systemic administration of high doses of IL-2 for 1 year after ABMT in stage IV neuroblastoma in patients. IL-2 was administered in 5-day cycles, with intervals adjusted to maintain the level of NK activity higher than control values, evaluating the feasibility, clinical toxicity, and immunological response. The final objective was to avoid the tumor relapse. The first four patients entered into this trial have finished the entire treatment.

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TABLE I. Patient Data

Patient	Age (months)	Primary site	Cycles IL-2[a]	First IL-2 post-ABMT[b]	Outcome[c]
1	3	Adrenal	6	70	CR[d]/52
2	34	Adrenal	5	69	D[d]/15
3	18	Adrenal	6	100	CR/33
4	44	Thoracic	5	110	CR/21

[a]Number of cycles administered.
[b]Days from ABMT to first IL-2 cycle.
[c]Time of outcome expressed in months from ABMT.
[d]CR: complete remission; D: dead.

TABLE II. Courses of IL-2 in Neuroblastoma Patients

Patient	IL-2 Cycles 1st[a]	2nd[b]	3rd[b]	4th[b]	5th[b]	6th[b]
1	70	60	125	160	245	303
2	69	70	146	180	227	
3	100	55	98	136	212	266
4	110	55	131	212	270	

[a]Days after autologous bone marrow transplantation (ABMT) at which interleukin-2 (IL2) therapy was initiated (day 0 of IL-2 treatment).
[b]Days of starting of each IL-2 cycle from first cycle.

PATIENTS AND METHODS

Patients

We started this protocol in January 1990. Four stage IV neuroblastoma patients entered into this trial after accomplishing the eligibility criteria: to have obtained complete remission after surgery, adjuvant chemotherapy and ABMT. Profiles of the four patients are summarized in Table I. The response to treatment was evaluable by abdominal computerized scan and ultrasound, thoracic scan, MIBG bone scanning and cytohistological and immunological analyses of two bone marrow biopsies. No patient received cytotoxic or corticosteroid treatment 30 days before and during IL-2 treatment. All patients had normal cardiac, renal, and hepatic function, and well as hematological recovery after ABMT, (leukocyte levels $>2{,}500/mm^3$, neutrophil count $>1{,}000/mm^3$, platelet count $>100{,}000/mm^3$, and hemoglobin >10 g/dl), without transfusion since 30 days before. The whole treatment programme was explained in detail and written informed consent was obtained from the children's parents.

Chemotherapy Treatment

Chemotherapy treatment consisted of cycles of CAD (7 days oral cyclophosphamide 150 mg/m^2 and i.v. adriamicyn 35 mg/m^2 on day 8) alternating every 3 weeks with CP-VM26 (4 days i.v. cisplatin 50 mg/m^2 on days 1,2,4 and 5, and VM-26 90 mg/m^2 as a 24-hour infusion on days 3 and 6. Conditioning regimen for ABMT consisted of BCNU (300 mg/m^2 day 1), VM-26 (250 mg/m^2 days 1,2,3, and 4) and melphalan (180 mg/m^2 day 5). Bone marrow was infused on day 7 [9].

IL-2 Administration

IL-2 (Euro-Cetus Corporation, Amsterdam, the Netherlands) treatment was started when hematological recovery was reached after ABMT (Table I). The dose was 18×10^6 IU/m^2/day in saline solution, via an electric pump as continuous infusion over 24 hours through a central venous catheter. IL-2 was administered in 5-day cycles, with variable intervals depending on the level of NK cytotoxic activity achieved. A new cycle was started whenever the patients' NK activity was equal of less than a normal childs' NK activity; this level was estimated as 40 lytic units (LU)/10^9 of mononuclear cells in a parallel study with 25 healthy controls from a population of patients with no tumor or immunologically related diseases, ages ranging between 2 and 15 years (unpublished data). The treatment was maintained throughout 1 year from the start of IL-2 therapy (Table II). Toxicity was graded from 0 (no toxicity) to 4 (life-threatening) according to the World Health Organization (WHO) scale [10].

Hematological and Immunological Monitoring

Complete blood counts, differential cell count and serum chemistries were evaluated before each cycle of IL-2 treatment and daily until return to normal values. NK and LAK cytotoxic activities were measured at the end of IL-2 infusion 1 month later and then weekly until the next treatment. Peripheral blood MNC were obtained by differential centrifugation of heparinized blood samples through a Ficoll-Paque gradient (Pharmacia LKB, Piscataway, NJ) [11]. NK and LAK cytotoxic activities were determined from freshly isolated MNC by a ^{51}Cr release assay using the NK-sensitive K 562 and NK-resistant Raju cell lines respectively, as target cells [12]. Lytic Units (LU) per 10^9 effector cells were calculated from the specific cytotoxicity at each of the effector/target ratios according to a modification [13] of the formula originally described by Heney [14]. Results are expressed in LU per ml of blood instead of the more usual LU per MNC in order to better reference the level of systemic cytotoxic activity. Therefore, the experimental values of cytotoxic activities become dependent on the number of circulating effector cells per ml of blood, which in turn, largely depend upon the effects of exogenous IL-2 administration.

Supportive Care

All patients had a venous central line, and were monitored in each IL-2 cycle for heart and respiratory rates, arterial blood pressure, temperature, weight and urine flow output. Fluid intake was restricted to 1.2 l/m^2 in

TABLE III. Clinical Toxicity of IL-2 Treatment in 22 Cycles Administered in 4 Patients

	Number of cycles	%
Fever	22	100
Anorexia	22	100
Skin rash	22	100
Hepatomegaly	22	100
Diarrhea	21	95
Splenomegaly	20	91
Edema	14	64
Sepsis	4	18
Weight gain (>10%)	0	0
Hypotension	0	0

TABLE IV. Hematologic Toxicity of IL-2 in 22 Cycles Administered in the 4 Patients

		Number of cycles	%
Hemoblobin	<8 g/dl	2	9
Thrombocytopenia	<100,000/mm^3	17	77
Leukocytosis	>10,000/mm^3	17	77
Neutrophilia	>7,500/mm^3	9	40
Lymphocytosis	>4,000/mm^3	19	86
Eosinophilia	>400/mm^3	20	90
Monocytosis	>1,000/mm^3	9	40

order to avoid fluid overload and interstitial edema. Acetaminophen and hydroxyzine hydrochloride were given to control fever and pruritus.

Statistical Evaluation

Two-tailed Wilcoxon signed rank test was used to compare pre- and post-treatment paired data, and two-tailed Wilcoxon rank-sum test to compare two groups of unpaired experimental data. The correlation coefficient (c) between kinetics was determined using the two-tailed Spearmen rank-order correlation. Significance level was set at $P < 0.05$.

RESULTS

Feasibility and Toxicity

A total of 22 cycles of IL-2 were administered, 6 to patients 1 and 3, and 5 to patients 2 and 4. Systemic toxicity was moderate and limited to grade 2, generally worse during the last 2 days of treatment (Table III). Fever (more than 38°C), anorexia, skin rash consisted in disseminated erythema followed by desquamation, and enlarged liver were always present, appearing within few hours from the start of the infusion. Diarrhea was always moderate in severity and responded to symptomatic treatment. Hepatic transaminase and bilirrubin levels were permanently normal. Splenomegaly occurred after most cycles. Facial edema and minor electrolytic disturbances were frequent findings in our patients. Side effects attributed to fluid retention were tolerable and rapidly responded to diuretic treatment without any severe pulmonary or central edema. None of the patients experienced central nervous system treatment-related adverse effects. Renal failure was not observed. All symptoms resolved within 48 hours after cessation of therapy except for the skin rash which lasted up to one week. None of the patients required management in the intensive care unit. No deaths occurred.

Patients 3 and 4 suffered bacteremia due to a gram-positive organism; each one was treated with ev Vancomycin. The infections were considered catheter-related. Patient 1 had an episode of gram-negative sepsis related with a pneumonia after the third cycle of IL-2, as well as patient 3 after the fourth cycle, both successfully treated with oral antibiotics.

The level of hemoglobin dropped below 8 g/dl in patients 1 and 2 after the first cycle of IL-2, and they received blood transfusions. The platelet count dropped below 2,0000/mm^3 in patient 2, requiring transfusion support, although thrombocytopenia (platelet count <100,000/mm^3) occurred following most of the IL-2 courses, as well as leukocytosis (white blood cell count >10,000/mm^3), lymphocyte amount upper 4,000/mm^3, and significant eosinophilia (Table IV). It is important to note this point because all four patients were below lymphopenic (<4,000/mm^3) status after ABMT, and IL-2 administration induces a dramatic decrease on circulating lymphocyte count mainly on early days of initiating the each cycle of treatment. Lymphocyte median before treatment was 44.5% of total leukocyte cells (range 39% to 51%); after the first day of IL-2 administration, it decreased to 8.2%, and a rebound lymphocytosis developed shortly after the end of each therapy cycle. All changes returned to previous values within a few days after IL-2 infusion was discontinued.

NK and LAK Activity

The levels of NK cytotoxic activity before each cycle of administration of IL-2 in the four patients (median value 17.3×10^{-3} LU/ml blood, range 12.2 to 23.7×10^{-3} LU/ml blood) were significantly lower than the levels found in the healthy control group (median value 93.5×10^{-3} LU/ml blood, range 87.4 to 169.3×10^{-3} LU/ml blood). After IL-2 treatment, NK activity increased significantly (median 742×10^{-3} LU/ml blood, range 105 to $7{,}119 \times 10^{-3}$; (Fig. 1). A similar situation occurred with LAK activity levels with a median pretreatment level of less than 10 LU/ml blood and a post-treatment level of 186.8×10^{-3} LU/ml blood (range 16.6 to 952.7) when IL-2 was administered (Fig. 2). The kinetics of NK and LAK activities (Figs. 3, 4) showed significant correlations with each other (c = 58.8%, critical value = 41.2%), reaching increscent levels along the cycles.

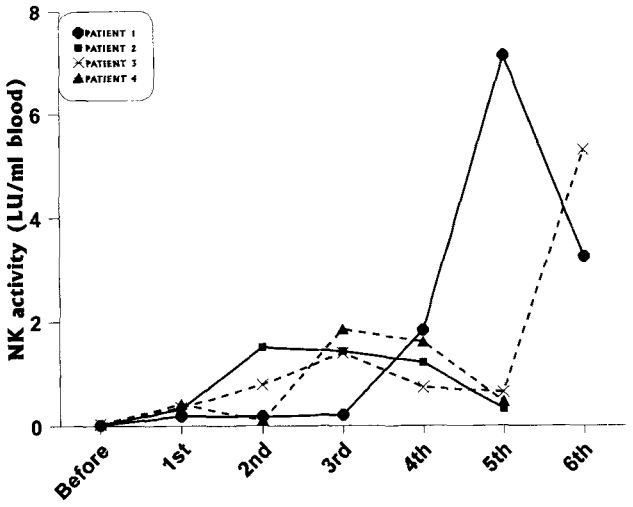

Fig. 1. Effect on IL-2 infusion on NK cytotoxic activities. Values wer 22 paired control data obtained before each cycle of treatment and 36 hours after the completion of IL-2 infusion. NK activities were expressed in Lytic Units (LU) per ml of blood. Horizontal line represents the median values. There are overlapping of some data points.

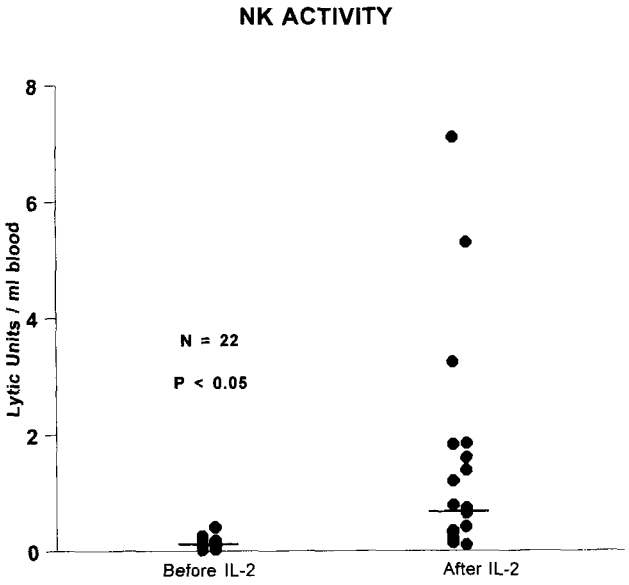

Fig. 3. Kinetics of NK activity after completion of each IL-2 infusion of four patients. Values were experimental data obtained 36 hours after the end of IL-2 infusion.

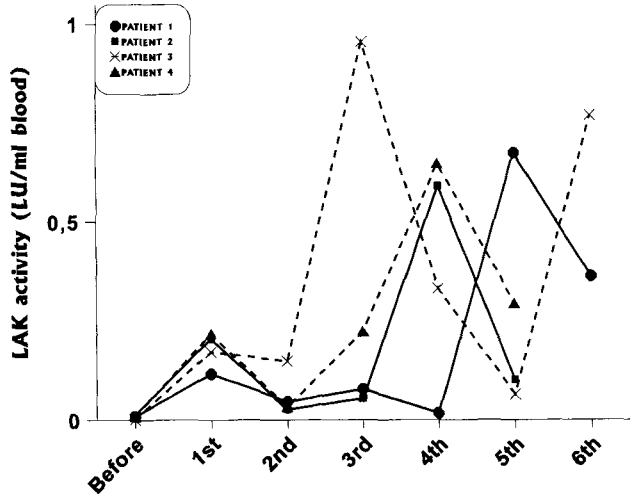

Fig. 2. Effect of IL-2 infusion on LAK cytotoxic activities. Values were 22 paired control data obtained before each cycle of treatment and 36 hours after the completion of IL-2 infusion. NK activites were expressed in Lytic Units (LU) per ml of blood. Horizontal line represents the median values. There are overlapping of some data points.

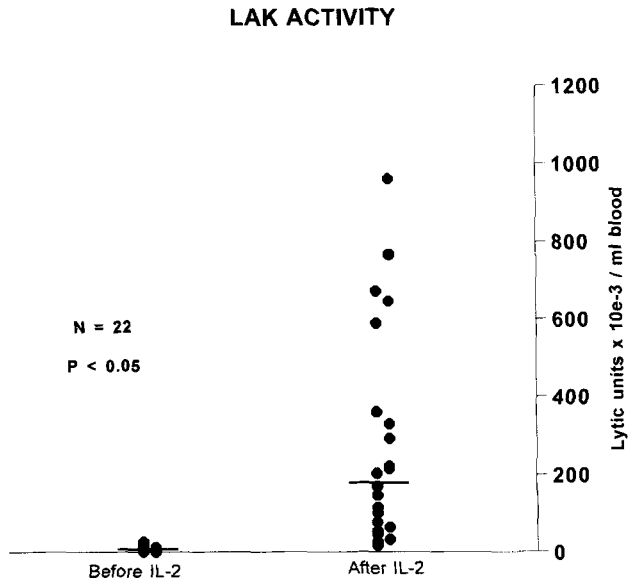

Fig. 4. Kinetics of LAK activity after completion of each IL-2 infusion of four patients. Values were experimental data obtained 36 hours after the end of IL-2 infusion.

Response to IL-2

Three patients are alive in complete remission (CR). Patient 1 is in CR 52 months after ABMT, and patients 3 and 4 at 33 and 21 months, respectively. Patient 2 suffered from cervical adenopathy one month after the third cycle, which shrank away with the next IL-2 treatment and reappeared after the fifth IL-2 treatment; tumoral relapse was confirmed and he died 5 months later.

DISCUSSION

Stage IV neuroblastoma continues to be a challenge for pediatric oncologist because of its poor prognosis. Combination therapy consisting of surgery, chemotherapy and irradiation achieves low patient survival rates, and other modes of therapy have thus been sought. Because even supralethal chemotherapy does not seem to have

any significant effect on minimal residual disease, other therapeutic appraches are urgently needed.

Low NK activity in patients with neuroblastoma was described by Gerson et al. [15], although whether this is a result of an intrinsic NK cell defect or other mechanism is not known. In vitro studies showed that it is possible to generate NK and LAK activity in peripheral lymphocytes from patients with neuroblastoma after a short incubation time with IL-2, suggesting that neuroblastoma cells are more susceptible to NK and LAK cell-mediated cytotoxicity than reported for other malignancies [16,17]. There is some doubt whether immunotherapy exhibits a dose-dependent effect, and many trials are searching to establish the optimum enhancement of in vivo immunological parameters that may correlate with clinical response [18–21].

Our study was undertaken to asses in vivo clinical toxicities and immunomodulatory effects associated with IL-2 therapy for a 1-year period after ABMT. The main objective was to stimulate the immune systems and induce a "graft versus disease" effect that could avoid the tumor relapse. Several authors have published the results of IL-2 treatment in patients with advanced or metastatic neuroblastoma, showing partial or complete transient remissions [22]. Experimental results suggest that the optimal timing for IL-2 immunotherapy could be during the first months after high dose chemotherapy and bone marrow transplantation. During this period patients have a profound T cell defect with undetectable IL-2 secretion, although patients' T-lymphocytes do respond to exogenous IL-2 [23]. Systemic administration of IL-2 after bone marrow transplant (BMT) for a short time (one or two 5-day cycles) seems to induce a high NK and LAK activity in peripheral blood mononuclear cells [24–26].

In our experience, continuous infusion of 18×10^{-6} IU/m^2/day for 5 days did not induce major or nonreversible toxicities. It must be emphasized that children probably tolerate IL-2 much better than adults [27], although some authors have reported serious complications [28].

Adverse effects accompanying high-dose intravenous IL-2 therapy may be severe, with cardiovascular, pulmonary, hematologic, hepatic, neurologic, and dermatologic complications [29–32], but in our experience no patient required discontinuation of therapy due to side effects. An adequate control of fluid intake could decrease the incidence of capillary leak syndrome, although mild edemas and minor electrolytic abnormalities can be observed [33,34]. No neuropsychological disturbances were observed in our patients [35]. Transient moderate hematologic toxicity occurred in all four patients. Thrombocytopenia was not complicated by bleeding diathesis in any case. Eosinophilia an dlymphocytopenia followed by rebound lymphocytosis after completion of IL-2 infusion were constant and have been previously described [36].

High rates of bacterial sepsis in patients receiving high doses of IL-2 have been attributed to acute and reversible defects in neutrophil chemotaxis [37,38]. These infections are usually caused by *S. aureus*. Bacteremias are unrelated to the presence of neutropenia, whereas the concentration of IL-2 significantly correlates with the occurrence of infection [39]. The mechanisms for the induction of these chemotactic defects has not been established [40].

We conclude that it is feasible to maintain high levels of NK and LAK activities in children with neuroblastoma during a 1-year period post-ABMT. The small group of patients studied does not allow the establishment of any conclusion regarding the capacity of the putative IL-2-induced immunomodulatory effect in eliminating minimal residual disease, but the results seems promising enough for the evaluation of larger groups of patients.

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REFERENCES

1. Hayes FA, Smith EI: Neuroblastoma. In Pizzo PA, Poplack DG (eds): "Principles and Practice of Pediatric Oncology." Philadelphia: J.B. Lippincott, 1989, pp. 607–622.
2. Evans AE, August CHS, Kamani N, Bunin N, Goldwein J, Ross AJ III, D'Angio GJ: Bone marrow transplantation for high risk neuroblastoma at the Children's Hospital of Philadelphia: An updata. Med Pediatr Oncol 23:323–327, 1994.
3. Garaventa A, Ladenstein R, Chauvin F, Lanino E, Philip I, Corciulo P, Brisigotti M, Favrot M, Dini G, Philip T: High dose chemotherapy with autologous bone marrow resuce in advanced stage IV neuroblastoma. Eur J Cancer 29A:487–491, 1993.
4. Duan DS, Farmer D, Rayner AA, Sadee W: Cytotoxicity of lymphokine-activated killer cells against human neuroblastoma cells: Modualation by neuroblast differentiation. Med Pediatr Oncol 18:339–344, 1990.
5. Clayberger C, Medeiros LJ, Link MP, Warnke RA, Wright A, Koller TD, Smith SD, Krensky AM: Absence of cell surface LFA-1 is a mechanism of scape from innumosurveillance. Lancet 2:533, 1987.
6. Sugimoto T, Horii Y, Hino T, Kemshaed ST, Kuroda H, Sawada T, Morioka H, Imanishi J, Inoko H: Differential susceptibility of HLA class II antigens induced by gamma-interferon in human neuroblastoma cell lines. Cancer Res 49:1824–1926, 1989.
7. Handgretinger R, Bruchelt G, kimming A, Dopfer R, Niethammer D, Truener J: In vitro induction of lymphokine-activated killer (LAK) activity in patients with neuroblastoma. Pediatr Hematol Oncol 6:307–317, 1988.
8. Favrot M, Floret D, Michon J, Negrier S, Bouffet E, Coze C, Gaspard M, Cochat P, Thiesse P, Andreu G, Costil J, Zucker JM, Bernard JL, Fridman WH, Mathiot C, Bijmann JT, Franks CR, Kremens B, Philip I, Philip T: A phase-II study adoptive immunotherapy with continous infusion of interleukin-2 in children with

advanced neuroblastoma. A report on 11 cases. Cancer Treat Rev 16:129–142, 1989.
9. Castel VS, Badal MI, Bezanilla JLR, Herrero AD, LLombart AB, Ruiz JJ, Sanchez de Toledo J: Neuroblastoma. Resultados del protocolo N-I-87. An Esp Pediatr 38:471–476, 1993.
10. Miller AB, Hoogstraten B, Staquet M, Winkler A: Reporting results of cancer. Cancer 47:207–214, 1981.
11. Boyum A: Isolation of mononuclear cells and granulocytes from human blood. Scand J Clin Lab Invest 97:77–79, 1968.
12. Davidson WF: Cellular requirements for the induction of cytotoxic T cells in vitro. Immunol Rev 35:263–265, 1977.
13. Martí F, Miralles A, Peiró M, Amill B, Dalmases C, Piñol G, Rueda F, García J: Differential effect of cryopreservation on natural killer and lymphokine activated killer activities. Transfusion 33:651, 1993.
14. Heney CS: Quantitation of the cell mediated response. The number of cytolytically active mouse lymphoid cells induced by immunization with allogeneic mastocytoma cells. J Immunol 107:1551–1554, 1971.
15. Gerson JM, Herberman RB: Systemic and in situ natural killer activity in patients with neuroblastoma. In Evans AE (ed): "Advances Neuroblastoma Research." New York: Raven Press, 1980, pp. 251–259.
16. Chien CH, Hsieh KH: Interleukin-2 immunotherapy in children. Pediatrics 86:937–943, 1990.
17. Rossi AR, Pericle F, Rashleigh S, Janiec J, Djeu JY: Lysis of neuroblastoma cell lines by human natural killer cells activated by Interleukin-2 and Interleukin-12. Blood 83:1323–1328, 1994.
18. Rosenberg SA, Lotze MT, Yang JC, Aebersold PM, Linehan WM, Seipp CA, White MS: Experience with the use of high-sode interleukin-2 in the treatment of 625 cancer patients. Ann Surg 210:474–485, 1986.
19. Nasr S, McKolanis J, Pais R, Findley H, Hnath R, Waldrep K, Ragab AH: A phase I study of interleukin-2 in children with cancer and evaluation of clinical and immunologic status during therapy. Cancer 64:783–788, 1989.
20. Berthold F, Himmelmann U, Pohl U: Natural interleukin-2 and lymphokine activated killer cells in the treatment of neuroblastoma in vitro and in vivo. Adv Neuroblastoma Res 3:417–421, 1991.
21. Whittington R, Faulds D: Interleukin-2. A reveiw of its pharmacological properties and therapeutic use in patients with cancer. Drugs 46:446–514, 1993.
22. Foreman NK, Rill DR, Coustan-Smith E, Douglas EC, Brenner MK: Mechanisms of selective killing of neuroblastoma cells by natural killer cells and lymphokine activated killer cells. Potential for residual disease erediction. Br J Cancer 67:933–939, 1993.
23. Favrot M, Michon J, Bouffet E, Negirer S, Cochat P, Floret D, Gaspard M, Coze C, Andreu G, Franks CR, Philip I, Philip T: rIL-2 Immunotherapy for 19 Children with advanced metastatic neuroblastoma. In Freund, Link, Welte (eds): "Cytokines in hemopoiesis, oncology and AIDS." Heidelberg: Springer-Verlag, 1990, pp. 684–690.
24. Negrier S, Michon J, Floret D, Bouffet E, Gentet JC, Philip E, Cochat P, Stamm D, Costil J, Gaspard M, Andreu G, Palmer P, Franks CR, Zucker JM, Bernard JL, Fridman WH, Favrot M, Philip T: Interleukin-2 and lymphokine-activated killer cells in 15 children with advanced metastatic neuroblastoma. J Clin Oncol 9:1363–1370, 1991.
25. Maraninchi D, Blaise D, Olive D, Attal M, Gaspard MH, Boule D, Jasmin C, Pourreau C, Palmer P, Negrier S, Philip I: Interleukin-2 after autologous bone marrow transplantation (ABMT): A pilot study of late administration, 2–3 months post ABMT. In Freund, Link, Welte (eds): "Cytokines in Hemopoiesis, Oncology and AIDS." Heidelberg: Springer-Verlag, 1990, pp. 691–697.
26. Dopfer R, Handgretinger R, Klingebiel T, Reuland P, Eppinger T, Scheel-Walter H, Ehninger G, Niethammer D: IL-2 treatment in a patient with stage IV neuroblastoma after bone marrow transplantation. In Freund, Link, Welte (eds): "Cytokines in Hemopoiesis, Oncology and AIDS." Heidelberg: Springer-Verlag, 1990, pp. 699–705.
27. Chien CH, Hsieh KH: Interleukin-2 immunotherapy in children. Pediatrics 86:937–943, 1990.
28. Michon J, Negrier S, Coze C, Zucker JM, Frappaz D, Oskam R, Palmer P, Frank CR, Bouffet E, Floret D, Favort M, Fridman WH, Philip T: Administration of high dose recombinant interleukin 2 after autologous bone marrow transplantation (ABMT) in 23 patients with metastatic neuroblastoma: Abstract 4204, 19th Meeting of the EBMT 1993; Garsmisch, Germany.
29. Ravaud A, Negrier S, Mercatello A, Cany L, Coronel B, Ranchere JY, Bécouarn Y, Bui BN, Philip T: Effects secondaires de l'interleukine 2. Bull Cancer 78:989–1005, 1991.
30. Mercatello A, Hadj-Aïssa A, Negrier S, Tognet E, Bret M, Favrot M, Poret N, Philip T, Moscovtchenko JF: Modifications rénales au cours de l'immunothérapie par interleukine 2. In: "Réanimation et Médecine d'Urgence." Paris: Expansion Scientifique Française, 1991, pp. 479–489.
31. Webb DE, Austin III HA, Belldegrun A, Vaughan E, Linehan WM, Rosenberg SA: Metabolic and renal effects of interleukin-2 immunotherapy of advanced cancer. Clin Nephrol 30:141–145, 1988.
32. Gaspari AA, Lotze MT, Rosenberg SA, Stern JB, Katz SI: Dermatologic changes associated with interleukin-2 administration. JAMA 258:1624–1629, 1987.
33. Ettinghausen SE, Puri RK, Rosenberg SA: Increased vascular permeability in organs mediated by the systemic administration of lymphokine-activated killer cells and recombinant interleukin-2 in mice. J Natl Cancer Inst 80:177–188, 1988.
34. Rosenstein M, Ettinghausen SE, Rosenberg SA: Extravasation of intravascular fluid mediated by the systemic administration of recombinant interleukin 2. J Immunol 137:1735–1742, 1986.
35. Caraceni A, Martini C, Belli F, Mascharoni L, Rivoltini L, Arienti F, Cacinelli N: Neuropsychological and neurophysiological assessment of the central effects of interleukin-2 administration. Eur J Cancer 29:1266–1269, 1993.
36. Blaise D, Olive D, Stoppa AM, Viens P, Pourreau C, Lopez M, Attal M, Jasmin C, Monges G, Mawas C, Mannoni P, Palmer P, Franks C, Philip T, Maraninchi D: Hematologic and immunologic effects of the systemic administration of recombinant interleukin-2 after autologous bone marrow transplantation. Blood 76:1092–1097, 1990.
37. Klempner MS, Noring R, Mier JW, Atkins MB: An acquired chemotactic defect in neutrophils from patients receiving interleukin-2 immunotherapy. N Engl J Med, 322:959–965, 1990.
38. Snydman DR, Sullivan B, Gill M, Gould JA, Parkinson DR, Atkins MB: Nosocomial sepsis associated with interleukin-2. Ann Intern Med 112:102–107, 1990.
39. Pockaj BA, Topalian SL, Steinberg SM, White DE, Rosenberg SA: Infectious complications associated with interleukin-2 administration: A retrospective review of 935 treatment courses. J Clin Oncol 11:136–147, 1993.
40. Mier JW, Vachino G, Klempner MS, Aronson FA, Noring R, Smith S, Brandon EP, Laird W, Atkins MB: Inhibition of interleukin-2 induced tumor necrosis factor release by dexamethasone: Prevention of an acquired neutrophil chemotaxis defect and differential suppression on interleukin-2-associated side effects. Blood 76:1933–1940, 1990.