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Can interleukin-2 reverse anthracyclin chemoresistance in metastatic soft tissue sarcoma patients. Results of a prospective phase II clinical trial

Abstract

Anthracyclin-based chemotherapy is the most efficient chemotherapy for advanced or metastatic soft tissue sarcoma (STS). Development of anthracyclin chemoresistance has been widely documented. In a previous clinical trial, we evaluated a possible reversal of anthracyclin chemoresistance after exposure to subcutaneous IL-2. The current phase II clinical study entered 17 proven

metastatic STS patients, refractory to anthracyclin chemotherapy, who received IL-2, and subsequent anthracyclin-based chemotherapy. Subcutaneous IL-2 was administered at 18 million Units/day, 5 days a week for two consecutive weeks. Treatment was administered safely at the full dose for 16 out of 17 patients, and toxicity was mild. One patient had treatment stopped because of rapidly progressive disease. As soon as patients met biological and clinical criteria, chemotherapy was administered. The median delay was 12 days (2-23) from the end of IL-2 administration. Only 13 patients received anthracyclin chemotherapy after IL-2. The other 4 patients did not receive chemotherapy for progressive disease. One partial response was observed out of 13 evaluable patients (7.7% overall response, 95% confidence interval: 0.2 to 36). The overall response rate was 5.9% (95% CI: 0.15 to 29), so the study was stopped due to lack of efficacy. In previous and current studies, a few patients have developed restored anthracyclin chemosensitivity following exposure to IL-2. No conclusive evidence of IL-2 chemoresistance reversal was obtained from this study. Further investigations need to be performed with perhaps a larger group of more carefully selected patients using a different schedule and sequence of combined cytokines and chemotherapy.

Full text

INTRODUCTION

Advanced metastatic soft tissue sarcoma (STS) remains incurable in the majority of patients. Chemotherapy has demonstrated moderate activity with low response rate. The most active drugs available are anthracyclin, ifosfamide, and dacarbazine. Anthracyclin is currently considered one of the cornerstones of treatment for metastatic STS, either as a single agent or in combination, and with an average response rate of about 20% [1]. Drug resistance remains one of the major problems, with many patients exhibiting primary or secondary resistance after exposure.

New treatments such as cytokines have been investigated in this disease and IL-2 has been found to have broad-spectrum antitumoral activity. Disappointing results, however, have been obtained in advanced and/or metastatic STS [2].

In a previous study involving 12 metastatic STS patients, in whom disease progressed after chemotherapy, only one partial response was observed.

However, since all progressing patients received subsequent chemotherapy following IL-2, 2 resistant patients became responders to chemotherapy, suggesting that IL-2 could modulate previous chemoresistance. Similar observations have been already described *in vitro* [3].

To explore, quantify and document this hypothesis, we established a prospective clinical trial where patients with metastatic STS, refractory to anthracyclins, were treated with IL-2 followed by identical anthracyclin-based chemotherapy: we report here the results of 17 patients prospectively treated within this trial.

PATIENTS AND METHODS

A multicentric, prospective, phase II clinical trial was conducted between November 1995 and May 1997. The principal objective of this study was to determine the response to anthracyclin-based chemotherapy following IL-2 treatment in patients refractory to similar chemotherapy. The secondary objective was to evaluate clinical tolerance of subcutaneous r-IL-2 at 18 million Units/day over two successive weeks. This trial was approved by the ethical committee of Marseille and set up by the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) - The French Immunotherapy Group, in accordance with French Regulations.

Eligibility

Patients were required to have unresectable, advanced local or metastatic soft tissue sarcomas, which had been refractory to first line anthracyclin-based chemotherapy. They were to receive a minimum of two cycles of 50 mg/m^2 doxorubicin per cycle. Patients were required to have measurable disease, and the age requirement was > 18 years and < 70 years, with a Karnofsky performance scale > 60%. All patients had adequate bone marrow (neutrophils > 1,500/mm^3, platelet > 100,000/mm^3), renal (serum creatinine < 180 mumol/l) and hepatic function (AST < less than three times the upper limit of normal, bilirubin < 2.5 x normal, gammaGT < 5 x normal expected for patients with hepatic metastases). Patients were required to have a left ventricular ejection fraction of 50% or greater. No patient had a history of debilitating cardiac or pulmonary disease, or uncontrolled co-morbid disease. Written informed consent was obtained from each patient.

Study design

IL-2 was initiated after patient inclusion and no later than 6 weeks from the last chemotherapy treatment. Immunotherapy (Proleukin kindly supplied by CHIRON, Suresnes, France) was administered at 18 million Units/day subcutaneously, 5 days a week for 2 consecutive weeks. The schedule was: 1 or 2 subcutaneous injections with 9 million units each into two distinct subcutaneous sites, depending on the patient's cutaneous reaction. To prevent fever, patients routinely received acetaminophen (1,000 mg), two hours before IL-2 and repeated 4 hours after, if necessary. Other medication given to improve symptoms has been previously described [4]. Patients were hospitalized for the first injection, and if good tolerance was observed, they were thereafter treated as outpatients.

Toxicity was graded according to World Health Organization (WHO) criteria. IL-2 was stopped for unresolutive grade > III toxicity, for refusal or disease progression.

Subsequent chemotherapy was identical to that prior to administration of IL-2 and was administered as soon as possible until resolutive toxicity of IL-2. Chemotherapy was started no later than 4 weeks after the last IL-2 injection.

Evaluation

Baseline investigations before entry into study included physical examination, complete blood cell count and platelet count, biochemical profile, chest radiograph, and electrocardiogram. Computed tomography scans and additional imaging studies were performed on clinical indication for tumor measurement. During IL-2 treatment, patients were monitored weekly for physical and vital signs, full blood count, and serum chemistry. The same monitoring was done at the end of IL-2 and before subsequent chemotherapy.

Response to chemotherapy was assessed after two courses of chemotherapy or one course in the case of clinical evidence of progression. Tumor measurements were performed using the same imaging technique used at baseline. After completion of protocol chemotherapy, patients were followed-up one month later for tumor measurement, and every 3 months until progression for responding patients.

Clinical and radiological tumor response was graded according to WHO standard criteria.

Statistical analysis

Participation in this prospective study was planned to last for 18 months. An objective response (OR) rate of 20% was believed to be of clinical interest. A Gehan plan was chosen to test this hypothesis, with a beta risk error of 5% [5]. Duration of response was calculated from first day of demonstration of response until disease progression. The time to tumor progression was estimated from the study entry until documented disease progression. Survival was measured from the first day of IL-2 injection until death. Kaplan-Meier product limit estimates were used to evaluate survival probability and time to tumor progression.

RESULTS

Patient characteristics

As listed in Table 1, 17 patients with proven, progressive soft tissue sarcomas were enrolled into the study. Eight were male and 9 female, the median age was 49 years (range 33 to 64 years). Most pa- tients had leiomyosarcoma histological subtypes (10/17 patients), seven immediately metastatic and 10 secondary metastatic. All patients received anthracyclin-based chemotherapy for metastatic or locally progressive disease. Four patients received doxorubicin and ifosfamide, and eleven received a combination of doxorubicin, ifosfamide and dacarbazine. Two other patients were treated with an association of doxorubicin, cyclophosphamide, dacarbazine and vincristine. The median number of courses of chemotherapy was 5 (range 2 to 6). Overall, patients had documented progressive disease despite chemotherapy.

Treatment completion

IL-2 was administered over an average of 4 weeks from the last course of chemotherapy. Sixteen out of 17 patients received a total dose of 18 million Units/day of IL-2, 5 days a week for two consecutive weeks. One patient had treatment stopped early for progressive disease, but none of the 17 patients had disruption or interruption of treatment because of toxicity. Median

hospitalization duration was 2.5 days, 4 days during the first week of IL-2 treatment and one day during the second week.

Four patients experienced > grade III toxicity. One patient (N° 1), previously treated with anticoagulants for thrombosis had a coagulation disorder during the first and second week of treatment, however there was no dose modification or treatment disruption. Another (N° 3), had similar toxicity during the second week of IL-2 treatment, but did not require treatment to be discontinued. This patient had disseminated thrombosis in a context of progressive disease. Patient N° 4 had severe anemia during the first and second week and received one red blood cell transfusion. The last patient experienced pain and dyspnea without dose modification. Overall, 4 patients did not receive chemotherapy following IL-2 because of severe disease progression. Thirteen patients were rapidly treated by chemotherapy following IL-2, with a median delay of 12 days (range 2 to 23 days) from the last IL-2 injection.

Response and outcome (Table 2)

Seventeen patients were included in this study. Thirteen received chemotherapy following IL-2 and were fully evaluable, 4 patients did not receive chemotherapy because of disease progression.

Only one patient had a partial response after chemotherapy, 11 were in progression disease (PD) and one was maintained in stable disease (SD). The responding patient (N° 17) was a 33 year-old man with myxoid liposarcoma of the lower limb with bone received node metastasis. He underwent surgery and then two courses of doxorubicin and ifosfamide in combination and was in disease progression. He received a full dose of IL-2, followed by three courses of doxorubicin and was in partial response, this lasted for only two months and 5 months later this patient died.

One patient had remained in a stable condition by the last follow-up. This 48 year-old man (N° 13) had gut leiomyosarcoma with liver metastases at diagnosis. He had received surgical treatment, followed by 4 courses of an association of dacarbazine, ifosfamide and doxorubicin and remained stable. After L-2 and two cycles of the same chemotherapy his disease remained stable for 25 months from the initiation of the IL-2.

At the last follow-up, 15 out of 17 patients had died from progressive disease. Median overall survival was 9 months (0-33 months).

DISCUSSION

Advanced or metastatic STS have poor clinical outcome. Anthracyclin chemotherapy is the most efficient chemotherapy, but can induce resistance and secondary refractory disease.

New strategies need to be developed to tackle this problem. IL-2 has antitumoral activity, but results are disappointing in advanced or metastatic STS. Only 1 out of 12 patients had a response in our pilot study involving treatment of metastatic STS patients with progressive disease after chemotherapy with IL-2 [2]. Two patients refractory to primary anthracyclin chemotherapy had a response to subsequent anthracyclin-containing chemotherapy following treatment with IL-2. Response was maintained for 17 and 10 months. A possible reversal of chemoresistance has been suggested.

Intrinsic and acquired drug resistance after previous exposure to chemotherapy has been documented in sarcoma cell lines. One of the mechanisms of resistance described in sarcoma cell lines is the expression of a multidrug resistance (MDR) gene [6]. Other genes, such as that for multidrug resistance-associated protein have been associated with clinical multidrug resistance.

Modulation of chemoresistance has been evaluated with several cytokines, such as IL-2 or interferon (INF). It has been shown that interferon can modulate chemosensitivity in tumors which have become resistant to anticancer drugs. *In vitro* models using LoVo-Dox cells suggest that IFN-alpha increases adriamycin cytotoxicity through modulation of the multidrug resistance phenotype [7].

Chemotherapy efficacy can be improved by combination with cytokines. The rationale for studying the sequential administration of IL-2 and adriamycin was based on preclinical data demonstrating immunomodulatory effects of doxorubicin and its potential for favorable action with IL-2. It had been previously reported in a murine renal cell carcinoma model that sequential administration of adriamycin and IL-2 is superior to treatment with adriamycin alone or IL-2 alone [8].

Doxorubicin has been shown to potentiate the release of IL-2, and to augment several T cell-mediated immune responses [9, 10].

Our objective was to evaluate the possible modulation of adriamycin chemoresistance by high dose, subcutaneous IL-2 and subsequent identical anthracyclin-based chemotherapy. Subcutaneous IL-2 was chosen for its better tolerance and a non-documented, lower effect than intravenous IL-2 [11]. In our study, high dose IL-2 (18 million Units/day) was well tolerated and chemotherapy was reintroduced shortly after the last IL-2 injection (median 12 days).

Anthracyclin was administered at a dosage of 50 mg/m^2 adriamycin equivalent. This dosage was possibly more adapted to antitumoral activity than the lower dose immunomodulatory effect. Patients received IL-2 over a median of 4 weeks from last chemotherapy, and no later than 6 weeks. Sequential chemotherapy with a consistent dose of adriamycin (minimum of 50 mg/m^2 adriamycin equivalent/cycle) before and after IL-2 has shown no evidence of enhanced cardiotoxicity. The spectrum of toxicity during IL-2 was minor, with no treatment discontinuation for toxicity, and most patients were treated in an outpatient setting. Subsequent adriamycin-based chemotherapy after IL-2 therapy was administered safely with no major hematotoxicity or other complications.

Only 13/17 patients were able to receive chemotherapy following IL-2, because 4 patients had rapidly progressive disease during or soon after IL-2. Only one good response was observed in 13 patients who received chemotherapy after IL-2 (7.7% overall response, 95% CI: 0.2 to 36). Response was maintained for two months. Our initial statistical analysis design expected a 20% OR rate, but only a 7.7% OR rate was obtained. Considering the 17 patients, the overall response rate was 5.9% (95% CI : 0.15 to 29). Despite the fact that 4 out of these 17 patients did not receive chemotherapy after IL-2, it was decided to stop the study due to inefficacy considering the "intent to treat" analysis.

However, it is still difficult to definitely refute the hypothesis that cytokines in general, and IL-2 in particular, have no clinical potential to reverse chemotherapy resistance.

In this scheme of administration, mechanisms implicated in reversal chemoresistance by IL-2, if it exists, may be through the modification of the multidrug phenotype, but no documented biological data have been obtained.

The direct potential of adriamycin to release IL-2 or an increase in the T cell-mediated immune response could be excluded with this scheme of administration because the median delay of administration between IL-2 and chemotherapy was 12 days. Probably this delay is too long to expect a direct and/or an immunomodulatory effect.

A previous study evaluated combined modality treatment with adriamycin, followed by IL-2 or concomitant association. Le Cesne *et al.* conducted a pilot study to evaluate the combination with adriamycin and IL-2 on immunological, pharmacological and clinical effects [12]. Twelve out of 21 patients had advanced chemoresistant STS. Two partial responses were observed. Both had anthracyclin refractory tumor which became sensitive after the combination of subcutaneous IL-2 and adriamycin. A hypothesis concerning outpacing adriamycin resistance by concurrent administration of adriamycin and IL-2 has been suggested. These 2 patients had unusually high tumor necrosis factor (TNF-alpha) before the combination treatment. IL-2 and TNF are synergistic activators of lymphokine-activated killer cells. Synergistic antitumoral activity was also observed with TNF and adriamycin in preclinical testing.

These data suggest that for certain patients, the association of chemotherapy and IL-2 could be beneficial. Moreover, the method of administration and the dose schedule of both drugs could be of great importance.

The currently available standard treatments such as chemotherapy, surgery or radiotherapy have a very limited impact on the evolution of advanced or metastatic STS. Until new strategies become widely available, clinicians are obliged to optimize the current resources and make the best use of these modalities.

Despite the low response rate found in this prospective phase II study, modulating chemotherapy efficiency with cytokines should remain an open field of research.

CONCLUSION

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Figures

Table 1
Patient characteristics

Pt N°	Age	Sex (M/F)	Histological diagnosis	Primary site	Metastases at diagnosis (Yes/No)	Sites of metastases or tumor	Treatment for non-metastatic patients surgery/ radiotherapy/chemotherapy
1	40	F	Clear cell sarcoma	Lower limb	Y	Lung/nodes	
2	37	M	Fibrosarcoma	Upper limb	N		Surgery/radiotherapy
3	64	M	Fibrosarcoma	Upper limb	N		Surgery
4	49	M	Leiomyosarcoma	Gut	N		Surgery
5	38	F	Leiomyosarcoma	Uterus	Y	Nodes	
6	62	F	Leiomyosarcoma	Uterus	N		Surgery/radiotherapy
7	53	F	Chondrosarcoma	Lower limb	N		Surgery
8	43	M	Leiomyosarcoma	Gut	N		Surgery
9	57	F	Leiomyosarcoma	Lower limb	N		
10	58	M	Leiomyosarcoma	Gut	N		Surgery
11	59	M	Diffuse cell sarcoma	Pleural	N		Surgery/radiotherapy/ chemotherapy
12	48	F	Leiomyosarcoma	Ovary	N		Surgery/radiotherapy
13	49	M	Leiomyosarcoma	Gut	Y	Liver	
14	51	F	Leiomyosarcoma	Uterus	Y	Liver	
15	55	F	Leiomyosarcoma	Stomach	Y	Liver/adrenal	
16	56	F	Synovial-sarcoma	Lower limb	Y	Lung	
17	33	M	Myxoide liposarcoma	Lower limb	Y	Bone/nodes	

Pts: patients, F: female, M: male, Y: yes, N: no.

Table 2
Response and outcome

Pts N°	CT before rIL-2 (Nb cycle)	Doxorubicin mg/m²/cycle	Response to CT pre-rIL-2	CT post-rIL-2 (Nb cycle)	Response to CT post-rIL-2	Deceased/alive Follow-up (months)
1	D/I/DTIC (4)	60	PD	D/I/DTIC (1)	PD	Deceased (1.5)
2	D/I (6)	75	PD		NA	Deceased (12)
3	C/VCR/D/DTIC (5)	60	PD		NA	Deceased (0.7)
4	D/I/DTIC (3)	60	PD	D/I/DTIC (1)	PD	Deceased (11)
5	D/I/DTIC (3)	60	PD	D/I/DTIC (2)	PD	Deceased (33)
6	C/VCR/D/DTIC (6)	60	PD	C/VCR/D/DTIC (1)	PD	Deceased (12)
7	D/I/DTIC (6)	60	PD	D/I/DTIC (2)	PD	Deceased (4)
8	D/I/DTIC (3)	60	PD	D/I/DTIC (2)	PD	Deceased (8)
9	D/I/DTIC (5)	60	PD		NA	Deceased (16)
10	D/I/DTIC (3)	60	PD	D/I/DTIC (2)	PD	Deceased (10)
11	D (5)	55				
	D/I/DTIC (2)	40	PD		NA	Deceased (11)
12	D/I (4)	50	PD	D (3)	PD	Deceased (24)
13	D/I/DTIC (4)	60	PD	D/I/DTIC (2)	SD	Alive (25)
14	D/I/DTIC (5)	60	PD	D/I/DTIC (2)	PD	Deceased (7)
15	D/I/DTIC (3)	60	PD	D/I/DTIC (3)	PD	Alive (8)
16	D/I (4)	60	PD	D (2)	PD	Deceased (4)
17	D/I (2)	60	PD	D (3)	PR	Deceased (11)

Nb: number, CT: chemotherapy, Y: yes, N: no, PD: progressive disease, SD: stable disease, PR: partial response, NA: not available, D: doxorubicin, I: ifosfamide, DTIC: dacarbazine, VC: vincristine, C: cyclophosphamide.

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In this issue

Regulation of helper T cell responses to staphylococcal superantigens

S.B. Cameron, M.C. Nawijn, W.W.S. Kum, H.F.J. Savelkoul, A.W. Chow
cytokines, Th1, Th2, Tr1, IL-10, staphylococcal superantigens.

Fibronectin increases the migration induced by stromal cell-derived factor-1a (SDF-1a) in pre-B acute lymphoblastic leukemia cells

E. Sbaa-Ketata, M. Vasse, B. Lenormand, P. Schneider, C. Soria, J.P. Vannier
acute lymphoblastic leukemia, SDF-1a, CXCR-4, VLA-4, VLA-5, fibronectin.

Hematopoietic growth factors in patients receiving intensive chemotherapy for malignant disorders: studies of granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-3 (IL-3) and Flt-3 ligand (Flt3L)

O. Bruserud, B. Foss, H. Petersen
chemotherapy, acute leukemia, G-CSF, GM-CSF, IL-3, Flt3L.

Can interleukin-2 reverse anthracyclin chemoresistance in metastatic soft tissue sarcoma patients. Results of a prospective phase II clinical trial

G. Gravis, M. Mousseau, J.Y. Douillard, T. Dorval, M. Fabbro, B. Escudier, L. Mignot, P. Viens
immunotherapy, soft tissue sarcoma, interleukin-2, chemoresistance, anthracyclin.

Activation of two distinct anti-proliferative pathways, apoptosis and p38 MAP kinase-dependent cell cycle arrest, by tumor necrosis factor in human melanoma cell line A375

T. Hattori, H. Hayashi, T. Chiba, K. Onozaki
melanoma, tumor necrosis factor, apoptosis, cell cycle arrest, p38 MAPK.

Impaired interleukin-5 (IL-5) production by T cells as a prognostic marker of disease progression in human immunodeficiency virus type 1 (HIV-1)-infected children

S. Resino, S. Sanchez-Ramon, J.M. Bellon, J.L. Jimenez, M.A. Munoz-Fernandez
HIV-infected children, cytokine production, interleukin-5, PBMC, prognostic markers.

Cytokine-mediated inflammatory hyperalgesia limited by interleukin-13

B.B. Lorenzetti, S. Poole, F.H. Veiga, F.Q. Cunha, S.H. Ferreira
inflammatory hyperalgesia, interleukin-13, tumour necrosis factor alpha, interleukin-1b, interleukin-8, prostaglandin E2.

Expression of thrombopoietin by umbilical vein endothelial cells

A. El Andaloussi, P. Duchez, J. Rieffers, J. Ripoche, C. Grosset
thrombopoietin, umbilical vein endothelial cells.

Production of cytokines by immature erythroid cells derived from human embryonic liver

S.V. Sennikov, S.V. Krysov, T.V. Injelevskaya, A.N. Silkov, V.A. Kozlov
erythroid progenitor, IL-1b, IL-2, IL-4, IL-6, fetal liver.

Inflammatory cytokine production in interferon-g-primed mice, challenged with lipopolysaccharide. Inhibition by SK&F 86002 and interleukin-1b-converting enzyme inhibitor

S. Spinelle-Jaegle, P. Devillier, S. Doucet, S. Millet, C. Banissi, A. Diu-Hercend, E. Ruuth
interferon-g, lipopolysaccharide, interleukin-1b, cytokine, interleukin-1b-converting enzyme inhibitors.

The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines

V. Barak, T. Halperin, I. Kalickman
Sambucol, inflammatory cytokines, IL-1b, TNF-a, IL-6, IL-8.

Interferon (IFN)-g and Herpes simplex virus/tumor necrosis factor-a synergistically induce nitric oxide synthase 2 in macrophages through cooperative action of nuclear factor-kB and IFN regulatory factor-1

S.R. Paludan, L. Malmgaard, S. Ellermann-Eriksen, L. Bosca, S.C. Mogensen
macrophages, NOS2, Herpes simplex virus, NF-kB, IRF-1.

Negative regulation of onconstatin M signaling by suppressor of cytokine signaling (SOCS-3)

F. Magrangeas, O. Boisteau, S. Denis, Y. Jacques, S. Minvielle
cytokine signaling, inhibition, Jak-STAT pathway.

Increased expression of interleukin-8 and aminopeptidase N by cell-cell contact: interleukin-8 is resistant to degradation by aminopeptidase N/CD13

A. Kehlen, I. Egbert, K. Thiele, K. Fischer, D. Riemann, J. Langner
cell co-culturing, leucine aminopeptidase, plasma membrane preparations, CD13, proteolysis of IL-8, interleukin-8.

Functional characterization of the mouse lymphotoxin-beta receptor promoter

P. Muller, D.N. Männel, T. Hehlgans
LTbR-promoter, transcriptional activation, dexamethasone.

Glucose potentiates interleukin-1b (IL-1b)-induced p38 mitogen-activated protein kinase activity in rat pancreatic islets of Langerhans

A.M.E. Sprinkel, N.A. Andersen, T. Mandrup-Poulsen
interleukin-1b, p38, ERK1/2, JNK, nitric oxide, diabetes mellitus.

Sustained parasite burden in the spleen of Leishmania infantum-infected BALB/c mice is accompanied by expression of MCP-1 transcripts and lack of protection against challenge

D. Rousseau, S. Demartino, F. Anjuère, B. Ferrua, K. Fragaki, Y. Le Fichoux, J. Kubar
murine leishmaniasis, acquired immunity, inflammation, chemokines, spleen cell subpopulations.

Effects of cytokines and prolactin on the replication of Toxoplasma gondii in murine microglia

N. Benedetto, A. Folgore, C. Romano-Carratelli, F. Galdiero
T. gondii, cytokine, PRL, MGC.

Strip test for bedside detection of interleukin-6 in cervical secretions is predictive for impending preterm delivery

H. Trébéden, F. Goffinet, G. Kayem, F. Maillard, E. Lemoine, D. Cabrol, B. Weill, F. Batteux
cytokine, IL-6, prematurity, cervicovaginal secretions, strip test.

Serum levels of interleukin-18 in patients with uncomplicated Plasmodium falciparum malaria

D. Torre, M. Giola, F. Speranza, A. Matteelli, C. Basilico, G. Biondi
interleukin-18, malaria, Plasmodium falciparum, gamma interferon.

The ecdysone inducible gene expression system: unexpected effects of muristerone A and ponasterone A on cytokine signaling in mammalian cells

S. Constantino, R. Santos, S. Gisselbrecht, F. Gouilleux
ecdysone, PI 3-kinase, AKT, survival.

Presence of estrogen receptors in human myeloid monocytic cells (THP-1 cell line)

M. Cutolo, B. Villaggio, A. Bisso, A. Sulli, D. Coviello, J.M. Dayer
THP-1 cells, macrophages, estrogen receptors, estrogens, monocytes.

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