Interleukin-2 for the treatment of solid tumors other than melanoma and renal cell carcinoma

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Interleukin-2 (IL-2) is a lymphokine produced by T cells whose main function is to stimulate the growth and cytotoxic response of activated T lymphocytes. It has been used to stimulate the immune system for the treatment of multiples tumors. This article is intended to review the reports published from 1990 to 2004 on the IL-2 treatment of tumors other than melanoma and renal carcinoma. A literature search was made in various databases (MEDLINE, EMBASE and BioAssay), focused on IL-2 clinical efficacy in such tumors. A selection was made over 150 publications reporting on administration of IL-2 in multiple tumors: lung carcinoma (small cell and non-small cell), colorectal, gastric, pancreatic, ovarian and breast cancer, sarcomas, hepatocarcinoma, mesothelioma, and brain, urological, and head and neck tumors. IL-2 was mainly used in metastatic disease, associated with other immunotherapy or chemotherapy schedules. We conclude that adjuvant IL-2 may be of value in early stages combined with standard treatment for colon and pancreas cancers. In other neoplasms, the indication for adjuvant IL-2 has been sporadic and does not allow conclusions to be drawn. Assessment of the efficacy of IL-2 combined with chemotherapy as treatment for advanced stages is complex, due to the lack of a control, and the variety of dosages and schemes. The activity of IL-2 in monotherapy or in association with immunotherapy is clinically relevant in hepatocarcinoma, mesothelioma and in malignant overflows as palliative treatment. Randomized trials would be required in order to be able to draw conclusions about its indication in other tumors. *Anti-Cancer Drugs* 17:1–12 © 2006 Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2006, **17**:1–12

Keywords: efficacy, immunotherapy, interleukin-2, solid tumors other than melanoma and renal carcinoma

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Received 5 August 2005 **Accepted** 9 August 2005

Background

Interleukin-2 (IL-2) is a lymphokine produced by activated T cells whose main action is to enhance the growth and cytotoxic response of activated T cells [1–6]. It has been shown that low IL-2 levels are correlated to a decreased survival in patients with advanced disease [7,8]. After the studies by Rosenberg in the late 1980s in the National Cancer Institute (NCI) that showed the anti-neoplastic activity of IL-2, various trials were undertaken with different IL-2 regimens which showed a 15–20% response rate in melanoma and metastatic renal cancer, as well as a significant activity in other neoplasms such as lymphoma, and lung, colorectal and ovarian cancer [9–14].

In the early 1990s, in an attempt to improve activity, multiple trials were conducted with IL-2 in combination with other forms of immunotherapy and chemotherapy [15,16]. Subsequent studies analyzed the doses and administration routes, supported the efficacy and showed 10-year survival in 5–10% of patients [17–20].

Objective

We have reviewed studies conducted with IL-2 in many neoplasms other than hypernephroma and melanoma in order to evaluate the evidence to use this drug in such tumors.

Methods

A selection was made of 153 articles published from 1990 to May 2004 on the effects of IL-2 in solid neoplasms other than melanoma and renal cell carcinoma, paying particular attention to articles reporting therapeutic efficacy. As a general rule, articles in which this lymphokine has been investigated in animal experiments, in preclinical studies or as an immune response mediator from other therapeutic modalities were not included. A literature search was made in standard medical databases such as MEDLINE, PubMed and BioAssay.

Results

Non-small cell lung carcinoma (NSCLC)

In recent years, extensive research has been conducted in lung cancer, both on the role played by the immune system in the recognition of specific tumoral antigens and on the development of new therapeutic strategies against critical biological changes, such as inhibition of growth factors and transduction signals, induction of apoptosis,

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antiangiogenesis, immunotherapy using cytokines, vaccine treatments, and gene therapy [21,22].

Various studies have established the relationship of IL-2 with NSCLC and its prognostic value in this condition: a decrease in IL-2 has been correlated to tumor progression and the development of metastatic disease, and has been shown to be a negative predictor for response to chemotherapy and survival [23–28].

The role of immunotherapy alone or combined with chemotherapy has been extensively reviewed in advanced or metastatic NSCLC for the purpose of improving the poor results achieved with standard cytostatic treatment in terms of response rate and survival [22,29].

With regard to IL-2, its activity has been investigated in small series of patients with advanced NSCLC (Table 1), both as monotherapy [30–33] and in combination with other immunotherapy schemes, such as tumoral necrosis factor (TNF) [34,35], melatonin [33], interferon (IFN)-α [36,37], IFN-β [32], lymphokine-activated killer (LAK) cells [38] and tumor-infiltrating lymphocytes (TILs) [39]. Efficacy was minimal, with an objective response (OR) rate of 5% (nine of 175 patients) in all of the 10 series reviewed [30–39].

Lissoni *et al.*, authors who extensively researched the efficacy of IL-2 in this and other neoplastic sites, conducted a randomized study in 60 patients with advanced NSCLC [40] treated with immunotherapy based on IL-2 s.c. plus oral melatonin versus chemotherapy with cisplatin and etoposide. Similar response rates of 24 and 19% were found, but a significant improvement was seen in 1-year survival for the group treated with immunotherapy (45 versus 19%, $P < 0.02$).

The potential role of biochemotherapy in advanced NSCLC has also been investigated. Trillet-Lenoir [41] reported one partial response (PR) and one minor response, both in bronchoalveolar carcinoma in three patients treated with IL-2 as continuous infusion followed by cisplatin. In the Tummarello study, consolidation with IL-2 and IFN-α in combination with cisplatin, vinblastine and mitomycin did not improve survival and clearly increased toxicity [42]. Finally, the combination of cisplatin and epirubicin with IL-2 as biochemotherapeutic treatment in 33 patients in stages IIIB and IV achieved 30% ORs, with a median survival of 15 months and a 1-year survival of 55% [43].

Table 1 **Use of IL-2 in NSCLC**

Author	Reference	Treatment	Route	*n*	OR
Ardizzoni *et al.*	[30]	IL-2	i.v.	11	0
West *et al.*	[31]	IL-2	i.v.	5	1
Tester *et al.*	[32]	IL-2	i.v.	39	2
		IL-2 + IFN-β	i.v.	37	1
Lissoni *et al.*	[33]	IL-2	s.c.	9	0
		IL-2 + melatonin	s.c.	12	3
Yang *et al.*	[34]	IL-2 + TNF	i.v.	16	1
Schiller *et al.*	[35]	IL-2 + TNF	i.v.	15	0
Rosenberg *et al.*	[36]	IL-2 + IFN-α	i.v.	7	0
Jansen *et al.*	[37]	IL-2 + IFN-α	i.v.	11	0
Rosenberg *et al.*	[38]	IL-2 + LAKs	i.v.	5	1
Kradin *et al.*	[39]	IL-2 + TILs	i.v.	8	0

Various authors have investigated the role of intrapleural administration of IL-2 as palliative treatment for metastatic pleural effusion secondary to different solid tumors including NSCLC [44–49]. Miyao *et al.* [47] published the results of treatment with intrapleural IL-2 of eight patients with pulmonary adenocarcinoma and pleural effusion. According to Paladine evaluation criteria, two complete responses (CRs) and three PRs were obtained. Massotti *et al.* [48] subsequently administered intrapleural IL-2 in 21 patients, obtaining seven CRs and six PRs, with a median response duration of 8 months. Finally, Lissoni [49] reported his experience with intracavitary IL-2 in 100 patients with metastatic pleural effusion. In this study, in addition to other primary tumors, 20 patients had lung cancer and pleural effusion. Five CRs (25%) and nine PRs (44%) were reported. Seven additional patients with lung cancer and pericardial effusion were also treated with the same IL-2 regimen by the intrapericardial route, and four CRs and two PRs were obtained.

IL-2 has been occasionally used in early NSCLC stages combined with surgery and administered before surgery or as an adjuvant.

In 1998, Massotti *et al.* [50] reported the results of a randomized phase II study on 40 patients comparing IL-2 followed by surgery and surgery alone in stage II and IIIA NSCLC. The objective was to show that treatment with this cytokine can prevent lymphopenia secondary to the immunosuppressive effect of surgery [51]. In the treatment group, IL-2 was administered for 3 days before surgery; in this group, the counts of total, $CD3^+$, $CD4^+$ and CD4/CD8 lymphocytes were significantly higher in the 14th post-operative day as compared with the control group. After a 24-month follow-up, eight patients remained disease free in the treatment group, as compared to four patients in the control group.

Adjuvant post-surgery treatment with immunotherapy based on IL-2 has been investigated in combination with TILs [52–54] or LAK cells [55,56]. In the Ratto study [52], 113 patients with stage II and III NSCLC undergoing surgery were randomized to IL-2 plus TILs versus observation in stage II patients or the same immunotherapy regimen plus radiotherapy versus radiotherapy alone in stage III patients. The median survival was 14 months in the control arm as compared with

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22 months in the immunotherapy arm ($P < 0.05$). In stage II patients, survival was 22 months for the control group and 31 months for the immunotherapy group ($P = 0.5$). In stage III patients, survival was 8 months in the control group and 22 months in the group receiving IL-2 ($P < 0.01$). In this stage, a significantly greater number of local relapses were seen, but no statistically significant differences were found in distant relapses.

In a study by Yano *et al.*, 19 patients with post-surgical stage I NSCLC received IL-2 and LAK cells obtained from regional lymph nodes during surgery. When the results were compared with those of a control group, consisting of 21 stage I patients undergoing surgery during the same period and with no adjuvant treatment, no differences were found either in disease-free interval or overall survival [55].

A second study, Kimura *et al.* [56] randomized 105 patients with non–curative pulmonary resection to standard treatment with radiotherapy and/or chemotherapy versus the same approach, but followed by therapy with IL-2 and LAK cells for 2 years. Survival at 7 years was 12% in the first group, as compared with 39% in the group associating biological therapy ($P < 0.01$). In the analysis by histological types, the subgroup showing a significantly favorable effect of immunotherapy was the adenocarcinoma group (survival of 5 versus 39%).

Small cell lung carcinoma (SCLC)

In SCLC, studies have also documented that IL-2 suppression at the time of diagnosis is an independent predictor of response and survival [57–59].

In two consecutive studies [60,61], the Cancer and Leukemia Group B (CALGB) investigated the potential role of IL-2 in SCLC. In the first study, IL–2 was administered as continuous infusion to 24 patients who had not achieved a CR after chemotherapy with cisplatin, doxorubicin, cyclophosphamide and etoposide. A CR was achieved in four patients and a PR in 1 patient, with an overall response of 21%. The median survival was 12 months. The same group subsequently investigated the activity of the reverse sequence, consisting of IL-2 s.c. followed by chemotherapy with cisplatin and etoposide in 10 patients with disseminated SCLC. After the IL-2 regimen and with a significant toxicity, a PR and a stabilization were only seen, while eight patients showed early progression. In the eight patients who subsequently received chemotherapy, one CR and 7 PRs were achieved, with a median survival of 12 months.

A further therapeutic approach investigated in SCLC is administration of IL-2 with alternating chemotherapy schemes. Thus, Pollera *et al.* [62] designed a preliminary study in 17 SCLC patients (10 limited disease and seven extensive disease) treated with CAV/PE alternating chemotherapy, with IL-2 in continuous infusion being associated in 11 patients. Despite the high response rate of 93%, with 53% CRs, the median survival was 13 months for limited disease and 9 months for extensive disease – similar results to those reported with conventional chemotherapy. The study concluded that combined treatment with biochemotherapy does not improve results.

Colorectal cancer

Colorectal cancer is probably the solid tumor other than melanoma and renal carcinoma in which treatment with IL-2 has been most frequently tried, mainly for palliative purposes in metastatic disease and administered in combination with other forms of immunotherapy or chemotherapy.

With regard to immunotherapy regimens, in patients with colorectal carcinoma progressing on previous treatment with 5-fluorouracil, in an attempt to increase the efficacy of IL-2, the association of this cytokine with other immunotherapeutic agents (Table 2) such as IFN-α [63], IFN-β [64,65], arginine [66], melatonin [67], monoclonal antibody CC-49 [68], TILs [69] and more recently edrecolomab [70] has been tested. The efficacy of these combinations has been minimal, with an OR rate in the eight series analyzed of 6% (eight of 120 patients). In the article by Chang *et al.*, when IL-2 was combined with IFN–α, four short-lived PRs were recorded in 24 patients evaluable [63]. In another series where IL-2 was combined with IFN-β, one PR was achieved in 15 patients [64]. In the Barni *et al.* study, 50 patients pretreated with fluorouracil were randomized to treatment with s.c. IL plus melatonin or support care. In the treatment arm, PR was documented in three cases, and 1-year survival was nine of 25 patients, whereas in the support arm 1-year survival was three of 25 patients [67]. No response was shown in all other studies. A review of recent literature on immunology and immunotherapy in colon and rectum cancer, published by Dalerba in 2003, confirmed that immunotherapy based on IL-2 and IFN is clinically ineffective for the treatment of colorectal carcinoma [71].

In the field of biochemotherapy in metastatic colorectal cancer, usually as first-line treatment, IL-2 has been

Table 2 Use of IL-2 in colorectal cancer – I

Author	Reference	Treatment	Route	*n*	OR
Chang *et al.*	[63]	IL-2 + IFN-α	i.v.	29	4
DeBraud *et al.*	[64]	IL-2 + IFN-β	s.c.	15	1
Barni *et al.*	[65]	IL-2 + IFN-β	s.c.	15	0
Douillard *et al.*	[66]	IL-2 + arginine	s.c.	6	0
Barni *et al.*	[67]	IL-2 + melatonin	s.c.	25	3
Triozzi *et al.*	[68]	IL-2 + AC.CC49	i.v.	14	0
Ridolfi *et al.*	[69]	IL-2 + TILs	i.v.	4	0
Fiedler *et al.*	[70]	IL-2 + edrecolomab	s.c.	12	0

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Table 3 Use of IL-2 in colorectal cancer – II

Author	Reference	Treatment	Route	*n*	OR
Hiddemann *et al.*	[72]	IL-2 + 5-FU	i.v.	22	3
Hamblin *et al.*	[73]	IL-2 + 5-FU	i.v.	16	5
Tomita *et al.*	[74]	IL + OK-432 + 5-FU + mitomycin C	i.a.	2	2
Lygidakis *et al.*	[75]	IL-2 + 5-FU	i.a.	33	21
Nicolini *et al.*	[76]	IL-2 + 5-FU	s.c.	12	6
Yoshimura *et al.*	[77]	IL-2 + 5-FU + mitomycin C	i.a.	3	1

combined with chemotherapy in an attempt to improve the results obtained with cytostatic treatment alone. As shown in Table 3, IL–2, usually administered by the i.v. route as continuous infusion or by the i.a. route, has been used in combination with fluorouracil and mitomycin C [72–77]. A study also associated OK-432 antigen [74]. The results may be considered satisfactory in terms of efficacy, with an OR rate of 43% (38 of 88 patients) in the six publications analyzed, but the contribution of IL to chemotherapy is difficult to assess because of the small number of patients and the lack of a control group with cytostatic treatment alone, except in two reports [75,76]. The first of these was from a prospective, randomized study with a locoregional regimen of immunotherapy plus chemotherapy versus chemotherapy; the OR rate and median survival obtained were 13% and 9 months, respectively, in the chemotherapy arm, as compared to 64% and 20 months in the arm with combined treatment [75]. In the second report, corresponding to a non–randomized study, a 50% response rate was achieved in 12 patients treated with IL–2 and fluorouracil, as compared to a 23% rate in its historical control of 13 patients. Improved results were also achieved in time to progression and overall survival, 11 and 31 months, respectively, in the immunotherapy group, as compared to 4 and 13 months in the historical control [76].

For palliation, immunotherapy has been shown to be highly effective in the control of malignant ascitis caused by colorectal cancer. In a recent article published by Yamaguchi *et al.* [78], locoregional administration of OK-432 achieved a clinical response (evaluated as cytological negativity and decreased ascitis) in nine of 11 patients as monotherapy and in five of five patients in combination with IL-2.

With regard to the indication of IL-2 as adjuvant in colorectal carcinoma, some studies have been recently conducted with this lymphokine, with or without chemotherapy, as complementary treatment after surgery for metastases and/or primary tumor. In a 1998 study, based on the good tolerability of the combination of IL-2 and TILs, used for palliation in a group of patients with neoplasms of different etiologies, the same scheme was used in 10 patients with colorectal carcinoma after hepatic resection [69]. In another series, after surgical treatment and to prevent subsequent development of metastases, a combination of immunotherapy by vaccination with autologous tumoral cells, DCG and IL-2 was used in 65 cases of stage IV colon cancer [79]. Since the liver is an immunological organ rich in natural killer (NK) and Kupffer cells, which may be activated by cytokines and have a significant role in the prevention of recurrence in the liver, other authors used a combination of IL–2 with 5-fluoruracil and mitomycin by the i.a. route following a potentially curative hepatic resection in 20 patients with metastatic colorectal cancer, with an overall 5–year survival of 78%. The authors also documented that all six cases of recurrence in the series occurred at the extrahepatic level [80].

Finally, the Fu *et al.* [81] reported the results in 96 patients with stages B–D colorectal cancer (together with 42 patients with gastric cancer) who, after surgical resection, were randomized to i.p. treatment with thermochemotherapy (distilled water at 43–45°C containing fluorouracil and mitomycin) alone or combined with IL-2, followed by standard chemotherapy by the i.v. route in both groups. Three-year overall survival was 18% higher in the scheme including the cytokine, and the recurrence rates at the hepatic and i.p. level were, respectively, 6 and 17% lower in the treatment group with the combination of IL-2 and chemotherapy.

Gastric cancer

In 1993, Lissoni *et al.* investigated the combination of IL-2 s.c. with melatonin as an immune modulator in a group of 82 patients with advanced solid tumors, including 11 cases of gastric cancer and obtained an OR in three patients [82]. Another publication reported the use of the combination of IL-2 and TILs in 23 patients, and eight ORs (three CRs and five PRs) were achieved with good tolerability [83]. IL-2 has also been used by the i.a. route in combination with OK-432 and chemotherapy in hepatic metastases of gastric cancer. This regimen resulted in three cases of PRs in a series of 11 patients [84].

Yamaguchi *et al.* examined the efficacy of IL-2 in this neoplasm as treatment for malignant ascitis. When administered by the i.p. route in association with OK-432, IL-2 showed a significant activity, with ascitis decrease and cytological negativity in 18 of 22 patients [85].

For early stages, indication of IL-2 as treatment complementary to surgery has been exceptional and

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difficult to assess. This lymphokine was used by the i.v. route combined with fluorouracil in eight patients after potentially curative gastric resection [86]. IL-2 was also administered by the i.p. route, in association with fluorouracil and mitomycin, in the abovementioned study by Fu *et al.*, including 42 patients with stage II–III gastric cancer after surgery [81].

Pancreatic cancer

Publications about IL-2 in pancreatic cancer with palliative intent include the study by Lygidakis *et al.* [87], who randomized 238 patients after palliative surgery to locoregional therapy by the i.a. route with IL-2, IFN-γ and chemotherapy (gemcitabine, carboplatin and mitoxantrone) or an untreated control group, achieving a median OS of 26 months in the treated group – significantly higher than the 7 months of the control group. Similarly, 21 patients with advanced cancer of the pancreas were randomized in another study to i.a. treatment with IL-2 and chemotherapy (mitomycin, carboplatin, adriamycin and fluorouracil) or no treatment. In the immunotherapy arm with chemotherapy, ORs in seven of 10 patients and a median OS of 12 months were documented, as compared to 5.5 months in the 11 patients of the observation arm [88].

Recently, in a study published in 2002, they proposed the inclusion of staging laparoscopy for an adequate case selection and treatment as an approach to management of pancreatic cancer. In their series of 16 patients, hepatic metastases were found in the laparoscopy in three cases that were treated with IL–2 and chemotherapy by the i.a. route, achieving one CR and two PRs [89].

With regard to treatment in association with surgery of curative intent in carcinoma of the pancreas, IL-2 has also been used by the i.a. route and in schemes with chemotherapy. In the same article by Lygidakis *et al.* mentioned previously, 274 patients with pancreatic cancer undergoing curative surgery were randomized to observation versus locoregional treatment with the same scheme of IL-2, IFN–γ and chemotherapy. The treated group showed a median OS of 32 months – significantly better than the 14 months survival seen in the control group [87]. The same authors conducted another randomized study in which 26 patients underwent surgical resection with curative intent, with or without neoadjuvant treatment and adjuvant treatment with IL-2 and chemotherapy, administered by the intradermal route. Nine recurrences were documented in the 12 patients of the surgery alone group, as compared with three recurrences in the 14 cases in the treatment arm [90].

Finally, it should be noted that a recent article reviewing IL-2 for the treatment of tumors other than melanoma and renal cancer, previously mentioned in the lung cancer section, summarized a report stating that this cytokine, in association with standard treatment including chemotherapy, achieved an OR rate of 85% and doubled the unresectable survival time [29].

Ovarian cancer

In ovarian cancer, studies on IL-2 have been focused in the treatment by the i.p. route of advanced disease in pre-treated patients refractory to platin. Table 4 lists six series in which i.p. IL-2 was administered alone or in combination with other forms of immunotherapy [91–96]. Considering that this was an unfavorable population of patients refractory to chemotherapy, efficacy was acceptable, achieving 22% of clinical activity (21 of 96 patients), assuming as such ascitis control and/or decreased CA-125 marker levels with stable disease (SD). In cases with evaluable disease, the OR rate was 15% (14 of 96 patients) in the series analyzed.

In a group of neoplasms with malignant ascitis, including two patients with ovary cancer, Lissoni *et al.* [91] used i.p. IL-2 as monotherapy and OR was achieved in both cases. Also as monotherapy and in a phase I–II study, other authors compared in 41 patients with recurrent ovarian carcinoma the toxicity and efficacy of two different schemes of i.p. IL-2, weekly intermittent infusion versus continuous infusion for 7 days, alternated with 1 week with no treatment. In 35 patients evaluable for response, six CRs and three PRs (OR 25%) were documented by laparotomy, with a median OS for the whole group of 13 months. With regard to toxicity, the weekly infusion scheme was reported to be better tolerated [92].

In the First Symposium on Local Cytokine Therapy of Cancer [93] held in Hamburg in 1999, Characiejus presented a review on five studies of i.p. immunotherapy in ovarian cancer (included in this review) and reported 16 responses (23%) in a total of 69 patients. The author did not find in his own experience an OR in any of the four cases with malignant ascitis due to advanced ovarian carcinoma treated with IL-2 as monotherapy.

Association of other i.p. immunotherapy regimens does not appear to provide an additional benefit to monotherapy (Table 4). The combination of IL–2 with LAKs was used in two studies, each including 10 patients, and ORs were found in one and two cases, respectively

Table 4 Use of i.p. IL-2 in ovarian cancer

Author	Reference	Treatment	*n*	OR
Lissoni *et al.*	[91]	IL-2	2	2
Edwards *et al.*	[92]	IL-2	41	9
Stewart *et al.*	[94]	IL-2 + LAKs	10	1
Steis *et al.*	[95]	IL-2 + LAKs	10	2
Freedman *et al.*	[96]	IL-2 + TILs	11	4
Freedman *et al.*	[97]	IL-2 + IFN	22	3

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[94,95]. This cytokine has also been combined with TILs. Thus, in a study at the MDA of Texas University, a total of 11 patients with advanced, platin-refractory ovarian cancer were treated with IL–2 and TILs (eight patients) or with IL-2 monotherapy (three patients). Measurable ORs were not found, but some activity was shown in four cases as ascitis regression or reduction of CA-125 levels [96]. Finally, these same authors reported their experience with the combination of this lymphokine with IFN-γ (with or without TILs) in 22 patients with ovarian or peritoneal carcinoma, analyzed the biological effects derived from treatment and documented clinical activity in three cases [97].

Breast cancer

From 1995 to 2001, there have been various reports on series including a limited number of patients, usually from 10 to 30 cases, in which IL-2 and chemotherapy were used at high doses together with peripheral blood stem cell (PBSC) self-transplant in metastatic breast cancer [98–104]. IL-2 has been mainly used in this indication for response maintenance after chemotherapy in order improve disease-free survival (DFS). The s.c. route has been usually used for 3–12 months. Although these studies had no control arm, most authors found no survival benefit compared with the same schemes without IL-2 [98–102]. IL-2 has also been tested less frequently by the i.v. route as part of the high-dose chemotherapy and self-transplant protocol, exploring the ability of this lymphokine and LAK cells to suppress residual disease [103], and before cytostatic treatment to increase mobilization of stem cells, and LAK and NK effector immune cells [104].

The CALGB recently tested the combination of IL-2 by the s.c. route with trastuzumab in non-hematological neoplasms not amenable to standard treatment and with HER-2 overexpression. ORs were found in four patients with breast cancer [105]. Repka *et al.* [106] subsequently conducted a phase I pilot study on the combination of IL-2 and trastuzumab in 10 patients with metastatic breast cancer and HER-2 overexpression, in an attempt to achieve an increased efficacy by increasing NK cells and cytolytic function. One PR and five SDs were documented, with good tolerability, and the author concluded that this approach could benefit highly pre-treated patients.

For adjuvant treatment in high-risk breast cancer, IL-2 has been used in combination with IFN and chemotherapy with CMF in order to enhance complete recovery of the white blood cell series at nadir and increase NK cells [107].

Also for adjuvant purposes, the association of IL-2 with high-dose chemotherapy and PBSC self-transplant was tested in two studies of Georgetown University. The benefit is difficult to assess because the study had no control arm, although the disease-free rate was considered to be similar to that reported for other regimens not containing the cytokine [108,109].

Soft tissue and bone sarcomas

Table 5 reviews five series in which recurrent and refractory sarcomas were treated with IL-2. In these neoplasms, IL-2 was tested as monotherapy with no documented efficacy [110–112], with an OR rate of 2% (one of 48 patients). When IL–2 was combined with anthracyclines, activity was not significant either, with OR rates of 10% (three of 31 patients), probably attributable to the cytostatic agent [113,114].

In pediatric tumors, the Children's Cancer Group Study conducted a phase II study of IL-2 as continuous infusion in 38 patients with refractory tumors, including 20 cases of sarcoma, and did no find tumoral response [110]. The NCI, in turn, used a combination of IL-2 with vaccination of specific tumoral polypeptides in 16 pediatric patients with recurrent Ewing sarcoma or alveolar rhabdomyosarcoma and documented progressive disease in all cases [111].

In adults with soft tissue sarcomas refractory to chemotherapy, Gravis *et al.*, from the French Immunotherapy Group, treated 12 patients with high-dose IL-2 and achieve one PR, but all cases subsequently received cytostatic treatment again. There were two responses, suggesting that the cytokine had a low efficacy, but could revert prior resistance to chemotherapy [112]. Similarly, a pilot study conducted at the Institut Gustave Roussy treated 21 adult patients with advanced, highly pre-treated solid tumors, including 14 cases of soft tissue sarcoma, with a scheme consisting of IL-2 s.c. and adriamycin. Two responses were seen, both in patients previously refractory to anthracyclines, which supports the hypothesis of a potential modulation by the lymphokine of resistance to this cytostatic class, which would be mediated by TNF [113].

Finally, in order to elucidate the potential effect of IL-2 on reversion of anthracycline resistance, Gravis *et al.*, in a phase II prospective study including 17 patients with metastatic and refractory soft tissue sarcoma, used a treatment regimen consisting of IL-2 s.c. followed by anthracycline-based chemotherapy. Rapid progression was documented in four cases and only one PR was found in

Table 5 Use of IL-2 in soft tissue and bone sarcomas

Author	Reference	Treatment	Route	*n*	OR
Bauer *et al.*	[110]	IL-2	i.v.	20	0
Dagher *et al.*	[111]	IL-2 + vaccine	i.v.	16	0
Gravis *et al.*	[112]	IL-2	i.v.	12	1
Le Cesne *et al.*	[113]	IL-2 + adriamycin	s.c.	14	2
Gravis *et al.*	[114]	IL-2 + adriamycin	s.c.	17	1

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the remaining 13 evaluable patients. Thus, the study was closed due to the lack of efficacy and of any evidence of reversion of chemotherapy resistance [114].

Recently, and in a multidisciplinary approach, IL-2 was used for the treatment of localized osteosarcoma in a pediatric population. This study, published in 2003 by the Milan Cancer Institute, included 18 cases of localized osteosarcoma treated with IL-2 and chemotherapy before and after surgery. Changes induced by the cytokine in immunological parameters such as NK and LAK cell count were quantified, and a potential role in disease control was suggested [115].

Hepatocarcinoma

In hepatocarcinoma with unresectable or metastatic disease, IL-2 by the s.c. route, in combination with other forms of immunotherapy, such as IFN and melatonin [64,116], or as monotherapy [117] showed a significant activity, with approximately 20% ORs (eight of 42 patients), including some CRs, and 55% stabilizations (23 of 42 patients) in the review of the three series. As shown in Table 6, IL-2 has also been tested in combination with both immunotherapy, such as IFN or OK-432, and chemotherapy, mainly with adriamycin and cyclophosphamide, generally by the i.a. route [118–122]. A pooled review of the five publications shows that the efficacy of this combination is high, with an OR rate of almost 40% (30 of 77 patients), but the contribution of the cytokine in this combination is difficult to evaluate. The study with i.v. administration was the only one where no response was documented. In this study, four patients also experienced unacceptable toxicity that required treatment discontinuation [119].

IL-2 activity was studied at the NCI using intratumoral injection in five cases of small volume hepatocarcinoma before hepatic resection. Two PRs were documented [123]. Another article reported a study on 24 patients who underwent hepatic resection comparing adjuvant IL-2 treatment by the i.a. route, in association with LAK cells and adriamycin, to adriamycin alone. The OS rate of the whole series was 72% at 3 years, with no statistically significant differences in OS or DFS between the two treatment modalities, except in the subgroup with a negative surgical margin, where DFS at 2 years was 83% in the six cases with biochemotherapy, as compared with 37% in the eight cases with chemotherapy alone [124].

A review of the role of immunochemotherapy in hepatocarcinoma, published in 2002, emphasizes the promising results of a locoregional combination of chemotherapy and immunotherapy, including IL-2 and LAK cells, in the treatment of unresectable tumors, and also as adjuvant before or after surgery [125].

Mesothelioma

A study comparing the different efficacy of intracavitary treatment with IL–2, IFN-α and IFN-β in neoplastic effusions found that the response rate in patients with mesothelioma was significantly superior with administration of IL-2 [126]. There has been recent speculation on nitric acid production induced by the cytokine as the possible cytotoxic mechanism [127]. Table 7 shows five series published on intrapleural IL-2 as treatment for mesothelioma, generally in stages I–II and in patients with no prior treatment. A high efficacy is seen in this review of the literature, with a 40% OR rate (44 of 107 patients). This lymphokine is therefore considered by some authors as a treatment option for mesothelioma, which is often refractory to other therapeutic alternatives [49,128–131]. Some of these series also include the results in malignant pleural effusion secondary to other histological types [49,128].

In contrast, IL-2 has not been shown to be effective when administration routes other than the intrapleural route are used. In a phase II study of the Italian Group on Rare Tumors, 21 patients with mesothelioma received a combination of IL-2 s.c. and epirubicin i.v. as first-line treatment. Only one PR was seen, and DFS and OS were 5 and 10 months, respectively [132]. In another study where IL-2 was also given as first-line treatment, 29 patients with mesothelioma were treated with this

Table 7 Use of intrapleural IL-2 in mesothelioma

Author	Reference	Treatment	*n*	OR
Astoul *et al.*	[128]	IL-2	15	7
Goey *et al.*	[129]	IL-2	21	4
Astoul *et al.*	[130]	IL-2	22	12
Lissoni *et al.*	[49]	IL-2	18	14
Castagneto *et al.*	[131]	IL-2	31	7

Table 6 Use of IL-2 in hepatocarcinoma

Author	Reference	Treatment	Route	*n*	OR	SD
Aldeghi *et al.*	[116]	IL-2 + melatonin	s.c.	14	5	6
DeBraud *et al.*	[64]	IL-2 + IFN	s.c.	10	0	4
Palmieri *et al.*	[117]	IL-2	s.c.	18	3	13
Hazama *et al.*	[118]	IL-2 + chemotherapy + OK-432	i.a.	7	3	2
Chien *et al.*	[119]	IL-2 + chemotherapy	i.v.	9	0	1
Yamamoto *et al.*	[120]	IL-2 + chemotherapy	i.a.	17	6	3
Oka *et al.*	[121]	IL-2 + chemotherapy + OK-432	i.a.	24	7	14
Lygidakis *et al.*	[122]	IL-2 + chemotherapy + IFN	i.a.	20	14	

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cytokine by the s.c. route in combination with continuous infusion by the i.v. route. In the evaluable 25 patients, two PRs, 11 SDs and 12 progressions were documented, with median OSs of 18, 13 and 8 months, respectively [133]. The Krastev *et al.* review of three articles reports as favorable results, those obtained with IL-2 in pleural (69 patients) and peritoneal mesothelioma (six patients). Particular mention is made of intracavitary local application, with disease control in 56% of the cases [29].

Hematological neoplasms

Although not included in this review, in this section we give references to some articles on the use of IL-2 in hematological neoplasms. IL-2 activity in different types of lymphoma and leukemia was initially analyzed in the 1990s [133], but the greater development mainly occurred in studies conducted around 2000 [135–142]. A review of literature related to this indication has been recently published [29].

Other solid neoplasms

Brain tumors

In a phase II study of different refractory pediatric tumors, IL-2 as monotherapy was administered in nine cases of neuroblastoma with no objective response [110].

A review of the literature on immunotherapy and biological response modifiers in brain tumors published in 2003 [143] highlighted two articles related to IL-2. The first article reviewed the efficacy of this cytokine at high doses in brain metastases of renal carcinoma and melanoma [144]. The second article reported an experimental study of IL-2 encapsulated in microspheres of biodegradable polymers and administered by an intratumoral injection [145].

Urological neoplasms

A phase II study conducted in the MDA of Texas University, published in 2003, reported the efficacy of IL-2 in continuous infusion in advanced or metastatic transitional carcinoma of the bladder refractory to cisplatin. The analysis, including 17 patients, found no response and the study was closed [146].

Intravesical IL-2 has been tested in superficial carcinoma of the bladder following resection and chemotherapy in order to reduce the recurrence rate [147].

Krejci *et al.* [148], from the Urology Department of the Mayo Clinic, published a review of literature on immunotherapy in urological neoplasms in 2004. In the section on cytokine treatment, the authors review the potential value of IL-2 in tumors other than renal cell carcinoma and make particular mention of two articles. The first report refers to a pilot study of IL-2 with IFN by the s.c. route in hormone-refractory prostate cancer in which some PRs and a decrease in prostate-specific antigen levels were achieved [149]; the second to a trial of intravesical treatment in T1 papillary bladder carcinoma where promising results were seen, consisting of regression in eight of 10 patients treated [150].

Head and neck cancer

Some transient ORs were reported in recurrent neoplasms [151] and two cases of CRs in lip cancer were also reported in another study [152]. More recently, IL-2 has also been analyzed in a phase II study in refractory nasopharyngeal carcinoma [153].

Finally, in 2003, Feinmesser reported the results of a clinical trial on administration of a 'multikine solution' (consisting of a combination of IL-2, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, TNF, IFN and other ILs) by a peritumoral injection to 12 patients with epidermoid carcinoma of the oral cavity and oropharynx, before treatment with surgery or radiotherapy. Response assessment after local immunotherapy revealed two CRs and two PRs, and it was concluded that the treatment was safe and effective in terms of tumoral regression, possibly through activation of macrophages, NK cells and lymphocytes, as confirmed by the histopathological analysis of the surgical specimens and by serum tests using flow cytometry [154].

Conclusions

It is very difficult to summarize conclusions on the role of IL-2 in neoplasms other than hypernephroma and melanoma from this review of the literature because it generally includes isolated publications with a limited number of patients, studies were most often designed with no control arm, different primary tumors and histological types were sometimes included, the therapeutic regimen was not uniform but encompassed multiple different treatment schemes using IL-2 as monotherapy or in combination with other forms of immunotherapy or chemotherapy, there were multiple dosages and administration routes, and objectives ranged from adjuvant to palliative treatment.

With regard to the role of adjuvant IL-2 in early stages, some authors have stressed the benefit of this cytokine by the i.p. route and in combination with standard treatment as a complementary regimen after surgery in colon cancer, and by the i.a. route in unresectable pancreatic cancer. As to the use of IL-2 as adjuvant treatment in breast cancer, it is difficult to draw conclusions on the results in terms of survival in the reviewed reports since the studies used IL-2 in combination with chemotherapy and their design did not include a control arm, although the authors themselves state that no benefit was found, and the disease free-survival was similar to that reported with the same

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schemes without immunotherapy. In NSCLC, the results with adjuvant IL-2 have been conflicting. Finally, no conclusions can be drawn in all other neoplasms reviewed, because IL-2 was only sporadically administered in an adjuvant setting. Assessment of the efficacy of IL-2 in combination with chemotherapy as palliative treatment for advanced stages of the different tumors analyzed in this review is highly complex, mainly because its contribution is masked by the activity of cytostatic themselves in studies which do not usually have a control arm without IL-2.

Special mention should be made of the results found in the treatment of hepatocarcinoma and mesothelioma, where IL-2 may represent a therapeutic alternative to be considered in neoplasms for which few therapeutic options are otherwise available. The efficacy for palliation and control of pleural effusion in lung cancer and ascitis in colorectal, gastric or ovarian cancer is also significant. The future of IL-2 in the treatment of other tumors should be based on randomized studies that will allow us to test the contribution of this cytokine in the palliative or adjuvant setting. Research on administration routes for sustained efficacy with less toxicity and studies in combination with new drugs are required.

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