Clinical studies with biological response modifiers in the treatment of solid tumors
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1 Introduction

Biological therapy is referred to as the fourth modality in cancer treatment because it differs conceptually from surgery, radiation and chemotherapy as it acts not only directly by attacking the tumor cells but also by stimulating the immune system to mediate the regression of cancer (1,2). Translating the expanding knowledge of the immune system into biological therapies has been difficult because of the complexity of the immune system including cytokines, growth factors, antibodies, oncogenes and their products, and the vast array of effector and suppressor cells and their receptors. Furthermore, in patients with cancer cytokines and cytokine receptors are often deregulated and cytokines produced by the tumor may contribute to the pathophysiology of cancer. Early biological treatments were performed using crude preparations of immunostimulants mostly derived from bacterial products or tumor extracts with usually disappointing results (3). However, the development of recombinant DNA and hybridoma techniques has enabled the synthesis of purified proteins capable of more selective interventions in the immune cascade (4). Since then, intensive research has been devoted to define the therapeutic use of these proteins in the treatment of cancer. In this review the current state of clinical application of the biological response modifiers Interleukin-2 (IL-2) and Interferon-α (IFN) in the treatment of solid tumors will be discussed.

2 Interleukin-2

The first observations of mitogenic factors in the supernatant of stimulated leucocytes date from 1963 (5) but it was not until more than 10 years later that a growth factor for bone marrow derived T-cells was described by Morgan and coworkers (6). This T-cell growth factor (TCGF) was renamed Interleukin-2 (IL-2) in 1979 after discovery of its pleiotropic effects (7). IL-2 is a 15Kd glycoprotein produced by T-helper cells that plays a central role in the immune response. The human IL-2 gene has been mapped to chromosome 4q (bands 26 to 28). It has been isolated, cloned and expressed in E. Coli (8). The IL-2 gene consists of four exons separated by introns with strong similarity to the genes of interleukin-4 and the growth factor granulocyte-macrophage-colony stimulating factor (9). Subsequent to its production IL-2 undergoes a variety of different post-translational steps including cleavage of a 20 amino acid signal peptide, the addition of a carbohydrate at position 3 (threonine) and creation of a disulfide bond between cysteines located at positions 58 and 105. This bond guarantees the stability of the tertiary structure which is essential for its biological activity (10). Although IL-2 is naturally sialylated and glycosylated, the carbohydrate component appears to play no part in the activity of the peptide since non-glycosylated recombinant IL-2 is equally effective at stimulating T-cell proliferation as glycosylated IL-2 (11).
2.1 Biology

The biological effects of IL-2 have been described in detail by Smith (12,13). IL-2 is produced by T-helper cells upon activation by Interleukin-1 and an antigen. The regulation of IL-2 production is only partly understood. In many cells at least two signals are required for induction that are mimicked by phorbol ester and calcium ionophore stimulation (14). Presumably this usually involves ligation of the T-cell receptor and co-signaling through a second cytokine or a receptor pair (CD28-B7) (15,16). Biologic activities of IL-2 are mediated through both direct interaction with specific receptors on T cells, B cells, natural killer (NK) cells, monocytes, macrophages, and oligodendrocytes and through secondary effects resulting from the induction of a variety of cytokines.

2.1.1 IL-2 receptor

The IL-2 receptor consists of at least three transmembrane associated units, each with an external domain of approximately 215 amino acid residues: a 55kD α chain (IL-2Rα, Tac, p55), a 70 to 75kD β chain (IL-2Rβ, p70), and a 64kD γ chain (IL-2Rγ, p64) that combine noncovalently (17-20). Only NK-cells and possibly γδ T cells constitutively express the β chain (Kd of 10^-9 mol/L) in the absence of antigenic stimulation, and these cells are therefore the immediately IL-2 responsive cell population (21). The biological activity on unstimulated NK cells is presumably due to interaction of the slow binding intermediate affinity β/γ dimer that rapidly leads to upregulation of the fast binding α chain (Kd of 10^-8 mol/L) to create a high-affinity α/β/γ heterotrimer with a Kd of 10^-12 mol/L. Interaction of IL-2 with the high-affinity receptor results in internalization through receptor-mediated endocytosis. The 75 kD β chain, with the largest cytoplasmic domain of 286 amino residues, and the γ chain are probably responsible for triggering intracellular biochemical pathways (22). Signal transduction after receptor binding remains obscure. The IL-2 receptor itself has no known enzymatic activity. Upon IL-2 interaction with its receptors a variety of intracellular events occur. Hydrolysis of inositol phosphates and increases in intracellular calcium are coupled with activation of calcineurin, a calcium/calmodulin-responsive protein phosphatase, activation of tyrosine kinase and ultimately induction of transcriptional regulatory molecules. NK-506 and cyclosporine appear to block these early events (23).

2.1.2 Soluble IL-2 receptor

Soluble forms of the IL-2Rα chain have been identified in the serum of patients with malignant, autoimmune and allergic disorders, systemic parasitic infections and in patients undergoing graft versus host disease. The α chain is thought to be released from the cell-membrane of activated T cells by proteolytic cleavage. The presence of the soluble IL-2Rα is therefore thought to reflect the state of T cell activation in these patients (24). Soluble IL-2Rα has been found to be increased during IL-2 therapy (25). Some investigators suggest an
inhibitory effect of sIL-2Rα, the soluble form competing with the signal transducing membrane bound receptor for the IL-2 molecules (26). This is however debatable regarding the different affinities of the receptors for the IL-2 molecule.

2.1.3 Biological effect on cells

The phenotype of a variety of lymphoid cells proliferating in response to IL-2 in vitro appear to depend on the concentration of IL-2 and the duration of culture. At relative low concentrations IL-2 is able to induce cytolytic activity in MHC-restricted, antigen specific T lymphocytes (CTL) after 6-7 days. These CTL express CD3, CD8, CD10 and CD16 surface antigens. Natural killer (NK) cells exhibit a broad range of MHC-nonrestricted cytotoxic responses when exposed to IL-2 after 2 to 3 days. NK cells comprise 2-5% of the peripheral blood mononuclear cells and these cells may express CD2, CD3, CD7, CD8, CD11, CD16, CD35 and CD56 surface antigens. When incubated with higher concentrations of IL-2, resting peripheral blood large granular lymphocytes, T lymphocytes and possible even B lymphocytes become capable of non-specific lysis of fresh cancer cells but not normal cells after 5 to 10 days in short-term assays. This was named the Lymphokine Activated Killer (LAK) cell phenomenon (27). Lymphocytes expressing LAK activity may express CD2, CD3, CD5, CD6, CD7, CD8, CD11, CD16, CD45 and CD57 surface antigens (28,29). Lymphocytes infiltrating a tumor are frequently found in surgically removed tumors. These cells can be selectively expanded to large numbers from tumor cell suspensions using IL-2. These tumor infiltrated lymphocytes (TIL) are generally of the CD3 CD8 positive phenotype and have been reported to show specific MHC-restricted killing (30). Upon stimulation by IL-2 several secondary cytokines are induced. NK-cells produce IFN-γ, GM-CSF and TNF-α and -β (31). Monocytes release large amounts of IL-1, IL-6, and TNF-α when stimulated by cytokines in conjunction with bacterial agonists (32,33). In vivo IL-2 treatment induces the production of several growth factors including IL-5, GM-CSF, M-CSF and IL-6 (34).

2.2 Preclinical studies

In murine models, repeated systemic administration of high doses IL-2 induced LAK-cytotoxicity in vivo and resulted in significant antitumor responses in disseminated murine leukemia, as well as in fibrosarcoma and melanoma metastases (35-37). The intravenous administration of in vitro activated LAK-cells in combination with IL-2 induced also a significant reduction in the number and size of murine pulmonary and hepatic metastases (38-40). These effects were dependent on the dose and schedule of IL-2 administered (41-45), the number of LAK-cells infused (36,38,40) and on the extend of the tumor burden (36,46). Tumor inhibition has also been observed with low doses of IL-2 (43,47). Established 10-day metastases but not 3-day metastases were sensitive to low dose IL-2 (43). Athymic nude mice failed the low dose IL-2 treatment while they were responsive to high dose IL-2, suggesting that the antitumor activity of low dose IL-2 was T cell mediated (47). Local intratumoral
injections with low doses of IL-2 could cure mice bearing a large burden of metastatic tumor (48,49). How an effective antitumor response in vivo is orchestrated using these different mechanisms is poorly understood. Despite the direct cytotoxicity of LAK cells against tumor cells in vitro, in vivo studies have shown that LAK cells do not selectively localize to tumor sites. In a rat model, systemically infused labeled-LAK cells migrated first to the lung and subsequently to the liver and spleen in a 2 to 6 hours period. No difference in the distribution pattern was observed between normal and tumor bearing animals (50). Adoptively administered TIL cells have been shown to travel to metastatic sites in clinical imaging studies (30,51,52). Lymphocytes infiltrating renal cell carcinoma or lung carcinoma, however, have been shown to be functionally impaired, possibly due to tumor-derived immunosuppressive factors (53,54). Interestingly, lymphocytes of tumor bearing mice have been found to have structurally altered CD3-TCR complexes, including the loss of the signal-transducing CD3-ζ chain (55). If these findings also apply to human lymphocytes, this may have important consequences for future immunotherapy studies.

2.3 Pharmacokinetics
Under physiological conditions IL-2 is thought to act in an autocrine and paracrine way in localized areas of inflammation with no detectable levels in the circulation. Pharmacokinetics of exogenous administered IL-2 have been studied in rodents and in humans. The different mutated recombinant proteins of IL-2 do not differ significantly in their pharmacological properties and they will not be discussed separately. After intravenous administration, IL-2 is rapidly distributed to the extravascular, extracellular space. Approximately 30% of the administered dose initially distributes over the plasma volume. After high peak levels, serum concentrations decrease with an alfa and beta half-life of 13 minutes and 2 hours, respectively (56). With a clearance rate of approximately 120 ml/min, the kidneys appear to be the main site of clearance where IL-2 is probably metabolized by the proximal renal tubules, as minimal levels of active IL-2 are found in the urine (56,57). During 24-hour infusion serum IL-2 concentrations appear to reach a steady state after 2 to 6 hours (56,58). The hydrophobic nature of IL-2 necessitates formulation with albumin or a detergent to maintain solubility (59). At slow infusion rates and low concentrations the bioavailability of some IL-2 muteins may be reduced due to adherence to the infusion material (60). After subcutaneous bolus injection IL-2 serum concentrations rise slowly, reaching a maximum concentration after 3 to 4 hours. The serum levels decline slowly with prolonged mean half-lives of 4 to 5 hours (58). Intraperitoneal infusion of IL-2 results in long half-life times with medians of 22 and 6.3 hours in peritoneal fluid and serum respectively. The serum concentrations seem to reflect the efflux from the peritoneal cavity (56). Other routes of administration of IL-2 include inhalation (61) and regional injection of IL-2 (62). No pharmacological data on these routes are available. Modifications of IL-2 with monomethoxy-polyethylene-glycol (PEG-IL-2)(63,64) or a collagen matrix (65) alters its pharmacokinetics properties resulting in a
prolonged serum half life time.

2.4 Clinical spectrum of IL-2

In contrast to the broad spectrum of activity in pre-clinical models, IL-2 has in clinical oncology emerged as a treatment for renal cell cancer almost exclusively. The overall response in this tumor is around 20% and this is not different from the remission rate in patients with melanoma. Probably the acceptance of IL-2 as a treatment of renal cell cancer is dictated also by the lack of active alternatives in that tumor (although as is discussed later, activity of interferon is at least quantitatively not very different). In melanoma dacarbazine (DTIC) has the same response rate as IL-2 but since the introduction of 5-HT<sub>3</sub>-receptor antagonistic anti-emetics this treatment is less toxic. Alternatives for IL-2, in the sense of equally (in)effectivity exist in all tumors other than renal cell cancer. However occasional responses have been described for IL-2 in a broad spectrum of tumors. Colorectal adenocarcinoma for instance is relatively insensitive to IL-2 based immunotherapy. In the National Cancer Institute trials 5 out of 30 patients responded to IL-2/LAK treatment while no responses were observed in 12 patients treated with IL-2 alone (66). In a review of 15 trials with IL-2 containing trials, the National Biotherapy Group reported only one partial response among 76 patients treated (67). In patients with ovarian cancer with disease confined to the abdomen, intraperitoneal administration of IL-2 or LAK cells have been used with reported response rates of 20%. Intraperitoneal fibrosis and abdominal pain were dose limiting factors in this approach (68,69). In patients with bladder cancer, intravesical instillation of high dose IL-2 produced almost no toxicity. One complete response lasting more than 6 months was observed in a small group of 5 patients (70). In patients with lung cancer, a response rate of 16% was reported by the National Biotherapy Study Group, but most of these responses could be attributed to the concomitant treatment with etoposide or cisplatin (67). Clamon et al. reported a response rate of 21% in a phase II trial with continuous infusion IL-2 in patients with extensive small cell lung cancer who failed first line combination chemotherapy with cisplatinum, doxorubcin, cyclophosphamide and etoposide. Complete responses were observed in 17% of patients, but toxicity, especially pulmonary toxicity, was considerable, requiring discontinuation of treatment in 46% of patients (71). In patients with non-Hodgkin lymphoma, early trials showed promising results mainly with IL2/LAK treatment with reported response rates up to 40% but this has not been confirmed by other trials. Small patient numbers and conflicting results preclude any conclusions about the role of IL-2 in the treatment of non-Hodgkin lymphoma (66).

In conclusion, the actual activity spectrum of IL-2 in human tumors may not differ that much from the earlier experience with this drug in model systems. Its clinical use is influenced primarily by the alternatives in therapy and especially by the IL-2 related toxicity (and possibly economic considerations). The concept that there is a relation between "immunogeneity" of tumors and IL-2 activity is challenging but needs substantiating.
considerable clinical experience with the use of IL-2 in the treatment of patients with cancer, several important issues still remain unresolved. This review will address some of these key questions; 1) Is there a relation between tumor response and route of administration? 2) Is there a dose response relation for IL-2? 3) Does the addition of adoptively administered LAK or TIL cell increase response rate? 4) Does IL-2 based immunotherapy have an effect on survival?

Effect of route of administration on response
Most patients are treated systemically by the intravenous or subcutaneous route. Intravenous therapy, given either as bolus injections or as a continuous infusion is associated with considerable dose dependent toxicity which necessitates special care for patients treated. Subcutaneous administration produces local toxicity at the injection sites that can be inconvenient, but the systemic toxicity with the vascular leak syndrome is rarely observed. No randomized experiences concerning efficacy are available between subcutaneous and intravenous IL-2 treatment. However, in view of the range of activity of IL-2 given either way, a difference in response rate, if present, will be limited to 5%. Also the incidence of complete remissions after both administrations is limited to a narrow range. So differences in effects of the two routes of administration if present will be found in the duration of response and the quality of life of non-responders. If eventually comparative studies are going to be done, these questions will have to be addressed.

IL-2 has also been administered regionally by several other routes including intraperitoneal (69,72,73), intravesical (70), intrapleural (74), intraspinal (75), intralymphatic (76), extracorporal perfusion (77), arterial perfusion of the liver or spleen (78,79), local slow delivery pellets into the tumor (65), and by inhalation (61). Toxicity of these regional applications were mostly less than with intravenous administration, but patient numbers are too small to draw conclusions about the clinical efficacy of these routes of administration.

Legend to figure 1. Response rates with 95% confidence intervals of IL2 monotherapy studies in patients with metastatic renal cell carcinoma. The dashed line expresses the mean, the box the 95% confidence interval of the cumulative response of all patients included.

Legend to figure 2. Response rates with 95% confidence intervals of IL2 monotherapy studies in patients with metastatic melanoma. The dashed line expresses the mean, the box the 95% confidence interval of the cumulative response of all patients included.
Figure 1.

Figure 2.
Effect of dose and treatment regimen on antitumor efficacy

In a randomized phase II trial comparing intravenous high-dose IL-2 bolus injections with 24-hour continuous infusion at equivalent toxic doses in the treatment of patients with renal cell carcinoma, no difference was shown in antitumor activity (80). No comparative studies on the dose-response relationship of IL-2 among humans have been reported but numerous phase II studies have been performed using different doses and treatment regimens. Taking into account the limitations of comparing results between different phase II trials, a comparison of the impact of dose on clinical results in patients with renal cell cancer and melanoma is presented here (Fig. 1 to 4) To prevent the bias of small studies, a selection has been made, including only those trials with more than 20 patients. In figures 1 and 2 the response of several trials with the 95% confidence intervals is shown for patients with RCC and melanoma, respectively. In an attempt to compare different treatment schedules, the IL-2 dose is expressed as dose intensity (DI), defined as the dose of IL-2 administered in the first seven days of treatment. Figures 3 and 4 show the response rates in patients with renal cell cancer (66,80-104) or melanoma (66,88,89,101a,105-111). We conclude that no dose response relation is observed in either renal cell cancer or melanoma patients. IL-2 induces an objective response rate of 18% (14%-19%, 95% confidence interval) of the patients with renal cell cancer; in approximately 6% these responses are complete. In melanoma response rates of 15% (11%-19%, 95% confidence interval) are observed with complete responses in less than 5%. In both groups response duration in patients with a complete response can be durable with some of the patients remaining free of disease for more than 2 years.

Adoptive immunotherapy

We conclude (Figs. 3 and 4) that the considerable logistic burden of LAK acquisition is not translated into improved results. In a overview on 15 different phase II protocols with inpatient IL-2 treatment, the National Biotherapy Study Group reported a higher response rate in the protocols involving adoptive immunotherapy than in those without in vitro activated cells (15% versus 7%, respectively, p=0.003), but without any effect on survival (67). In another analysis of 327 patients treated in 5 different protocols Palmer, using multivariant analysis, could not observe any difference in objective response nor in survival when he compared treatment with IL-2 alone or in conjunction with LAK-cells (97). In three prospective randomized controlled trials, the addition of LAK-cell treatment to continuous infusion or high-dose bolus injection IL-2 in melanoma and renal cell cancer patients had no

Legend to figure 3. Dose intensity/response relation of IL-2 with or without adoptive immunotherapy in patients with metastatic renal cell carcinoma. Open points (○), IL2 monotherapy ; solid points (■) IL2 + adoptive immunotherapy.

Legend to figure 4. Dose intensity/response relation of IL-2 with or without adoptive immunotherapy in patients with metastatic melanoma. Open points (○), IL2 monotherapy ; solid points (■) IL2 + adoptive immunotherapy.
Renal Cell Carcinoma

Figure 3.

Malignant Melanoma

Figure 4.
effect on response rate or on survival (80,101,112). One study among melanoma patients reported a correlation between the number of TIL-cells infused and the clinical response, with responding patients receiving significantly more TIL’s than non-responders (113). Rosenberg reported initially a response rate of 50% in patients with melanoma (114) but these results could not be confirmed in other studies. Dillman could raise TIL’s in only 21 out of 82 patients with melanoma, and he reported responses in 5 out 21 patients (24%, 10% - 49%, 95% confidence interval) (115). Bukowski was able to raise TIL’s in 18 of 25 eligible patients with renal cell carcinoma, but no responses were observed (116). Baars et al also observed no responses in 4 patients with melanoma (117). The treatment with TIL’s is possible in only a minority of patients, it is technically difficult, costly, and the clinical results are not superior to those with other IL-2 based regimens.

**Effect on survival**

The effect of IL-2 treatment on survival remains unclear. Randomized trials comparing patients treated with IL-2 with control patients that could answer this issue are not available and ethical considerations limit the institution of these trials. Retrospective studies are limited by the influence of patient selection and changes in diagnostic procedures over time (118,119). In historical control groups the median survival of patients with metastatic renal cell carcinoma was 8 months (120). In an analysis of a cumulated single center experience in 181 patients with RCC who were candidate for IL-2 therapy, median survival after occurrence of metastases was 16 months in all patients irrespective of treatment with IL-2 (intention to treat). Comparison of this survival with a historical control group from the same institution was however impaired due to the lack of information on two important prognostic factors being weight loss and performance status in the control group. The relative high median survival of this group may reflect the difference in diagnostic procedures over time with the availability of a new treatment modality (121). Given the small numbers of responders in all series the effect of IL-2 therapy on survival is influenced by especially patients with stable disease and possibly also by non-responders.

**2.5 Markers of clinical response**

Only a minority of patients respond to IL-2 based immunotherapy, while toxicity occurs in all. Therefore, several investigators have looked for markers that could predict or monitor clinical response. Despite intensive research, no consistent relationship between immunological changes and clinical response has been found (97,101). Several factors have been partially related to treatment efficacy. These include the number of pretreatment lymphocytes, the number of eosinophils, the expression of CD56 on NK-cells, sustained serum levels of TNF, high levels of soluble CD8 and low pretreatment C-reactive protein (CRP) serum levels (122-128). Elevated levels of IL-6 before IL-2 treatment were associated with disease progression after therapy and shorter survival (129). Previous chemotherapeutic
treatments had a negative effect on clinical response in patients with renal cell carcinoma (130) but not in melanoma patients (113). Among melanoma patients HLA Class I phenotypes were correlated with response to IL-2 based immunotherapy. Responding patients had a significantly higher frequency of the alleles A11 and A19 than the overall melanoma patient population (113). High numbers of CD8\textsuperscript{bright} and CD56-cells that express the HLA-DR activation marker were found to be prognostic for a good therapeutic response to subcutaneous IL-2 treatment (123). As to the localization of responses, most responses are observed in the lung or soft tissues, while few responses are observed in the primary tumor or bone lesions.

2.6 Tolerability
Because of a dose relationship observed in animal studies the initial clinical studies were performed with high dose bolus injections of IL-2 (37,38,40,131,132). High dose treatment is associated with severe toxicity for which intensive care support is necessary in an number of patients. IL-2 therapy is accompanied by considerable side effects, including fever, chills, nausea, vomiting, skin toxicity, hepatic and renal dysfunction, mental status changes, and respiratory failure. The most frequent dose limiting side effect of high dose intravenous IL-2 is hypotension. Frequency and severity of IL-2 toxicity is dose-related and schedule-dependent. High dose intravenous regimens require intensive treatment care monitoring and patient selection. Most adverse reactions are self limiting and are usually reversible within 2 to 3 days after discontinuation of therapy. The mechanisms of IL-2 induced toxicity are partly understood. The release of secondary cytokines such as IFN-\(\gamma\) and TNF-\(\alpha\) are thought to be important mediators of toxicity (133,134). Passive immunization against TNF-\(\alpha\) could indeed partially abrogate IL-2 toxicity (135). More recently, the role of cytokine induced nitric oxide has been proposed as a central factor in IL-2 induced hypotension (134). The L-alanine analog N\textsuperscript{G}-methyl-L-arginine has been used in patients with renal cell cancer in order to reduce nitric oxide production to suppress IL-2 toxicity (136). Since the effector mechanism of IL-2 therapy in vivo is not defined care has to be taken with these approaches not to suppress the antitumor effects of IL-2 as well.

2.6.1 Cardiovascular effects
Several cardiac side effects have been observed during IL-2 therapy including arrhythmias, ischemia, myocarditis, hypocontractility and pericardial effusions (66,137-140). Supraventricular arrhythmias, particularly supraventricular tachycardia and atrial fibrillation, occur in 10% or more of the patients treated with intensive regimes and generally resolve after discontinuation of IL-2 (138). In patients over 65 years of age who were treated with intravenous IL-2, cardiac side effects, especially arrhythmias were the most important dose limiting toxicities (96). Angina and myocardial infarction have been observed by several
investigators in patients treated with IL-2. In large series ischemia occurred in 3% to 9% of patients and myocardial infarction in 1 to 4% (3,139,141). The frequency of these toxicities depend on patient selection and treatment regimen. ECG changes, CPK-MB band elevations, with or without chest pain have been described that may not represent infarction or ischemia but rather an IL-2 induced, nonischaemic myocardial injury or myocarditis (142). Hemodynamic changes after IL-2 administration resemble those observed in early septic shock. Shortly after IL-2 administration, a fall in mean arterial pressure resulting from the decreased systemic vascular resistance induced by IL-2 is observed, which is countered by an increase in heart rate and cardiac output (140,143). Subsequently, the development of a 'vascular leak syndrome' (VLS) leads to extravasation of fluid and albumin from the intravascular space, resulting in edema and extravascular fluid accumulation which may lead to or exacerbate pleural effusions and ascites. These effects may be due to a variety of lymphokines induced by IL-2 such as interferon-γ and tumor necrosis factor-α. Nitric oxide produced by macrophages and endothelial cells might play a role in the induction of hypotension during treatment with IL-2 (134,144).

2.6.2 Pulmonary effects
Pulmonary congestion, interstitial oedema, dyspnoea and pleural effusions are common results of the VLS (66,82,137,138). In high dose regimens, approximately 20% of the patients develop respiratory distress and 5- 10% require intubation and mechanical ventilation (66,137,138). Reversible bronchospasm has been observed in patients undergoing IL-2 therapy.

2.6.3 Renal effects
Renal dysfunction is one of the major complications of IL-2 therapy. Azotemia, oliguria, elevated plasma aldosterone and renin activity with low fractional sodium excretion and increased serum creatinine levels are found in more than 60% of patients. Prerenal mechanisms with impaired renal perfusion due to the reduced cardiac function, peripheral vascular dilatation and intravascular volume depletion are thought to be the cause of these abnormalities in renal function (145). An additional intrarenal defect has been postulated (146). Most nephrotoxicities are transient and tend to resolve after cessation of treatment, although in some patients recovery may be prolonged or incomplete (147,148). Administration of non-steroidal anti-inflammatory drugs can contribute to the impairment of renal function (81).

2.6.4 Gastrointestinal and hepatic toxicity
Nausea and vomiting, stomatitis, peptic ulceration, anorexia and diarrhea are frequently observed during IL-2 therapy. Rarely, bowel hemorrhage, perforation, infarction and exacerbation of Crohn’s disease have been reported (149-151). Elevated values of liver
enzymes are frequently observed. Intravenous IL-2 treatment related reversible intrahepatic cholestase with elevated billirubin levels has been described in a number of patients (152).

2.6.5 Endocrine effects
Thyroid dysfunction is reported by several investigators, with a frequency ranging from 20-90 percent of patients treated with IL-2. Initially LAK cells appeared to be essential for the development of hypothyroidism (153), but in later studies thyroid dysfunction has also been reported after treatment with single agent IL-2 (154), IFN (155), or combinations of IL-2 and IFN (156-159). Primary hypothyroidism, hyperthyroidism as well as biphasic dysfunction with hyperthyroidism followed by hypothyroidism have been reported. Thyroid dysfunction has been found to correlate with treatment duration (160), cumulative dose of IL-2 (161) and a favorable tumor response to treatment (161,162). However, in another study no relation between response and thyroid dysfunction was observed (160). The pathogenesis of hypothyroidism is probably multifactorial. Because of elevated anti-thyroglobulin antibody and anti-microsomal antibody titers, autoimmunity has been implicated as a mechanism for thyroid dysfunction. However, in most studies the presence of auto-antibodies did not correlate with hypothyroidism.

Increased hormone levels of beta-endorphin, adrenocorticotropic hormone (ACTH), and cortisol have been reported after intravenous IL-2 administration given as a bolus or constant infusion. The effect of IL-2 was not altered by the concomitant administration of LAK cells. Increased hormonal stimulation occurred upon re-exposure to IL-2 (163). Melatonin levels were found to be significantly decreased during IL-2 infusion. The IL-2-induced effects on cortisol, beta-endorphin and melatonin levels resulted in a complete abolition of their physiological circadian rhythm (164). Endocrine effects of subcutaneous IL-2 therapy were found to be similar to those observed with intravenous administration (165).

2.6.6 Neurological effects
Neuropsychiatric changes are frequently observed during IL-2 therapy. On intensive treatment regimens, patients become frequently agitated, combative, and disoriented, or somnolent and occasionally comatose (66,82,137). These symptoms may progress even in the first days after cessation of IL-2 therapy (166). Increased brain water content of both grey and white matter in patients receiving intravenous IL-2 therapy have been observed using magnetic resonance imaging (167). Perivascular demyelinization was observed on autopsy in a patient with a malignant melanoma who developed neurological symptoms (ataxia, visual disturbances) and subsequently died after receiving IL-2 therapy (168). Hyperesthesia and paresthesia have been observed in patients on IL-2 therapy. Transient ischemic attacks and cerebrovascular accidents have occurred during IL-2 administration (137).
2.6.7 Dermatological effects
Cutaneous toxicities include macular erythema, pruritus, and general erythrodermia with dry desquamation, especially of palms and soles, affecting almost all patients treated with the high dose regimens and approximately half of the patients at the intermediate dose regimens. The erythema resolves within 48 hours but the desquamation can last for several weeks. Sporadic erythema nodosum, angioneurotic edema, lobular panniculitis, urticaria, fatal pemphigus and life threatening bullous skin lesions have been observed (169-173). Subcutaneous administration of IL-2 caused transient inflammation at the injection sites, and nodular lesions resembling subcutaneous lipomas, that gradually disappeared within 6 months. Concomitant use of anticoagulant therapy can cause sometimes local hemorrhage at the injection sites (174). Exacerbations of pre-existing psoriasis and polymyositis/dermatomyositis have been reported after intravenous IL-2 therapy (137,175).

2.6.8 Hematological effects
Eosinophilia, probably due to an increase in IL-5 levels (176); early transient lymphopenia and rebound lymphocytosis are observed in all patients. Thrombocytopenia is frequently reported as a clinical important toxic side effect of intravenous IL-2 therapy. Thrombocytopenia was found to be directly related to IL-2 dose and indirectly to renal function. A peripheral clearing mechanism triggered by the IL-2 dependent release of a leukocyte-produced eicosanoid that initiates platelet degranulation and clearing by the reticuloendothelial system is hypothesized (177). Using a cDNA-polymerase chain reaction (PCR) with specific primer sets for the various colony stimulating factors, Schaafsma et al showed that IL-2 treatment induced the expression of mRNA for M-CSF, GM-CSF, IL-3, and IL-5, but not for G-CSF, in peripheral blood monocuclear cells. Furthermore no IFN-γ or TNF was detected in plasma (34).

2.6.9 Infectious complications
IL-2 therapy is complicated by development of bacterial infections in approximately 23% of the patients. *Staphylococcus Aureus* is the most commonly isolated organism (178-180). Bacterial sepsis is one of the major causes of death related to IL-2 therapy, and is frequently catheter related. Prophylactic use of antibiotics before the placement of central venous catheters markedly reduces the incidence of infection to approximately 7% (181). Subcutaneous administration may also limit the incidence of infection, although inflammation at the injection site is frequently observed (174,182). Reversible impaired neutrophil chemotaxis during IL-2 therapy has been reported that may contribute to the development of infection (183) These effects may be due to secondary release of TNF since concomitant use of dexamethasone both decreases IL-2 induced release of TNF and almost completely abrogates the chemotactic defect (184).
2.7 Combination treatment

IL-2 based immunotherapy has been investigated in combination with a number of other molecules including interferons (156,185-187), TNF (188-190), cytokines (26,191) and cytotoxic agents (192-196) to increase response rates or to reduce toxicity.

IL-2 and interferon

Synergistic activity of IL-2 and IFN-α has been suggested in preclinical studies (197,198), because interferon induces upregulation of MHC-molecules on tumor cells (199,200). In several phase I/II studies the activity of this combination was shown (156,185-187). However in 3 randomized controlled trials comparing IL-2 alone or combined with IFN-α no differences in immune parameters, nor antitumor activity were observed (100,111,201). In renal cell cancer the IFN/IL-2 combination induced response rates of 4 to 42%, with an average response rate of all patients of 18% and complete responses occurring in 5% (67,100,112,130,185,202-213) In melanoma response rates of 4 to 59% are reported with an average response rate of all included patients of 29% and CR occurring in 7% (111,196,214-216).

IL-2 and other cytokines

Combination of IL-2 and TNF resulted in synergistic activity in generating LAK-cells (217), enhanced activation of peritoneal macrophages (218), and antitumor activity in murine models against sarcoma cells (189). Clinical results were reported by Rosenberg and Dillman with responses only in patients with melanoma and renal cell carcinoma. The response rates in these trials were not different from that expected from the use of IL-2 alone (66,67). In a phase I trial with low dose IL-2 and TNF in patients with non small cell lung cancer, TNF showed a four fold lower MTD compared to the single-agent use of TNF with thrombocytopenia as dose limiting factor. One partial response was observed in 12 evaluable patients (188).

IL-3 and melatonin (MLT) inhibited neopterin release and significantly decreased IL-2 induced sIL-2R secretion when given in combination with IL-2 (191). The increase in soluble IL-2 receptor (sIL-2R) and neopterin levels were related to the generation of macrophage-mediated immunosuppression and these were associated with a reduced clinical efficacy during IL-2 therapy. In a phase II study with combined s.c. IL-2 and i.v. IL-3 treatment the increase in serum neopterin, serum sIL-2R and serum cortisol were neutralized by IL-3. Toxicity was decreased in the IL-3/IL-2 combination compared with treatment with IL-2 alone. One out of six patients treated with the IL-2/IL-3 combination had a partial response of a lung adenocarcinoma with a response duration of 7+ months (26).

IL-2 and chemotherapy

The combination of IL-2 based immunotherapy with chemotherapy has been studied in several
trials. In early studies low doses of cyclophosphamide have been used in an attempt to reduce immunosuppressive cell populations during IL-2 therapy without improving response rates (192,193). Sequential combination of IL-2/LAK immunotherapy with DTIC in melanoma patients resulted in a response rate of 26% (194). In two recent studies in melanoma patients promising results have been reported with sequential combined chemoimmunotherapy consisting of IL-2/IFN with CDDP(195) or CDDP, BCNU and DTIC resulting in response rates of 54 and 57%, respectively (196).

2.8 Conclusions and perspectives
Clearly the early promise of IL-2 as a major breakthrough in cancer treatment has not been fulfilled. Nevertheless IL-2 has permitted the conclusion that tumors in patients can regress as a result of the immune response from that patient. This confirmation of the applicability of the immune response in the setting of advanced cancer should form the basis for further studies. What directions should these studies take? In our opinion not much is to be gained by further analysis of modifications in dose or schedule. Also the impact of reducing toxicity will be marginal. The addition of other drugs to IL-2 does not seem to be promising although occasional observations such as the results of the combination IL-2, IFN and platinum in patients with melanoma are provocative (195). If such observations are reproducible they might lead to the direction of changes brought about by cytotoxic drugs, presumably membrane changes, that makes these cells more easily recognizable for activated lymphocytes. A systematic approach into the problem of non-responders to IL-2 should start with analyzing the mechanism for resistance. This could stem from a general lack of stimulation of the immune system, however, this seems not likely as with present day techniques no differences can be found between cell populations in responders and non-responders. If the relevant cells are present in the circulation, the problem may be for them to reach the tumor. This is not unlikely as homing experiments fail to demonstrate selective penetration of LAK cells into the tumor. The fact that TIL cells do home, suggests that these cells have some memory of their past migration pattern. Analysis of this pattern might solve some of the problems. However in clinical practice, at least during subcutaneous treatment a pattern of mixed response is often seen; some lesions grow, others remain stable or diminish. This suggests clonal differences in the metastases with regard to recognition by LAK cells. Retargetting of LAK cells to a more common antigen may deal with this problem. Another way would be to trigger tumor cells to express recognizable antigens, this will probably require the application of gene transfer techniques into clinical oncology.

3 Interferon
The use of the interferons in solid tumors has been reviewed by several investigators
Originally they were described as antiviral factors (223), but after discovery of their antiproliferative and immune modulatory activities, partly purified human leucocyte derived interferon (IFN) was investigated as a potential anticancer agent. Numerous clinical trials started after highly purified interferons produced by recombinant DNA-technology became available. Today, interferon is used in the treatment of several hematologic malignancies as well as in patients with solid tumors. In this review the role of IFN-α in the treatment of solid tumors will be discussed.

3.1 Biology
Interferons are a family of more than 20 proteins which are produced by different cell types under specific activating conditions. Type I IFNs are synthesized in response to viral infections or following exposure to B-cell mitogens, foreign cells or tumor cells. Lymphocytes produce primarily IFN-α, whereas IFN-β is produced by fibroblasts. The originally termed IFN-β2, now renamed interleukin-6, will not be discussed here. Type II IFN, IFN-γ is produced by antigen- or mitogen-activated T lymphocytes. A new interferon family, IFN-ω, has been distinguished from other interferons (224). The genes for IFN-α, IFN-β and IFN-ω have been found on chromosome 9 and the one for IFN-γ on chromosome 12. There are 23 IFN-α genes (8 pseudogenes) encoding acid-stable peptides of 18-20 kD. Only one single gene for IFN-β has been identified encoding 166 amino acids. IFN-β is an acid stable glycoprotein of 23 kD. For IFN-γ a single gene encoding for a protein of 144 amino acids has been identified. There are two active forms of IFN-γ: glycosilated proteins of 20 kD and 25 kD. The genes for the α, β and γ interferones have been cloned and expressed in bacterial systems. Interferons bind specifically to receptors on the target cell membrane. IFN-α and IFN-β share the same receptor, found on the surface of most cells. The gene for the receptor for IFN-α and -β has been found on chromosome 21 while chromosome 6 encodes for the IFN-γ receptor (225,226). The IFN-γ receptor is found on T-cells, B-cells, monocytes, neutrophils, fibroblasts and colony forming cells. Antineoplastic activity of IFN probably results form a direct inhibitory effect on cell growth and proliferation, and from indirect effects on the immune system, including increased NK-cell activity, enhanced expression of MHC class I and II cell surface antigens (200, 227) and stimulatory or inhibitory effects on certain B- and T-cell functions.

3.2 Preclinical studies
Pharmacokinetics
The pharmacokinetics of IFN-α have been studied in healthy volunteers. After an intravenous injection plasma levels of IFN-α decrease with an alfa and beta half life times of 5-10 minutes and 4-5 hours, respectively. Intramuscular or subcutaneous injections results in peak levels occurring after 4 to 7 hours. The area under the plasma concentration-time curve (AUC) after subcutaneous or intramuscular injection is approximately 80 to 100% of that after
intravenous administration. The distribution volume at a steady state condition was 31.4 L. The clearance of IFN-α occurs mainly by catabolism in the renal tubulus, no active protein is found in the urine (228,229).

3.3 Clinical spectrum
The clinical use for oncological purpose of IFN-β and IFN-γ has been investigated less intensively than IFN-α. IFN-β has been studied mainly in patients with RCC (230,231). IFN-γ has been studied alone (232-234), or in combination with IFN-α (235), or IL-2 (236-238) or TNF (239). This review will focus on the clinical use of IFN-α in solid tumors. Most questions as to potential influence of dose and route of administration seem to have been solved and the answers have been dictated by acceptability of toxicity. A narrow field of indications seem to be emerging, although recently its limits may have been changed by descriptions of influence of IFN-α on chemotherapeutic effects especially on 5FU. IFN-α is approved for the treatment of patients with hairy cell leukemia, where response rates of 80% could be achieved. In chronic myeloid leukemia treatment with IFN-α has resulted in therapeutic responses in up to 70% of the patients and occasional in the reversion to a normal chromosomal state (240). Responses to IFN-α are also reported in patients with Kaposi’s sarcoma (30%), myeloma (10-20%), and carcinoid tumors (40%). Reproducible activity also was found against tumors such as melanoma and renal cell carcinoma, which are unresponsive to conventional chemotherapy.

3.3.1 Renal cell carcinoma
The use of the interferons in renal cell carcinoma has been reviewed by Muss (241). Interferon induces responses in 13% of patients with renal cell carcinoma, with mostly partial responses. Median response duration was 6 months. Routes of administration do not appear to influence response rates or toxicity although intramuscular or subcutaneous administration may be preferable. Maximal response rates are obtained with both low and intermediate doses. Randomized studies addressing the dose-response issue suggested in two trials that a high dose regimen was superior, while a third study did not show any difference between the low and high dose treatment. Toxicity was substantially enhanced using the high dose IFN in all trials (242-244). A dose of 5-10 MU, given subcutaneous or intramuscular, at least three times a week appears to result in the best therapeutic index. In one study, antibody formation, occurring in up to 38% of the patients was associated with a loss of toxicity and a decrease in median survival and remission duration (243).

3.3.2 Malignant melanoma
The use of IFN in the treatment of patients with malignant melanoma has recently been reviewed by Kirkwood (245). In several clinical trials response rates of 12% - 22% were reported with occasional complete responses. No dose response relationship has been found
in melanoma patients in the range of 10 to 100 MU IFN with daily or alternate-day dosing. Responses may be observed late during therapy after 3 - 6 month, with most of them being partial, with a median response duration of 4 months. However, a small minority of patients may achieve long term disease free remissions of several years following IFN-α therapy (246). IFN-α has been used in combination with cimetidine (247), zidovudine (248) and cytotoxic agents with either no or small improvement in response rates. The combination of DTIC with recombinant interferon α-2a has been shown to produce objective response rates of 26%, with low toxicity and maintenance of quality of life. In some, but not all randomized trials with DTIC as a single agent, the combination treatment showed improved response rates (249-252). The combination treatment of patients with melanoma using IFN, IL-2 and cytotoxic agents is discussed in section 2.7.

3.3.3 Aids related Kaposi’s sarcoma
Kaposi’s sarcoma is a rare malignant disease that is associated with the acquired immunodeficiency syndrome (AIDS). Numerous controlled trials have demonstrated reproducible response rates in the range of 20-40% with IFN-α therapy; a substantial proportion have been complete responses. Higher doses IFN (≥20 MIU/m²/day) have been associated with better responses than lower doses. The total lymphocyte count, CD4 lymphocyte count, and CD4/CD8 ratio, as well as the beta-2- microglobulin level have been associated with better responses (253). Combination of IFN-α with chemotherapeutic agents have not produced significant enhanced response rates compared with IFN alone. However the hematological and other organ related toxicity were enhanced and dose reductions of both IFN and the cytotoxic drug were often necessary. Combination of IFN with zidovudine produces good results, with reproducible response rates of approximately 40%, while suppressing HIV-infection (248,254). The clinical use of this combination is however frequently complicated by the overlapping myelotoxicity, particularly neutropenia, of these agents. Hematopoietic growth factors such as granulocyte (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) can be useful in restoring neutrophil counts and preventing of otherwise required dose modifications, but it did not have an effect on the response rate, the CD4-cell count, or the improvement in any other hematologic parameter. The use of growth factors was not associated with an increased toxicity or a change in serum HIV p24 antigen (255).

3.3.4 Colorectal cancer
IFN-α as a single agent has only little activity in the treatment of patients with colorectal cancer, with response rates of approximately 10% (256,257). In vitro IFN-α synergistically augments the cytotoxic effects of the antimetabolite fluorouracil (5-FU) against human colon cancer cell lines (258). IFN-α can also improve 5-FU/Leucovorin mediated growth inhibition in fluoropyrimidine sensitive colon cancer cells (259,260). In animal studies interferon
potentiates the effect of 5-FU in inhibiting liver metastases in nude mice (261). The mechanisms of the synergy between IFN and 5-FU are not clarified. IFN-α treatment of HT-29 colon carcinoma cells induced a greater than two-fold increase in the intracellular levels of the active metabolite of 5-FU, FdUMP. Using cell extracts from HT-29 cells and 5-FU as substrate, IFN-α produced a 1.9- and 8.7-fold increase, respectively, in the activities of uridine phosphorylase and pyrimidine nucleoside phosphorylase (PyNP). The effect was selective for the conversion of 5-FU to FdUMP, as IFN-α did not increase the cellular levels of FUTP, nor did it change the extent of incorporation of 5-FU into RNA (or DNA). IFN-α also had no effect on thymidine kinase activity, the second step in the activation of 5-FU. Hence the effect of IFN-α on PyNP-activity is likely a critical biochemical event that modulates the cytotoxicity of 5-FU (258). IFN also alters the pharmacokinetics of 5-FU, inducing higher serum levels of 5-FU and increased drug exposure (262,263). In a clinical trial, treatment of patients with advanced colorectal carcinoma with the combination of 5-FU 750 mg/m²/d for 5 days as a continuous infusion followed by weekly outpatient bolus therapy and IFN 9 MU subcutaneously starting day 1 and administered three times per week resulted in objective tumor regression in 62% of patients (264). In a multi-institutional setting phase II clinical trial by the Eastern Cooperative Oncology Group (ECOG) the addition of IFN to 5-FU enhanced the objective response rates achieved in patients with advanced colorectal carcinoma with acceptable toxicities. IFN also enhances fluorouracil-induced toxicities, especially mucositis (265). The triple combination of 5-FU, IFN and Leucovorin was highly active in patients with advanced colorectal cancer, at the cost of increased toxicity, mainly mucositis and diarrhea (262,266).

3.3.5 Carcinoid
The malignant carcinoid is a slowly growing tumor arising from cells of the neural crest that are capable of amine precursor uptake and decarboxylation. Multiple small tumors in the gut or metastases in the liver may produce a variety of biological active peptides that can cause the carcinoid syndrome, which includes severe diarrhea, cutaneous flushes, hypotension, and cardiac valvular lesions. The primary form of treatment in this disease is surgery. When the tumor is unresectable or metastatic, chemotherapeutic approaches have been investigated, with combination treatment of streptozocin and fluorouracil being the most effective regimen reported (267,268). Besides the symptomatic treatment with somatostatin analogues (269,270), interferons have been investigated in the treatment of the malignant carcinoid. IFN-α, at doses of 2.5 to 42 MU/week induced responses in 30% to 60% of the patients with reduction of serum tumor marker levels and symptomatic improvement, rather than a reduction in tumor size (271-278). Side effects, consisting of anorexia and fatigue, were observed in approximately one third of the patients treated. These side effects were dose related and they required dose reductions of IFN or discontinuation of treatment in a number of patients. Dose escalation of IFN did not improve response rate (277). Low doses of 3 to 9 MU/d i.m. at least
3 times a week have been reported to have the best therapeutic index with prolonged symptomatic improvement and tolerable toxicity.

3.3.6 Ovarian cancer
Despite the improved results of platinum-based combination chemotherapy, local tumor recurrence remains a major problem in the treatment of patients with ovarian cancer. Interferon has been used intraperitonally in patients with ascites from a local relapse. In three studies, using high doses (50 MU) of IFN-α administered in 2 L dialysate, response rates up to 52% were observed (279-281). When alternated with intraperitoneal cisplatin, a response rate of 50% was described in one study (282).

3.3.7 Bladder cancer
Treatment of superficial bladder cancer with IFN administered intravesically has been effective with complete responses against both carcinoma in situ and recurrent noninvasive low-grade transitional cell carcinomas. In a phase II study intravesical instillations of recombinant IFN-α, at a daily dose of 54 MU for 5 days for 2 consecutive weeks resulted in a response rate of 79% of patients. The median relapse time was 40 weeks, while clinical and local tolerance were optimal (283).

3.3.8 Benign Tumors
Interferon-α appears to induce the early regression of life-threatening corticosteroid-resistant hemangiomas including pulmonary hemangiomatosis of infancy (284,285).

3.4 Tolerability
The clinical toxicity of interferon has been reviewed by Quesada (219) and Dorr (221). The most common acute toxicity is a flu like syndrome with fever up to 38 to 40°C, starting within 6 hours after a parenteral dose and lasting for 4 to 8 hours, if untreated. Chills, myalgias, arthralgias and headache may accompany the febrile reaction. These side effects can be partially inhibited with acetaminophen. With repeated daily treatment the febrile reaction and accompanying symptoms usually decrease in intensity in seven to ten days. With intermittent cyclic administration no such tachyphylaxis is observed, with symptoms frequently reoccurring after re-exposure to IFN. Fatigue and anorexia are the most prominent dose limiting toxicities of chronic interferon treatment. Alternate-day administration may be better tolerated than daily administration in this setting. At high doses IFN can be neurotoxic, with symptoms of vertigo, confusion and decreased mental status. Severe IFN toxicities are rare, but isolated reports of coma, cerebrovascular accidents have been reported. Hematological toxicity consists of mild leucopenia, and sometimes anemia and thrombocytopenia. Few gastrointestinal symptoms are observed with low dose IFN (3-5 MU/day). With higher doses toxicity consisting of nausea, vomiting, and diarrhoea become
more prominent. Cardiovascular effects of IFN are uncommon and rarely serious. Elevation of serum transaminases may reflect hepatic toxicity. Renal toxicity is usually low, but severe renal toxicities with reversible renal failure and nephrotic syndrome have been reported. Interferon toxicity is dose related. In general, tolerance and compliance are excellent with doses of 1-9 MU. At doses above 18 MU there is a significant increase in the incidence of severe adverse effects particularly gastro-intestinal and neurological effects. Doses over 36 MU are rarely tolerated for more than 8 weeks.

3.5 Conclusions and perspectives
The clinical spectrum of IFN seems, as far as oncology is concerned to have almost crystallized. It is an active agent in some hematological tumors, but usually alternatives are available. This is important considering its side effects and high costs. However in view of the reversibility of these side effects, in contrast to those of many cytotoxic agents, doubtless IFN-α will remain part of the armamentarium in the fight against cancer. In solid tumors its place is still uncertain, until now the only synergy that has reproducibly been found is that with the cytostatic 5-FU. However, the possibilities to translate this into clinical practice deserve further study.

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