Management of Patients with Past or Present
Solid Cancer or Haematological Malignancy

Evidence Based Medicine | Official recommendations | Expert opinion

When evaluating a new immunomodulating agent, the potential for increasing the risk of malignant disease should always receive close attention, particularly when the drug interferes with the cytokines involved in innate immunity such as TNF-α or interleukin-6 (IL-6).

The preclinical development program for tocilizumab found no evidence suggesting an increased risk of malignancy. During the clinical development program (phase II and III studies), a very limited number of patients were diagnosed with cancer, the prevalence being comparable to that seen in the methotrexate-treated control groups of monotherapy trials and in the groups given conventional DMARDS and a placebo in the combination trials [46] (Table 7).

In the LITHE trial, after 2 years of follow-up, the rate of cancer was higher in the group given tocilizumab 4 mg/kg plus methotrexate compared to the other groups: 0.4/100 patient-years (1/284.81 patient-years) with the placebo, 1.9/100 patient-years (10/521.9 patient-years) with tocilizumab 4 mg/kg, and 0.9/100 patient-years (12/1,320.41 patient-years) with tocilizumab 8 mg/kg [46]. Given the current state of knowledge, the observed differences are not relevant but warrant continued surveillance.

An analysis of the Roche database including all patients who participated in randomized trials showed no cancer risk increase with tocilizumab 8 mg/kg compared to the control groups Only four haematological malignancies were recorded (two non-Hodgkin lymphomas, one Hodgkin lymphoma with pre-existing manifestations, and one gammapathy, also with pre-existing manifestations). There was no excess of non-melanoma skin cancers [11]. In this database, the risk of developing malignant disease does not increase with the duration of tocilizumab exposure (Table 8).

This meta-analysis of controlled randomised trials produces a control group of patients selected at random, which enables a valid risk analysis. However, the limited number of patients and fairly short period of double-blind therapy does not provide information on the risk of delayed events that may develop after prolonged exposure. In addition, the patients included in the trials were selected; more specifically, patients with solid cancer diagnosed within 5 years before study initiation were not eligible. These restrictions should be borne in mind when comparing the solid cancer and lymphoma rates in tocilizumab-exposed patients to those expected in the general population or observed in historical cohorts of rheumatoid arthritis patients treated with non-biological or biological agents.

What steps should be taken before tocilizumab therapy in patients with a history of solid cancer or haematological malignancy?

No studies have evaluated the advantages or risks of tocilizumab therapy in patients with cancer or lymphoproliferative disease, or a recent history of these diseases.

Given the absence of data, prudence dictates that tocilizumab not be used in patients with a history of solid cancer or haematological malignancy in the past 5 years, except for basal or squamous cell epithelioma removed with tumour-free margins. Nevertheless, in patients with localized cancer that was completely removed (no risk of metastasis), the use of tocilizumab may be discussed with the oncologist on a case-by-case basis.

In patients with myeloma (or a past history of myeloma) or monoclonal gammopathy of undetermined significance, the use of tocilizumab may be considered according to the risk/benefit ratio in the individual patient. Tocilizumab therapy can be considered, as sound preclinical and clinical data suggest a beneficial effect of IL-6 inhibition in this situation.

In patients with a history of lymphoma, given the absence of data, the initiation of tocilizumab therapy is not indicated. Nevertheless, when all other treatment strategies including rituximab fail, the appropriateness of tocilizumab therapy may be discussed with the haematologist after an analysis of the risk/benefit ratio. Theoretical considerations suggest that IL-6 inhibition might have beneficial effects on non-Hodgkin B-cell lymphoma. In contrast, in patients with EBV-induced lymphoproliferative disease, tocilizumab therapy is not recommended.

No data are available on the risk of malignancy in patients with risk factors (smoking, HPV infection, exposures to toxic agents such as asbestos). Although these risk factors do not contraindicate tocilizumab therapy, the risk/benefit ratio should first be assessed carefully in conjunction with the oncologist or other relevant specialist.

What are the warning signs during tocilizumab therapy?

During tocilizumab therapy, the development of several clinical signs may suggest a malignancy, particularly the following:

- unexplained fever
- decline in general health
- weight loss
- asthenia
- suspicion of lymphoma: peripheral lymphadenopathy, hepatomegaly, splenomegaly, recurrent infections, diaphoresis, pruritus
- suspicion of solid cancer: local signs depending on the organ involved.

Course of action in patients with solid cancer or haematological malignancy during tocilizumab therapy

When a solid cancer or haematological malignancy is found in a patient on tocilizumab therapy, the steps listed below should be taken.

- Perform investigations to confirm the diagnosis and assess the stage of the disease.
- Discontinue tocilizumab therapy (i.e., do not administer the next scheduled injection).
- Adjust the maintenance RA treatment regimen and determine whether concomitant immunomodulators (methotrexate, leflunomide...) should be stopped, at least during the treatment for the malignancy.
- Report the case to the pharmacovigilance centre and start appropriate treatment if the diagnosis is confirmed.

The need for permanently discontinuing tocilizumab therapy should be assessed on a case-by-case basis according to the nature of the malignancy.

- In patients with generalized cancer or cancer having a high risk of metastatic dissemination (e.g., breast cancer), the reintroduction of tocilizumab therapy is not recommended in the absence of additional data suggesting that there is no risk in this situation.
- In patients with localized tumours that were removed completely during surgery, tocilizumab therapy should be stopped until the end of the evaluation and surgical treatment. Subsequently, the appropriateness of re-starting tocilizumab therapy may be discussed with the oncologist on a case-by-case basis depending on the risk/benefit ratio.
- In patients with myeloma or lymphoma, tocilizumab therapy should be stopped until the anticancer treatment is completed. Then, in the event of a partial remission of the malignancy, and *a fortiori* of a complete remission, tocilizumab therapy re-initiation may be discussed with the oncologist based on the risk/benefit ratio.

Any malignancy occurring during tocilizumab therapy must be reported to the pharmacovigilance centre.

Additional information on the role for IL-6 in carcinogenesis

The role for IL-6 in carcinogenesis has been extensively investigated.

- IL-6 was investigated in vitro using cell lines and in vivo using animal models (mice) lacking IL-6 (IL-6 -/-) or treated with dominant negative IL-6 inhibitors. In these models, the behaviour of induced tumours was investigated. Overall, these studies showed a pro-tumour effect of IL-6. Thus, IL-6 facilitated cancer-cell survival (by inhibiting the apoptosis) and proliferation, and also promoted metastatic dissemination by stimulating cellular adhesion and angiogenesis. IL-6 can also act by interfering with hormonal or enzymatic factors, for instance by increasing the production of aromatase (which may promote breast cancer). IL-6 also promotes the development of chemoresistance. The effect of IL-6 on the immunological response against tumours is more controversial [56, 57]. These overall pro-carcinogenic

effects of IL-6 are mediated by activation not only of the JAK-STAT (STAT3) pathway, but also of the MAPkinases pathway. Only a few studies in in vitro and in vivo models, all relatively old, suggest a possible anti-tumour role for IL-6 [58, 59]. Thus, overall, IL-6 is considered a pro-tumoural factor in lymphoproliferative syndromes (myeloma, lymphoma, Castleman's disease) and in several solid cancers (breast, ovary, prostate, lung, kidney, colon, glioma, melanoma...).

➢ The role for IL-6 in various malignant diseases in humans has been investigated

- Studies have shown that the -174G/C polymorphism of the IL-6 promoter (associated with high serum IL-6 levels) correlates with the development of lymphoproliferative syndromes (lymphoma, myeloma) and solid cancers (colon, breast) [60, 61]. Data reported about other cancers (e.g., head and neck cancers and gastric cancer) are more controversial.
- IL-6 serum and tissue levels in patients with various types of cancer have been assessed in nearly 200 studies [62]. Overall, serum IL-6 levels seemed elevated in patients with cancer. However, no prospective studies are available to establish a causal link between IL-6 production and the development of cancer.
- Pathophysiologic studies in a number of cancers strongly support a pro-tumour effect of IL-6.
  - In patients with myeloma, lymphoma, or Castleman's disease, IL-6 is considered a marker of adverse prognostic significance. IL-6 may be produced not only by the malignant cells (B cells or plasma cells), but also by the tumour environment (stromal cells). This autocrine and paracrine IL-6 production acts on the tumour cells, which express the IL-6 receptor. The role for IL-6 is particularly prominent in Castleman's disease. In Castleman's disease induced by human herpes virus 8, this virus can produce an IL-6 analogue that induces tumour proliferation.
  - In hepatocarcinoma, IL-6 has been shown to play a key role in the malignant transformation of hepatocytes subjected to a viral, toxic, or immunological insult. Elegant studies in a model of diethylnitrosamine-induced hepatocarcinoma confirmed the major importance of IL-6 in hepatocarcinoma development [63-65].
- Thus, in most of the malignancies seen in humans, IL-6 is believed to contribute to carcinogenesis and metastatic dissemination. Among the few controversial data, those obtained in studies of melanoma deserve to be mentioned. In vitro, on cell lines, IL-6 can inhibit melanoma, whereas in a murine melanoma model, IL-6 increases the risk of metastatic disease [66]. Serum IL-6 levels are elevated in humans with metastatic melanoma and correlate with tumour proliferation [67].

Taken in concert, this body of evidence pointing toward a pro-tumour effect of IL-6 prompted studies of various IL-6 inhibitors in several tumours [56]. The main malignancies studied to date are myeloma and Castleman's disease, although IL-6 inhibition has also been evaluated for the treatment of lymphoma and other disseminated cancers, most notably renal cancer, with conflicting results [68, 69].