IL-6 Blockade Limitations as an Anticancer Strategy: Literature Review and Proposal of Explanations for Unexpected Results

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Author’s contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

IL-6 is a cytokine with multiple protumorigenic effects, making it an interesting therapeutic target. IL-6 inhibitors with an acceptable safety profile had been developed and tested in experimental and clinical trials. However, the outcomes were not as expected theoretically. Possible explanations of this discordance had been advocated by authors and will be reviewed in this paper. Additional reasons, such as the antitumoral effects of IL-6 and overcompensation by alternative agents will be proposed. These may also explain the trending to negative results constated in some clinical trials.

Keywords: IL-6; cxcl-12; pre-metastatic niche; siltuximab.

1. INTRODUCTION

Cytokines are soluble mediators that regulate the functions of the immune system. They are subdivided into subgroups including chemokines, interleukins and interferons. Interleukin 6 (IL-6) is an interleukin secreted by various cell types including T cells, B cells and even some tumour cells [1]. It has multiple effects on inflammation, immune response, and hematopoiesis that are mediated by its receptor IL-6R. There are two forms of IL-6R; the transmembrane one with a short cytoplasmic domain mIL-6R, and the extracellular secretory domain.

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receptor sIL-6R [2]. Expression of mbIL-6R is restricted to some types of cells mainly the hepatocytes and is responsible for classical IL-6 signalling. In contrast, the soluble sIL-6R is ubiquitous, widening IL-6 effects to various cell types via a trans-signalling mechanism. The signal transduction of IL-6 via gp130 induces the activation of Janus Kinase (JAK), which in turn will activate the Signal transducer and activator of transcription 3 (STAT3) [1]. The activated STAT will then translocate to the nucleus, and activate the transcription of target genes. The list included notably genes encoding proinflammatory, proliferative and antiapoptotic proteins. Also, IL-6 has generally a stimulatory effect on immune cells. It induces T helper cell differentiation and inhibits regulatory Treg generation. Also, IL-6 stimulates the transformation of CD8+ T cells and B cells into cytotoxic T cells and plasmocytes, respectively. In seeming autoregulation of IL-6 signalling pathway, the transcription of Suppressor Of Cytokine Signalling (SOCS) gene, which is an inhibitor of JAK activity, is also induced [2].

2. IL-6 IN TUMORIGENESIS AND METASTASIS

The link between IL-6 level and cancer invasion has been established. Kim and al. found a correlation between preoperative IL-6 level and tumour invasion depth, lymph node metastasis and TNM stage [3]. IL-6 role in tumorigenesis extends from the early phase of neoplastic degeneration in inflammation-induced carcinogenesis to tumour growth and survival [4]. IL-6 induces the transcription of proliferation genes such as cyclin D and proliferating cell nuclear antigen (PCNA) while suppressing apoptosis ones such as B-cell lymphoma extra-large (Bcl-xL), B-cell lymphoma 2(Bcl-2), and Induced myeloid leukaemia cell differentiation protein (Mcl-1) [4]. Moreover, it provides an immunotolerant microenvironment to tumour cells at their primary sites via induction and expansion of myeloid-derived suppressor cells (MDSC), which are heterogeneous immature myeloid cells that suppress innate and adaptive immunity [5,6]. As for metastasis, IL-6 induces the premetastatic step of epithelial-to-mesenchymal transition (EMT) by upregulating key transcription factors such as The Drosophila embryonic protein (Snail) and Twist [7]. It also intervenes in tumour cells motility by promoting the formation of premigratory filopodia and facilitates the invasion by upregulating the Matrix metallopeptidase 1 (MMP1) that degrades the extracellular matrix (ECM) [7,8]. The prometastatic role of IL-6 is also evident at later stages of metastasis, such as the homing of tumour cells to the premetastatic niches [9].

3. IL-6 AS A CANCER THERAPEUTIC TARGET

The multiple protumorigenic effects of IL-6 have made it an interesting therapeutic target [10]. Inhibition of IL-6 may be achieved by targeting either IL-6 itself or its receptor IL-6R by monoclonal antibodies. Blockade of JAK/STAT signalling pathway is also an alternative although less specific. In this paper, IL-6 monoclonal inhibitors will serve as an illustration of IL-6 blockade as they are more specific and included in clinical trials. The successful development of the IL-6 inhibitor siltuximab and its FDA approval for the nontumoral condition of multicentric Castleman’s disease, added to the encouraging results in experimental tumour models permitted a smooth transition to clinical settings for evaluation of its antitumoral activity. Two studies will serve here as an illustration; the first by Rossi and colleagues and the second by Angevin et al. [11,12]. These are phase II/III dose-escalation study of siltuximab in patients with advanced cancer disease. The first trial interested in patients with metastatic renal cell carcinoma, while the second included different types of solid tumours. The goal of dose escalation was to determine the highest safe dose that patients it will receive during the second phase. These doses were 6 mg/kg and 15 mg/kg every 3 weeks, respectively. The primary end-points were complete response (CR), partial response (PR), and stable disease (SD). The drug has shown an acceptable safety profile, with some common adverse events including fatigue, dizziness, and hepatic function abnormalities. Discontinuation due to adverse events was rare. However, the efficacy was lower than expected theoretically. CR was not reported. In the study of Rossi there was only one patient who had PR in phase II, while in the study of Angevin, there was no PR. 37% of patients in the first study and 6% in the second had SD, but this stabilization was only temporary and it ranged at best from 78 to 254 days [11]. Of note, the limited outcome of IL-6 inhibitors was not only seen with solid tumours but also with other types such as myeloma [13,14].

An important fact to keep in mind when interpreting the results of single-target therapeutics such as IL-6 inhibitors is that
evoked by Orlowski and his colleagues [13]. Tumour metastasis result from the collaboration of many agents in a way that inhibition of one among them may be compensated by the others. This is the reason that drugs combination is a rational approach that some trials have already adopted. The study of Voorhees et al. had demonstrated a better therapeutic response under dexamethasone-siltuximab combination compared to siltuximab but it was still unsatisfying [14]. This may be due to the high number of all intervening agents compared to those suppressed by the combination. Authors have also suggested the inefficacy of IL-6 inhibitors against local IL-6 present at the tumour microenvironment. Thus, the protumorigenic effects of IL-6 would be maintained even if serum IL-6 suppression had been achieved. Developing a technique for evaluation of local IL-6 suppression is needed to verify this proposition. Another plausible explanation is that studies were carried among patients with advanced tumours, which may become independent of IL-6 for survival and invasion. Clinical trials should include patients with tumours at earlier stages to eliminate this eventuality.

In this section, two additional propositions will be suggested that may also explain the trend to negative results reported in some studies, such as the multicenter phase II trial of Fizazi and al., which had shown a reduction in progression-free survival in the group receiving siltuximab added to mitoxantrone/prednisone compared to the group under mitoxantrone/prednisone alone (97 days compared to 228 days p: 0,048) [15]. The first proposition is the overcompensation of the effects of the suppressed agent by other protumorigenic factors. For example, given that tumour progression definition in the previous study includes apparition of new metastatic sites, the relative accelerated tumour progression after IL-6 blockade may imply that metastatic sites induction by the compensator agent is superior to that of IL-6. But even if this argument is validated, could the identification of the responsible agent be possible? A rational approach consists of comparing the actors responsible for tumour cells homing, according to indices of metastatic niches development. For initial simplification, we refer to only one index which is immunotolerance. This parameter is dependent, among others, on the infiltration of immunosuppressors cells such as MDSC, and activity of immunocompetent cells. A factor that induces more MDSC infiltration and has a more pronounced inhibitory effect on immune cells would induce more immunological tolerance and thus would be more prometastatic. On the other hand, a molecule that induces less MDSC infiltration and has more stimulatory effect on antitumor immune cells would be less prometastatic. Factors falling into this latter category have, in some sort, an antimetastatic effect and the prometastatic sites where they prevail should be considered as traps for circulating tumour cells rather than niches. As an illustration, we will compare IL-6 to the chemokine CXCL12, another tumour homing factor [9,16]. Concerning MDSC, the role of CXCL12 as an inducer of their infiltration has been documented [17]. As for IL-6, although tumour expression of IL-6 is correlated with MDSC infiltration in primary tumour sites, the effect of IL6 on MDSC migration to premetastatic niches has not been reported [9,18]. Regarding the effects on immunocompetent cells, CXCL12 decrease the infiltration of these antitumoral cells, notably cytotoxic T cells and natural killers NK, to premetastatic niches [19]. In contrast, IL-6 is an inducer of cytotoxic T cells homing to these niches and their subsequent activation and proliferation [20,21]. Two important conclusions can be drawn from this comparison. First, CXCL12 seems to induce more immunotolerance than IL6 and so it would be more prometastatic, and responsible for the overcompensation effect. The availability of inhibitors of CXCL12 and its receptor CXCR4 allows an experimental comparison between the two inhibitors. If this proposition is confirmed, the addition of CXCL12/CXCR4 inhibitors to IL-6 inhibitors would be justified. Secondly, the fact that IL-6 induces activation and infiltration of antitumoral immune cells suggests the possibility that IL-6 is attracting CTC to antitumoral traps. This would be more probable if IL-6 effects on MDSC infiltration to premetastatic niches proves to be not as important as those on immunocompetent cells. This would confer to IL-6 an antimetastatic role at least at some sites, and this proposition would be the second additional explanation of the unexpected results.

In summary, this review highlights the discordance between the multiple protumorigenic and prometastatic effects of IL-6 and the modest outcomes of its blockade in clinical trials. We have reported some possible explanations from authors of these trials and suggested two additional reasons. However, these propositions have some limitations to be mentioned. We have compared IL-6 to CXCL12 for illustration purpose
as there are many other potential candidates. Also, the comparison has been made according to their roles in premetastatic site development using only one determinant which is immunotolerance induction, but other factors should be considered such as angiogenesis. Moreover, premetastatic site development is only one protumorigenic effect, and there are many other protumorigenic and prometastatic effects to be taken into account. These limitations give an idea about the complexity of the issues to be addressed to obtain a complete response from IL-6 blockade. While not the optimal one, a wise approach consists of identifying the overcompensated effect that is more deleterious, and then the agent that would have the most important role in the overcompensation should be targeted. Finally, the above-mentioned reasons are still at the theoretical level, and experimental verification is needed to adopt solutions to only the validated ones.

4. CONCLUSION

IL-6 blockade as a cancer therapeutic approach has demonstrated the limitations of targeting certain intrinsic protumorigenic actors. The fact that these agents tend to have redundant effects implies the compensation or even overcompensation of the suppressed one's effects by others. Also, they may have, in addition to their protumorigenic roles, some antitumoral effects that may be more prominent in certain patients or at least certain tumoral sites, explaining the drug response variability. Addressing these issues would be the key to optimize the clinical outcomes of these inhibitors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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