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# Monitoring Disease Status in Multiple Myeloma in View of Proliferation-leading Cytokines

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## Introduction

Multiple Myeloma (MM) is a haematological disorder of clonal malignant plasma cells, accounts for 1% to 2% of all human cancers. Plasma cells are non-dividing cells of the B-cells; myeloma cell is a malignant plasma cell. It is reported that myeloma plasma cells constitute 10% to 90% of the total bone marrow cell counts in patients with multiple myeloma [1].

Multiple myeloma is characterised (a) by slow proliferation of the tumor cells in the bone marrow, (b) by production of large amounts of immunoglobulins, (c) osteolytic lesions.

Growth Factors act as signaling molecules between cells. In the health condition growth factors affect a wide variety of physiological processes as cellular growth, differentiation, survival, inflammation, and tissue repair.

Cytokines are subtypes of Growth Factors. In the health condition cytokines modulate the balance between humoral and cell-based immune responses. To the cytokines belong: Interleukins, Lymphokines, Tumor Necrosis Factors and Interferons.

In the pathological condition Growth Factors and Cytokines influence stepwise the development of cancer cells. The pathological effects include all deviations compared with normal conditions as apoptosis, cell proliferation, angiogenesis, and cell-metabolisms.

Interleukin-6 (IL-6) is a major proliferative factor for malignant plasma cells. Interleukin-6 produces by the malignant plasma cells (endogenous production/autocrine regulation mechanism) and by bone marrow stromal cells (exogenous production/paracrine regulation mechanism). Interleukin-6 exerts its biological function through binding to specific receptors on the membrane: (1) Interleukin-6 receptor alpha (IL-6R, also called CD126) and (2) signal-transducing component gp130 (also called CD130). The complex IL-6 + IL-6R + gp130 activate the intracellular signaling cascades: JAKs (Janus Kinases) and STATs (Signal Transducer-Activator of Transcription) and the RAS/MAPKs (RAS/mitogen activated protein kinase) pathways.

*The interleukin-6 receptor alpha-chain (CD126) is expressed by neoplastic but not normal plasma cells. The signal-transducing component gp130 (CD130) is expressed ubiquitously on all viable cells in the body.*

The membrane receptors are released from the cells as soluble receptor proteins (sIL-6R and sgp130). As agonist, sIL-6R enhances the biological activity of IL-6. Sgp130 is an antagonist against the complex IL-6+sIL-6R.

The serum level of the sIL-6R is an important parameter in the evaluation and in the progression of multiple myeloma [2]. The serum levels of IL-6 and/or sIL-6R show a relation to the clinical manifestation of multiple myeloma [3].

It was reported for the first time that the simultaneous measurement of IL-6, sIL-6R and sgp130 in serum is an important factor in evaluating the biological effect of IL-6 in malignant diseases [4].

Interleukin-10 (IL-10) is a proliferative factor for malignant plasma cells. It is produced by the malignant plasma cells (endogenous production/autocrine regulation mechanism) and by Interleukin-6 (exogenous production/paracrine regulation mechanism) [5].

Interleukin-10 exerts its biologic effects on cells by its specific cell surface receptor (CD210) to activate the JAK/STAT signaling-pathway. The receptor is composed of two distinct subunits (chain alpha and chain beta).

Tumor necrosis factor-alpha (TNF-alpha) is a proliferative factor for malignant plasma cells.

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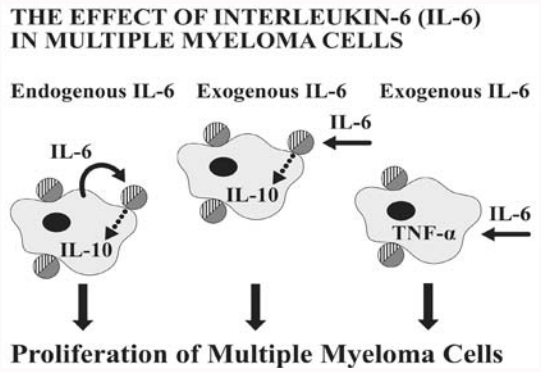


**Figure 1:** Endogenous or exogenous IL-6 leads via its receptors to a marked production of Interleukin-10 (IL-10). Exogenous IL-6 leads to Tumor necrosis factor-alpha (TNF-α) in myeloma cells. Interleukin-6 receptor (IL-6R) is not responsible for the production of TNF-α.

It produces by exogenous IL-6 (exogenous production/paracrine regulation mechanism) but not by myeloma cells [6]. Tumor necrosis factor-alpha binds to the TNF receptor1 and TNF receptor2. TNF receptor1 is expressed in most tissues, whereas TNF receptor2 is found typically in cells of the immune system.

Bone disease is the major feature of multiple myeloma. This is due to increased activity of osteoclast and decreased activity of osteoblast. The cytokines Interleukin-6 and Tumor necrosis factor-alpha are chief factors for producing bone disease in myeloma patients.

## Summary

Figure 1 presents the effect of Interleukin-6 in myeloma cells.

- Interleukin-6 is produced in the myeloma cells by activation its membrane receptors: Endogenous IL-6 production, leading via its receptors (complex: IL-6+IL-6R) to Interleukin-10 production.

- Bone marrow stromal cells produce Interleukin-6: Exogenous IL-6 production. This leads via its receptor to Interleukin-10 production and without activation of its receptor to TNF-alpha production.

- Both endogenous and exogenous IL-6 lead to increased expression of its membrane-bound receptor (IL-6R) consequently to enhanced release of sIL-6R.

It is a very important finding that Interleukin-6 leads to production of Interleukin-10 and Tumor necrosis factor-alpha in myeloma cells.

These cytokines are proliferative factors for malignant plasma cells (multiple myeloma cells).

There are different steps in the development of a malignant tumor cells. Different morphological and biochemical features identify the different steps during the tumor development. These features constitute the stages of the tumor.

Staging is important for prognosis of the disease, treatment options, and the evaluation of treatment. Multiple myeloma may be staged using the Durie-Salmon System and recently by the International Staging System. It relies mainly on levels of albumin and beta-2-microglobulin in the blood. Levels of beta-2 microglobulin can be elevated in multiple myeloma [7,8]. Low serum albumin level, in association with high serum interleukin-6 level is a significant prognostic factor in multiple myeloma patients [9].

**Table 1:** Serum values of Interleukin-6 (IL-6), Interleukin-10 (IL-10), Tumor-necrosis-factor-alpha (TNF-α) in myeloma patients.

| | IL-6 | IL-10 | TNF-α |
|---|---|---|---|
| Significant increase | YES | YES | YES |
| Correlation with disease activity | YES | YES | YES |

Different clinical studies.
Clinical experimental studies: E. Kovacs-Benke.

**Table 2:** Serum values of Interleukin-6 (IL-6), soluble Interleukin-6 receptor (sIL-6R), soluble gp130 (sgp130), Interleukin-10 (IL-10) and Tumor-necrosis-factor-alpha (TNF-α) in healthy persons.

| | IL-6 | sIL-6 R | sgp130 | IL-10 | TNF-α |
|---|---|---|---|---|---|
| M ± SEM n=18-39 | <5 pg/ml | 30,6 ± 1,5 ng/ml | 263 ± 12 ng/ml | <5 pg/ml | <4 pg/ml |

Clinical studies: E. Kovacs-Benke.

Other factors that may be important are: Kidney function, platelet count, serum proteins, calcium, and hemoglobin.

## Basis of the Therapy

The majority of anticancer drugs have antiproliferative effects or they induce the cell death. The substances with cytostatic effect inhibit proliferation of tumor cells. The substances with cytocidal effect kill tumor cells. The cytocidal effect can be apoptotic or necrotic.

The types of the therapy modality are dependent on

(1) Tumor-Types, (2) Tumor-Stages, (3) Progression.

Both chemotherapy and targeted therapy are two effective methods for cancer therapy. Targeted therapies are often cytostatic (block tumor cell proliferation), standard chemotherapy agents are cytotoxic (kill tumor cells).

Targeted therapies are currently in the focus of anticancer drug development. The difference between targeted therapy and chemotherapy: (1) Chemotherapy can also kill the normal cells when eliminating the cancer cells, (2) Normal cells can survive the targeted therapy, when the growth of cancer cells was limited.

Today multiple myeloma is diagnosed in earlier stages than a few years ago. For this reason targeted therapy modalities have priority.

*Targeted therapy demands targeted diagnostic steps.*

The cytokines IL-6, IL-10 and TNF-alpha are proliferative factors in myeloma. All three cytokines present a significant increased serum values in myeloma patients showing a correlation with disease activity (Table 1). High serum values of Interleukin-6 (IL-6) were found on average in 58% of myeloma patients [10,11,3] an elevated Interleukin-10 (IL-10) serum levels in 50% of the patients [12].

*These findings are given evidence, that about in half of myeloma patients these cytokines are promoters in the development of multiple myeloma*: It is known that myeloma cells are classified into four groups: (a) IL-6 affects both proliferation and survival of the cells, (b) IL-6 affects only proliferation, (c) IL-6 affects only survival, (d) the cells are independent of IL-6 both for survival and proliferation.

If a correlation exits between the cytokines and disease activity in a tumor, then this is an indication for a targeted therapy. It is mentioned above that IL-6 was increased in 58% of myeloma patients: in 35% or in 42% or in 97% [10,11,3]. This finding suggests that IL-6 can be affected differently in different myeloma stages.

A specific-targeted therapy is important and efficient in the treatment of tumor diseases. This tendency is known and becoming

more and more significant: To enhance the prediction of prognosis and individualize the treatment of myeloma patient.

For this reason, the serum values of IL-6, IL-10 and TNF-alpha will be evaluated in accordance:

(A) With the clinical/laboratory parameters in the different stages of multiple myeloma.

Additionally the following parameters also will be measured: soluble Interleukin-6 receptor (sIL-6R) as agonist to the biological activity of Interleukin-6 and soluble gp130 (sgp130) is an antagonist against the complex IL-6+sIL-6R.

## Monitoring Disease Status

For the evaluation and assessment the following serum parameters will be measured in the different stages (I. II. III) of myeloma.

The serum levels of Interleukin-6, its related serum proteins as soluble IL-6R and soluble gp130.

The serum levels of Interleukin-10.

The serum levels of Tumor necrosis factor-alpha.

*The serum parameters will be determined by ELISA according to the manufacturer`s instructions using commercially available kits.*

The serum values of the above mentioned parameters in healthy subjects are presented in Table 2. They are used for comparison. It is recommended to take samples from control subjects periodically.

## Aim

(I) In which stage of myeloma are the proliferation-leading cytokines effective?

(a) Correlation with Laboratory-Parameters.

(b) Correlation with Clinical Parameters/Condition.

(II) It is known that Interleukin-6 leads to production of Interleukin-10 and Tumor necrosis factor-alpha.

(a) Key aspect: Does this effect of Interleukin-6 occur in each stage of myeloma?

## Conclusion

The simultaneous determinations of these parameters with the Laboratory-Parameters simplify the monitoring disease status in multiple myeloma.

The findings can justify a specific-targeted therapy - a so called “made to order” therapy - in myeloma patients: A stage-related therapy, a cytokine-related therapy.

The advantage of a specific-targeted therapy:

(1) The dose of the component(s) can be lower.

(2) The reduction of side effects of the component(s).

(3) The duration of treatment can be shorter.

(4) To individualize the treatment in the myeloma patient.

*For the future we need new strategic-steps in the therapy of the multiple myeloma patients.*

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