Chemotherapy and immunomodulation in the elderly

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Abstract. Ageing brings about an impairment of all body functions. Any antimicrobial and oncological treatment must take into account the senescent condition of the patient. Aged people are considered an immunodepressed population and oncotherapy has envisaged the use of components of the immune system. Our hope is to dispose shortly such neuro-immunomodulators as to be able to activate the impaired immune system which is present in the elderly.

The response of our body to pharmacological therapies undergoes biological changes as a result of ageing. Pharmacokinetics (absorption, distribution, localization in the tissue, metabolism, excretion) and pharmacodynamics (drug–patient interaction) are the main biochemical processes to be considered [1,2]. In old age decompensating factors such as increase of total body adipose tissue, decrease of lean body mass, decrease of total body water, decrease of hepatic and renal blood flow, reduction of plasma proteins, reduction of glomerular filtrate, will influence the volume of drug distribution [3].

After the age of 70–75, humans are more sensitive to drugs, the relative response to which is altered on account of a decreased adaptation of the organism to repeated and different stress stimuli [4]. After the age of 50 haemopoiesis is modified. The marrow cell density becomes less and declines to ~50% at age 60 and 25% at 70, with an increase of both stromal component and adipose tissue. Hepatic metabolism also changes due to a decrease in the hepatic flow (~40% at age 65) and of the functioning parenchyma on account of alterations of the microsomal system, of oxidoreductase enzymes and enzyme induction capacity.

In the kidney there is a reduction in the number of functioning nephrons, causing the glomerular filtrate and tubular reabsorption and excretion capacity to be diminished and impaired [2]. Thus, most age-related biological changes are linked to the reduced capacity to maintain organ homeostasis.

On account of this, the treatment of infective diseases by chemotherapeutic agents must be carefully monitored to avoid or at least reduce the interfering action with homeostasis. In the elderly, with a view to obtaining the best advantages of anti-infective chemotherapy and limiting adverse drug reactions, it is necessary to comply with and carry out behaviour rules based on healthcare delivery, such as detection and identification of the aetiopathogenic agent, choice of proper bactericidal drugs from lab-test findings on the basis of Gram stain, bacteriological culture and sensitivity. As a further step, the use of a bactericidal agent with low plasma protein binding is advisable to ensure a rapid and high concentration in the tissues [5].

A careful regard to the daily dosing programme is also advisable, bearing in mind, for example, that in the renal parenchyma some antibiotics (aminoglycosides, vancomycin, cephaloridine) will bind substantially to cortical tissue cells, causing nephrotoxicity.

Careful attention is needed in cancer chemotherapy for the elderly as drugs may evidence a different pharmacokinetics and/or pharmacodynamics, increasing the risk of toxicity [6]. Ageing does not easily tune with chemotherapy; in some ways it is conflicting. Chemotherapy should be practised properly so that the right drug doses with minimum side effects may be administered [7]. Medullary toxicity and related risk of infection due to chemoinduced leukopaenia is the major limiting factor in the use of cytostatic drugs, in particular: actinomycin D, Adriamycin, methotrexate, lomustine, vinblastine. To provide ways of overcoming this problem, growth factors such as granulocyte-colony stimulating factor (G-CSF), and granulocyte macrophage-colony stimulating factor (GM-CSF), have entered clinical use [8–10].

Furthermore cardiac toxicity of anthracyclines, bleomycin-induced pulmonary fibrosis and neurotoxicity exerted by cisplatin and vincristine must be taken into account. Renal toxicity is due to impaired drug excretion and drug load with consequent tubular damage. Cisplatin, a toxic chemotherapeutic agent with specific renal impairment, requires an adequate administration of liquids through forced diuresis, whereas cyclophosphamide may bring about episodes.
of haemorrhagic cystitis requiring the administration of uroprotective and urine alkalizing drugs.

The data of some therapeutic protocols in the elderly, as compared with adult people, differ from one another. In advanced renal carcinoma (MRCC), for instance, mono- or polychemotherapy (vinblastine, CCNU, hydroxyurea, ifosfamide) offers very low clinical responses with an average survival of 6 months [11]. This is partly due to insufficient efficacy of chemotherapy probably because of MDR-1 (human multidrug resistant gene-1) on the surface of tumour cells [12]. The potential toxicity of cancer chemotherapy, not always accompanied by adequate therapeutic responses, has created a growing interest in biological response monitors (BRM).

Ageing brings about a decrease of the cell-mediated immunity (T-lymphocytes and lymphocyte subpopulations) and of the humoral immune system in its primary stage (response to new antigens), and this seems to be responsible, in the elderly, for multiple interacting infections, tumours and autoimmune senescent diseases [13,14]. In adult people the immune response is regulated by a group of interacting mechanisms. One of the primary ways of regulation is via antigen-specific types and this is due to lymphocyte subpopulations (T helpers and T suppressors), to cytokines [interferons (IFNs), interleukins (ILs), macrophage inhibition factors] and to antibodies. A non-antigen-specific mechanism involves α-globulins, lipoproteins, products of tumour origin, corticosteroids and radiation. Finally there is a third way of regulation based on neuropeptides, in particular the opioid endogenous peptides (endorphins) that have an analogous terminal sequence but different precursors. They fall into three groups: endorphins (α, β, γ) which are derived from the gene POMC (pro-opiomelanocortin); enkephalins (met-leu) from pro-enkephalin, and dynorphin from pro-dynorphin. It has been demonstrated that β-endorphin and met-enkephalin increase, in a dose-dependent way, the natural killer (NK) activity which is mediated predominantly by granulocytes [15,16]. Moreover some authors have found a reciprocal correspondence between reduced plasma β-endorphin and low NK activity, as an indicator of higher morbidity [17].

Neutrophils, monocytes or macrophages are the most important cells involved in phagocytosis (e.g. of bacteria). The role of the neutrophil in acute inflammation is taken over by the macrophage in the chronic stage of inflammation. These types of cells, under the influence of opioids, in particular β-endorphin and met-enkephalin, will stimulate chemotaxis of granulocytes and monocytes [18,19]. Furthermore met-enkephalin and β-endorphin enhance the production of γ-IFN of monocytes and of lymphocytes [20,21] and only β-endorphin determines an increase of production of IL-2 from lymphocytes under stimulation by either concanavalin A (Con A) [22] or by IL-1 [23], whereas β-endorphin and leu-enkephalin potentiate the production of IL-1 from mast cell macrophages under lipopolysaccharide (LPS) stimulation [24].

Recent studies on the interaction of opioids and cytokines have further proved that opioid peptides are strictly bound to the immune system, in particular β-endorphin has been shown to interact with receptors for IL-2 [25] and regulate the production of IL-1 and IL-2 [22-24]. Thus the opioids seem to act as dynamic agents produced within the immune system, endowed with a capacity to regulate both humoral and cellular immune response [26]. This demonstrates the complex interaction existing between the immune system and the neuroendocrine system mediated by endogenous opioids [26,27].

At present IFN and IL-2 are employed in onco-therapy in their capacity as cell-mediated immune response modulators. Interferons, on the other hand, are employed, alone or in association, in the therapy of multiple myeloma, tricho-leukaemia, renal cell carcinoma, non-Hodgkin lymphoma, and tumours of colon and rectum. The side-effects of interferon in the elderly do not differ from those of adults and the toxicity of treatment is low. IL-2 is actually indicated for the treatment of metastatic renal carcinoma and of melanoma in advanced stage, the only sensitive tumours. In neoplasms, IL-2 seems to work as a magnifier of a specific immune response already initiated spontaneously in the abortive form. In advanced renal cell carcinoma, better clinical responses are obtained by combining IL-2 with α-IFN, compared with IL-2 or α-IFN alone [28]. At the same time the toxicity of i.v. IL-2 is dose dependent and is more significant in patients treated with interferon [28,29]. However, a lower toxicity of IL-2 was reported by Lissoni et al. [30] using the combination of this cytokine and melatonin (MLT) in the treatment of some lung neoplasms (non-small cell lung cancer, NSCLC).

MLT is an endogenous substance produced in humans by the pineal gland according to a circadian rhythm with maximal activity of synthesis and release at dark [31,32]. The universally accepted and scientifically proven role of MLT is to synchronize endogenous rhythms to the light/dark cycle of the external world. A function of neuroimmunomodulation has been attributed to MLT, and this would justify its use in association with IL-2. Immunostimulant prerogatives of MLT have been demonstrated in senescent rats or under treatment with cyclophosphamide, in which the present or provoked immunodepression was resumed following a treatment of MLT that caused an increased production of IL-2 [33]. Recent studies have shown evidence that treatment with MLT, in animals, enhances the secondary response and not the primary one of cytotoxic T-lymphocytes [34].

A direct immunostimulating action of MLT is to be excluded because of the absence of its specific receptors on the immunocompetent cells [27]. Specific receptors are found only in the central nervous system [35]. The immunomodulating effect attributed to MLT could be mediated through an action of the endogenous opioidergic system [36]. Another hypothesis tends to consider a possible interaction of MLT with the hypothalamus—hypophysis—thyroid neuroendocrine system in the regulation of the immune response [37]. Recently,
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Reiter et al. [38] have shown a remarkable scavenger effect of MLT, which is more potent than any other natural substance hitherto described. Hence the scavenger effect can be attributed to the effects mentioned by Lissoni et al. [30].

Only with a wider clinical case-series together with confirmation of relevant results, can a judgement on the real role of MLT be possible in this context. More simply we could assume that MLT may influence, in some way and positively, the immune response through its proved action in the synchronization of endogenous rhythms, including those governing the immune system.

References

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