



Side by Side with Myeloma

Conscientization Week of the Multiple Myeloma



The newspaper 'Side by Side with Myeloma' has spoken to several public figures, with the purpose of introducing this type of cancer, still unknown to most of the Portuguese population. We interviewed Dr. Mário Mariz, Haematologist at the IPO - Instituto Português de Oncologia do Porto (Oporto Portuguese Oncology Institute), who explained us what Multiple Myeloma (MM) is.

Dr. Mário Mariz, could you explain our readers what is Multiple Myeloma?

Multiple Myeloma is a malignant tumour, originary from the bone-marrow cells. The malignant cells are plasmocytes which under normal circumstances produce antibodies that help fighting infections. The malignant plasmocytes usually grow within bone cavities and generally affect several bones, reason why the 'multiple' designation is used.

What symptoms are usually associated with this type of cancer?

The growth of malignant plasmocytes at the bone-marrow, prevent normal plasmocytes' activity as they stop producing antibodies which would fight infections; hence, recurring infections (such as pneumonia) are frequently manifested in a significant percentage of the patients. Other patients show bone pains, resulting from tumour destruction of the bones. It is also very frequent to hear complaints related to tiredness and easy weakness due to anaemia, settled in during the course of the disease.

É possível prevenir o aparecimento do MM?

Is it possible to prevent the appearance of MM?

Multiple Myeloma is a disease of unknown origin, reason why it cannot be prevented. However, many of the Myeloma's symptoms may lead to confusion with other diseases and that might delay the diagnosis and make it more difficult to control the disease.

Which treatments can be used to fight this disease?

Multiple Myeloma treatments are based on chemotherapy, aiming the destruction of plasmocytes. Nowadays, to fight the Myeloma, there are several active medications which may be used individually or associated. The bone-marrow transplant, especially the auto-transplant can be part of the strategy to treat younger patients. Multiple Myeloma is considered an incurable disease; however, the treatment allows patients to live longer and also improves their quality of life.

Which are the main differences in treating this type of pathologies and other oncological blood diseases (Leukaemias and Lymphomas)?

Most of bloods' malignant diseases are treatable with chemotherapy because surgery is not advised, unlike it happens with other tumours. The difference between treating Myeloma and other blood diseases isn't very

significant. As it happens with other pathologies, there are chemotherapy schemes which may use only one drug or a combination of drugs, administered orally or intravenously, depending on each situation. When it comes to Myeloma, besides chemotherapy, it's commonly used a medication (Biphosphonate) which decreases the risk of bone destruction caused by the tumour.

M.D.Herlander Marques is an Oncologist at the Hospital de S. Marcos, in Braga and also Vice-President of APLL Associação Portuguesa de Leucemias e Linfomas (Portuguese Association of Leukaemias and Lymphomas). The purpose of our conversation was to learn more about the treatments and developments achieved over the last years, concerning the fight against MM.

During these last years, we witnessed a large evolution in MM treatments. Can you specify the evolution of those treatments?

The first effective treatments of Multiple Myeloma appeared during the sixties and were based on the use of Prednisolone and mostly on the association of MelphalanPrednisolone. It was necessary to wait almost 40 years to witness significant advances through intensive chemotherapy with high dosage of Melphalan, supported by autologous stem cells (cells from the patient himself) previously collected. Over the last years, Thalidomide, Bortezomib and Lenalidomide were introduced as a new approach in treating this disease, especially when associated with formerly used drugs. It was demonstrated that these associations made possible the obtainment of higher response rates, prolonged lifetime without disease and even longer survivals than those achieved with former treatments. Another issue that shouldn't be ignored while treating Multiple Myeloma is the part played by the agents that stabilize the bone, such as Pamidronate and Zolendronate, which prevent the continued bone destruction so typical of this disease. They improve the patients' life quality and they probably contribute with some kind of anti-neoplastic action.

With these new drugs, is the access to the most recent treatments similar in every country of the E.U.?

The most recent drugs are very expensive and a certain resistance towards their introduction into the market has been noticed, coming from state organisms of several European countries. Generally speaking, Portugal has followed the commendations of the European Medication Agency (EMA) in a somewhat inertial way.

What is the incidence rate of this cancer on general population?

The Multiple Myeloma is a relatively rare disease, with an incidence rate of about 4 people / per 100.000 inhabitants / per year and it strikes mostly individuals above the age of 65 years.

What is the cure rate associated with this pathology?

Despite the advances achieved in treating Multiple Myeloma, the disease is still basically incurable. The only exceptions might be those rare patients that have gone through intensive chemotherapy and allotransplantation of stem cells. However, there are patients who show long survival rates after the treatments as opposed to others whose status evolves very slowly.

What is the role of the bone-marrow transplant?

Stem cells transplant was originally performed directly from the bone-marrow but during the last decade it was progressively replaced by collections made from the peripheral blood, using cytopheresis machines. It was a considerable approach in treating this pathology. However, the average age of patients suffering from MM is 66 years which reduces its applicability above 65-70 years, due to their growing complications and depending also on the patient's general health condition. Besides, it is not recommended for use in patients who suffer from significant organic dysfunctions such as serious cardiac, respiratory or renal insufficiency.

What reactions are mainly associated to the treatments?

The adverse effects of the above mentioned treatments are quite a few and somewhat diverse. I'll only name a few: the corticosteroids such as Prednisolone and Dexamethasone cause diabetic decompensation, increased risk of infection, psychiatric disturbances and muscular atrophy. The cytotoxic agents, commonly known as chemotherapy, such as Melphalan, Cyclophosphamide and Adriamycin may cause blood cells to drop and consequently increase the risk of infection, haemorrhage and anaemia. The new agents increase the risk of venous

thrombosis of lower limbs and although less intensively, pulmonary thromboembolism; quite a few are neurotoxic and sometimes serious, while others show haematological toxicity.

Are the treatments painful?

The treatments are adjusted to the patients' age and comorbidities (associated diseases), in such a way that they might be well tolerated without compromising their efficacy. As said above, an infinity of adverse effects might appear with the associations of drugs used to treat this

disease but an open dialogue between doctor and patient has managed to outline most of them and we might say that treatments are usually well tolerated.

What's the average life expectancy of a patient with MM?

The average survival rate has increased from 3 to more than 5 years over the last two decades. This improvement - quite significant as it was achieved in elderly patients - was made possible due to the transplant of stem cells and the association of new drugs to known chemotherapies and support drugs, which reduce bone destruction.

We also spoke to M.D. Maria José Parreira, Haematologist, University Professor and Vice-President of ADL - Associação de Apoio aos Doentes com Leucemias e Linfomas (Supportive Association to Patients with Leukaemias and Lymphomas), about the role of Patients' Associations in MM treatments, the differences between treatments in other countries and for last, the role of the family doctor in early diagnosis of this pathology.

What is the role of a Patients' Association towards improving the quality of life in a patient suffering from Multiple Myeloma?

Quality of life is a largely debated theme but not always a well understood one. Nowadays, most medical information refers to quality of life but is frequently (not to say always) perceived as an extension of life, with the least possible symptoms associated with the disease. Well, quality of life is a bit more than that. Alongside a bearable symptomatic situation, it means living as normally as possible socially and family wise, besides achieving an adjusted integration within each one's professional field of work. Among other things, this includes a dynamization of clinical reception with the least possible constraining: I'm talking about making appointments more easily; having better access to medical and nursing support; faster attendance; conveying information to other entities whenever necessary. I'm also talking about household attendance for patients in more advanced stages of the disease concerning transportation to / from the hospital and about the integration in psychological support groups. The truth is - clinically speaking - the quality of life begins to be more important face to radical therapeutical strategies, quite often ineffective and causing more suffering; socially speaking and by social I mean every aspect I referred to

before and many more there isn't a suitable response from healthcare institutions. Not a satisfactory one, anyway. This is where Associations could and should intervene by identifying needs, programming solutions, calling out other institutions' attention to what has to be done. This is just as true to MM patients as it is to all others. The Multiple Myeloma, as we know it, raises particular questions as to the mobility of some patients, considering the frequent occurrences of bone pains and fractures, all of which truly emphasize my earliest comments.

A patient with MM receives better treatment in Portugal or abroad?

This is a frequently asked question in many situations. The answer is: it depends. Mostly, it depends on the place of treatment, here in Portugal as in any other country. It matters to know that in Portugal, Medicine disposes of all the means currently recognized as adequate to approach such a disease as Multiple Myeloma. It also matters to know that Portugal has healthcare centres duly equipped with physical and human resources. During my professional life, I have received patients from other countries, considered to be in more advanced stages of the disease, who had received unsuitable treatments. Therefore, it all depends on 'where' they are treated. If

patients look for the proper centres to treat haematological diseases, there really is no need or benefit in looking for treatment in other countries, considering all the negative charge associated. This is, in fact, a very important factor for family doctors who, when asked about the diagnosis, are usually the first to guide their patients.

Should family doctors be more enlightened about the symptoms, thus enabling an earlier diagnosis?

Obviously all family doctors should be better informed about the initial symptomatology of such a disease as Multiple Myeloma. At first, complaints are common but a closer look and thorough observation - more precocious analytically speaking, could lead to an anticipation of the diagnosis, useful to allow an equally precocious treatment, very often stopping the occurrence of pathological fractures... it's frequently the ultimate event that ends up calling the doctors' attention.

The next interviewed, João Salazar, is both President of APLL Associação Portuguesa de Leucemias e Linfomas (Portuguese Association of Leukaemias and Lymphomas) and President of EMP European Myeloma Platform, which we are going to talk about next.

What can you tell us about the EMP?

European Myeloma Platform is an European institution without profit making purposes, managed by patients and kinsmen with MM. It is fundamental to stress out that this is a completely independent institution, both political and financially and all the workers involved are volunteers. The main goal is the defence of patients' rights face to the European Union political decisors.

As to its creation, EMP was funded on February 2006, in Vienna, by six European associations, namely Austria, Belgian, Denmark, France, Holland and Switzerland. During last year (in 2007), Portugal and Germany have also joined and are now part of the working group. Currently, EMP's motto is 'Patients for Patients' and its mission is about making European patients with Multiple Myeloma defend their interests personally, European wide. Therefore, the most important thing is to give voice to MM patients all over European institutions and health politics.

What are EMP's purposes?

Our main purposes are focussed on ensuring equal access to medication and treatments for all people; to pass on information to patients concerning the most recent developments, treatment options and clinical trials about MM; stimulate and promote the research of new treatment methods and medications through the commercialization of orphan medications and the approval of new ones for the Multiple Myeloma; represent MM patients close to European health authorities, aiming to provide them with the best possible treatment and

support.

What work has been developed so far?

I might add that we are currently working on the European Medicine Agency (EMA) Behaviour Code, concerning the relationships between patients' associations and the pharmaceutical industry. Previously, we worked on a program related to managing the risks of Thalidomide. EMA invited groups of patients and Thalidomide victims, for counselling. EMP had quite an active role on this programme. As a matter of fact, this was one of our greatest victories since the creation of EMP. Finally, it's important to refer that we also participated on a program for risk management of Lenalidomide. In two years time, we managed to establish ourselves as an European association. We are commonly invited to participate in several meetings of patients' associations, summits with members of the European Parliament and E.U. healthcare responsible members. Working together with EMA, the EMP is involved in revising documents addressed to patients, within the structure of marketing authorization and documents renewal.

Does EMP work with other entities in the area?

Nowadays, EMP is part of the European Cancer Patient Coalition (ECPC) and EURORDIS. We currently maintain strict relations with the International Myeloma Foundation (IMF) and other institutions as well as with local and European Public organisms.

The newspaper Side by Side with the Myeloma spoke to M.D. Paula Brito e Costa, President of FEDRA Federação de Doenças Raras de Portugal (Federation of Rare Diseases in Portugal), about rare diseases and the need to create a federation in this field of work.

'The Mysterious World of Rare Diseases'

Put this way, one would think they hardly exist and the few ones that are known are spoken of through civil hospital corridors or in the labs that diagnose them, but it isn't quite so. We are talking of a major problem on public health that the Health Ministry was faced with in the beginning of this century: we are effectively 6% to 8% of the Portuguese population, somewhere between 600.000 and 800.000 people. Until that time, no one had ever heard about these pathologies. Suddenly, the media awoke to this mysterious world. The associative movement had to reorganize itself and gather efforts because patients' welfare was endangered as was the access to information (practically non-existent), the government sensibilization to create and approve specific laws, the pressure over the pharmaceutical industry to invest more and more in orphan medications... We felt that all was yet to be done, wanted to do a lot and a lot we did, in fact! However, it was necessary to speak for all and not each one per se. It urged to create a superior structure to represent rare disease bearers. So, FEDRA (Federação de Doenças Raras em Portugal) was born.

And now, our dear readers will wonder about the reasons why rare diseases are being referred to in a journal about



Paula Brito e Costa (FEDRA President, Dr. José Robalo & Maria Cavaco Silva (First Lady)

oncological diseases? The point is rare diseases exist also in this area; besides, within this context, we feel responsible for giving voice also to these patients. It became imperative to invite the board of directors of APLL Associação Portuguesa de Leucemias e Linfomas to join FEDRA. Presently, the rare oncological patients as is the case of patients with Multiple Myeloma, have someone to fight for their rights and they are certainly not alone.

Paula Brito e Costa
President of FEDRA
(Federação de Doenças Raras de Portugal)

Multiple Myeloma

Multiple Myeloma is a malignant tumour of the blood, consisting of uncontrolled birth of blood cells called plasmocytes. The plasmocytes belong to our immunity system and their function is producing antibodies. The antibodies are specifically designed proteins to fight potential 'invaders' of the organism, such as bacterias and viruses. The Myeloma plasmocytes are devoid of this defence and in most cases also produce uncontrolled proteins without any functional use. These tumoral cells will increase progressively and fixate preferentially on

their birth place the bone-marrow. The Myelomas' main clinical characteristics come from this preferential accumulation on the bone and also from the production of an abnormal protein shed directly into the blood. The bone invasion causes fragility and enables the appearance of destructive lesions osteolytic lesions conducting to bone pains, spontaneous bone fractures (ex: fracture of a femur or a vertebrae), most of the time a characteristic of inaugural presentation.

Another consequence of this bone destruction is the increase of blood calcium (hypocalcaemia). On the other hand, this invasion also diminishes the physical space

within the bone-marrow cells, limiting the production of other normal blood cells - the red globules or erythrocytes, the white globules or leucocytes and the plaquettes or thrombocytes. This way, the decrease of the blood cells leads to a more or less severe anaemia, depending on the tumoral volume existing. The degree of anaemia will determine the appearance of a generalized tiredness somewhat incapacitating. On their turn, the decreased white globules cause a major vulnerability to infections and the reduction of plaquettes tend to provoke easy bleedings (bruises, gingival haemorrhages). The production of an abnormal protein in variable quantity and its release into the blood makes it thicker, hurting the normal circulation and causing the appearance of behavioural and eventually consciousness distress (syndrome of plasmatic hyperviscosity). These proteins end up degrading and dividing themselves into several fragments, some of which are eliminated through fesses and others through kidneys. In case of massive and persistent destruction, kidneys may suffer serious lesions leading to another frequent complication known as renal insufficiency; ultimately the patient may need haemodialysis.

Unfortunately, so far Myeloma revealed itself to be an incurable disease. However, during the last few years some new medications have appeared and although they don't cure, at least increase the survival time, diminish complications and lead to a better quality of life for these patients. Despite some uniformity, treatments partially depend on the experience and technical skills of hospital units whereat patients are referenced. Not all the Myelomas need immediate treatment. Such is the case of indolent Myelomas which due to their slow progression speed don't need specific medical intervention until a few years after. Generally, patients under 65 years, after an initial variable treatment phase (induction treatment) with good response to it, are good candidates to autologue transplant of progenitor haematopoietic cells, allowing a previous intensifying treatment with high dosage of chemotherapy. This last phase occurs at referenced Portuguese centres (Hospital de Santa Maria - Lisboa, Hospital de S. João - Porto, Hospitais da Universidade de Coimbra, Hospital dos Capuchos - Lisboa and IPO's - Lisboa e Porto).



Dr. João Raposo

The methodology might change from centre to centre, using one or two transplantations. With this attitude, patients manage to stay away from disease and treatments for a longer period of time. Sometimes, in most severe cases and in younger patients, one might try the transplant with a compatible donor (allogeneic transplant). However, this brings more complications and is only executed in referenced centres. Over the last years, transplants with donor have been experimented in elderly patients but using other technologies sub-myeloablative transplants of reduced intensity or mini-transplants with yet inconclusive results in the clinical research domain. However, most patients with Myeloma in need of treatment are over 65 years and / or have associated medical reasons that prevent the use of transplantation techniques. For this majority group of patients there are several medications available, with proven activity over Myelomas, from the conventional ones such as Melphalan, Cyclophosphamide, Dexamethasone, Prednisone and Liposomal Peguilated Doxorubicine. Normally they are used with other associated drugs to increase the efficiency and improve the results. The schemes are variable according to the protocols of each

hospital institution but the most important thing is the establishment of a sequential program of treatments adjusted to each patient and type of Myeloma, in such a way that the patients may survive longer and with a better quality of life. Some drugs and other combinations are in a stage of clinical investigation at several Portuguese centres, cooperating with wider international studies.

A final reference to the improvements in supportive and preventive treatments against possible complications such as the appearance of hematopoietic growth factors (Erythropoietin and growth factors of the white neutrophile cells) used to prevent anaemia and the lack of white globules, and also the Biphosphonates (Pamidronate and Zoledronic Acid) used to prevent bone

disease and Myeloma osteoporosis. Last but not least, a word of hope for patients with Myeloma, since the current possibility of rendering this disease more chronic, allows patients to benefit from new medications being discovered and used everyday. Most likely in a near future, cure will be achieved.

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