Proceedings of the

International Symposium on Medroxyprogesterone Acetate

Geneva, Switzerland, February 24-26, 1982

Editors: F. Cavalli, W.L. McGuire,
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Opening remarks

As a local oncologist, it is my particular pleasure to open this meeting and to welcome you all – participants, organizers and sponsors – to Geneva for this international conference on medroxyprogesterone acetate. I know that your time will be much taken up with the meeting, but I do hope that you will find a few minutes, or perhaps a few hours, for a short walk along the lake or in the streets of the old town, so that your short stay in Geneva will not only be useful but also pleasant.

Geneva has always been – and I believe still is – a place where leading people of the world like to live and to spend as much time as they can; Calvin, Voltaire, Einstein and Lenin all spent a major part of their active life in Geneva. I hope that this particular spirit of Geneva will pervade the next few days and allow us to have a rich, pleasant and useful meeting.

Medroxyprogesterone acetate is an old drug and was probably one of the first agents used in the treatment of cancer. However, despite its long use, its place and usefulness in the treatment of breast cancer is still not completely understood. A major contribution to oncology was made when Professor Pannuti, of Bologna, showed and explained that medroxyprogesterone acetate used at high dose has a particular place in the treatment of different malignancies, and especially in the treatment of breast cancer. Although this problem is not completely solved, I hope we will find a few more answers during this meeting.

I wish you all a pleasant stay in Geneva, and a great success to the Congress.

Professor P. Alberto,
Division d'Onco-Hématologie,
Hôpital Cantonal,
Genève,
Switzerland

It is a great pleasure for me to attend this symposium, representing the UICC. Meetings such as this, to discuss, in depth the different aspects of a limited subject, are a real need in order to facilitate, among specialists in a given field,

the exchange of ideas and discussions of details that are so frequently fundamental to the progress of science. This need is a natural consequence of the tremendous input of new information which is continually being added by research workers all over the world.

On the one hand, we need large meetings with a broad coverage of several fields of specialization, such as the international cancer congresses held every 4 years under the auspices of the UICC, for many important reasons, among which may be mentioned:

1. Education in all its aspects.
2. Promotion of the fight against cancer.
3. Feasibility.
4. Social and scientific contact among participants from several specialties.
5. International collaboration and friendship.
6. A multidisciplinary approach to many problems.

On the other hand, such enormous meetings are no longer sufficient to satisfy the needs of the sophisticated specialist who wants to develop as much as possible in his own limited field and to find the answers to his problems.

As a world organization with continuously growing activities, and a privileged international position, the UICC is expanding its activities in many directions. One of these is collaboration with international and regional organizations in order to co-ordinate activities, to join efforts, in order to get greater efficiency and avoid duplication and overlapping in some fields. Along these lines, the UICC is also promoting, supporting and participating in international meetings such as this.

Hormones play an important, complex and, in many aspects, until now, unclear role in human biology. These facts are reflected in their use in the treatment of cancer. Results (in some cases, very favourable ones with complete response in a proportion of cases) are seen frequently by those who use these drugs, attesting to their importance even if many aspects of why, when and how they produce results, remain obscure. However, progress is being made continuously, clarifying little by little these obscurities and, what may be of more significance, expanding the field of tumours susceptible to hormonal manipulation. A typical way of this may be found in the progestogens, and more than justifies the efforts of Farmitalia Carlo Erba in organizing and holding this symposium.

Medroxyprogesterone acetate is a very interesting substance whose antineoplastic action in endometrial and breast cancer has been known for many years. Numerous studies recently conducted in the fields of experimental and clinical pharmacology, pharmacokinetics, mechanism of action, immune and hormone modulation, influence of receptors as well as

schedules of treatment and combination with cytotoxic agents have shown a great potential which is already being explored, with good results in some instances.

Interesting studies already demonstrate possible responses in tumors of the prostate, ovary and kidney.

The presentation and discussion of the most recent findings in these fields by a select group of outstanding specialists is the purpose of this meeting. The careful planning, the list of invited speakers and topics to be discussed during the meeting serve as a guarantee of success.

On behalf of the UICC, it is with great pleasure that I congratulate the organizers of this symposium and extend a warm welcome to all the invited speakers and participants.

Professor A.C. Junqueira,
Hospital Santa Cruz,
São Paulo,
Brasil

I am very pleased to add a few words to the opening remarks of Professors Alberto and Junqueira during this opening session. I am here in the double role of scientific secretary of the symposium and also as a representative of Farmitalia Carlo Erba which has been pleased to sponsor this meeting.

As the scientific secretary, I have tried, with the help and collaboration of the Advisory Board, to build up a programme which would provide us with a really up-to-date description of the experimental and clinical profile of this drug. On Friday, at the end of the symposium, we will be able to see whether that target has been reached. Tonight, I am very optimistic, for several reasons. First, the number of speakers who accepted our invitation has been very high, and it includes almost all the investigators who have a direct and large experience with this drug at both the experimental and the clinical levels.

Secondly, the attitude of all the contributors was positive, so that it has been possible to obtain and print in advance before the symposium the abstracts of all the papers, some of which will be presented as posters.

Finally, it has been possible to integrate the presentation of the most recent results of various investigators in round table discussions on specific topics, which will certainly favour an interesting discussion among the experts and the audience.

As a representative of Farmitalia Carlo Erba, first of all I would like to thank everyone who has contributed to the organization of the symposium. I would also like to express our deep gratitude to Professor Alberto who has

agreed to be with us and to open the symposium. Professor Junqueira is not only an old friend but he is here also as the official representative of the UICC. The sponsorship of the UICC has been greatly appreciated, and certainly this sponsorship underlines the scientific importance of the meeting.

As both Professor Alberto and Professor Junqueira have said earlier, chronologically speaking, medroxyprogesterone acetate may be considered as an old drug; it was synthesized in the Farmitalia laboratories in 1958. More recently, however, through active clinical research on new dosage schedules – research carried out first in Italy and then in many other countries – it has been possible to identify a new role for medroxyprogesterone acetate in the modern treatment modalities.

As you know, Farmitalia Carlo Erba has been – and still is – involved mainly in anthracycline research, but the increasing interest in medroxyprogesterone acetate (and, in a broader sense, in hormonal therapy) testifies to our intention and to our willingness to follow a multidisciplinary approach (also at the level of industrial research) in line with progress in the oncological field. Thus, I hope that in the next two days this symposium may allow us not only to update the present knowledge of medroxyprogesterone acetate but also give us an opportunity to discuss, in a friendly and relaxed atmosphere, the more general problems concerning the management of hormone-dependent tumours.

Professor C. Praga,
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High-dose medroxyprogesterone acetate in oncology. History, clinical use and pharmacokinetics

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Introduction

Medroxyprogesterone acetate (MPA) was first synthesized by Babcock et al. [1] and Sala et al. [2], independently (Fig. 1). Its progestogenic activity became evident soon after. In the original papers of Babcock et al. it was, in fact, described as the most active progestational agent so far discovered.

Several published papers support this description, in respect to both animals [3, 4] and man [5].

Macromolecular components of normal human mammary cytosol which bind ^{3}H-labelled MPA in vitro have been largely characterized [6]. These components show a strong affinity for progestins, and are most likely the progesterone receptors of human mammary tissue.

From the clinical point of view, the progestational activity of MPA is clearly shown by delay in menstruation [7, 8], inhibition of ovulation [9], changes in cervical secretion [10], changes in the vaginal karyopyknotic index, and endometrial deposition of glycogen [5]. The active progestogenic dose is well below the doses found useful in the treatment of breast cancer.

At the beginning of 1972, we in Bologna started administering MPA intramuscularly (i.m.) at higher doses than the 100 mg/day traditionally used, to determine the maximum tolerated dose [11].

The results obtained suggested that the increase of dosages given to patients with hormone-sensitive tumours had resulted in significant antitumour activity, and a noticeable improvement in their general condition, especially as regards pain [12].

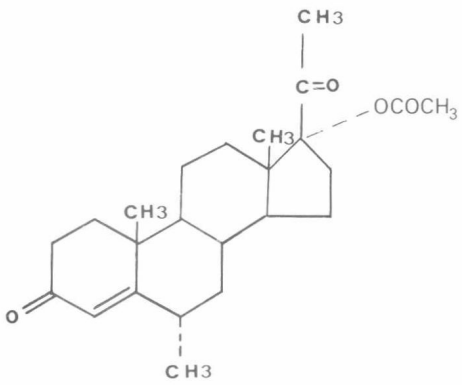

Fig. 1. 6α-Methyl-17α-acetoxyprogesterone (medroxyprogesterone acetate, MPA).

The effects were particularly apparent in patients with metastatic breast cancer. Further work with high-dose MPA in such patients confirmed that at doses of ≥ 500 mg/day the highest remission rates possible with endocrine treatment could be achieved. These rates could not be obtained using lower doses [13]. Subsequently, we demonstrated that high doses could also be given orally (p.o.), and that tolerance was excellent [14].

In Pavia, Robustelli Della Cuna et al. carried out a very well-designed study on high-dose MPA, which confirmed our results [15].

Other Italian investigators such as Pellegrini et al. [16], Amadori et al. [17], De Lena et al. [18] and Mussa et al. [19] obtained similar results, leaving aside a few differences resulting from different circumstances.

Mattsson, in 1978, was the first non-Italian investigator to confirm the significant antitumour activity of MPA at high doses [20]. Subsequently, Mendiola et al. [21], Madrigal et al. [22], Izuo et al. [23] and Becher et al. [24], reported results similar to ours, and a prospective controlled study by Cavalli et al. has recently demonstrated convincingly that high doses are more efficacious than low doses [25].

In other malignancies, such as endometrial carcinoma and renal carcinoma, in which progestogenic therapy is indicated, no conclusive data regarding the use of MPA at high doses are yet available. There have been encouraging results in relation to treatment with high-dose MPA in prostatic cancer, and in melanoma.

Hormonal interference

The idea of hormone dependence of tumours is based on the experimental and