LETTER TO THE EDITOR

Targeted cytotoxic analogs of luteinizing hormone-releasing hormone: a reply

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We read with great interest the Highlight Review by Dr C Gründker entitled 'Cytotoxic luteinizing hormone-releasing hormone conjugates and their use in gynecological cancer therapy' in the *European Journal of Endocrinology* (1). This excellent article provides a detailed description of recent developments in the field of targeted chemotherapy based on luteinizing hormone-releasing hormone (LH-RH) analogs. We agree with most of the views set forth in this paper. However, we believe that some of the particular statements regarding AN-201 and AN-207 are incorrect. According to one such remark: 'Newer examinations show that AN-207 disintegrates very fast without the action of carboxylesterase enzymes. AN-207, therefore, does not seem to be suitable for first line chemotherapy'. Such rapid disintegration of the cytotoxic LH-RH conjugate, AN-207, has never been observed and, in fact, its stability in serum was characterized as similar to that of its doxorubicin containing counterpart, AN-152. Regarding the importance of the development of a targeted cytotoxic LH-RH analog such as AN-207 containing 2-pyrrolinodoxorubicin, we would like to emphasize that this analog is active on tumors that are resistant to doxorubicin, and such resistance is still a major challenge to clinical oncologists. Thus, we demonstrated that 10 out of 10 mice bearing estrogen-independent, doxorubicin-resistant MX-1 human mammary carcinoma xenografts were cured after treatment with AN-207, while only 1 out of 10 mice was cured after treatment with the non-targeted cytotoxic radical (2). In addition, because of the high activity of AN-207, the usual effective and non-toxic dose of this analog is about 1% of that of doxorubicin. Consequently, relapsed patients with various cancers who have already received a maximum cumulative dose of ~450 mg/m² doxorubicin, which is determined by its cardiotoxicity, could still benefit from treatment with AN-207. This high efficacy may also make AN-207 suitable for the treatment of tumors with low receptor concentration.

Another statement in this article suggests that AN-152 should be favored for development because 'AN-201 is much more toxic than doxorubicin' and 'the effects of doxorubicin are well known'. We do not consider this viewpoint to be correct. Thus, in spite of the well-known effects of doxorubicin, some of its superactive, non-cross-resistant analogs such as methoxymorpholindoxorubicin (Nemorubicin) are presently in clinical phase II/III trials (3). AN-201 belongs to the same family of intensely potent doxorubicin derivatives as Nemorubicin although, unlike Nemorubicin, AN-201 is highly cytotoxic without *in vivo* enzymatic activation (4).

In conclusion, in addition to the expected clinical advantages of targeted as opposed to systemic chemotherapy, on which we are in full agreement with Dr Gründker, we also firmly believe that AN-207 clearly merits clinical development because of its expected benefits to patients whose cancers do not respond to doxorubicin therapy.

References

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