New therapies for relapsed castration-resistant prostate cancer based on peptide analogs of hypothalamic hormones

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Recommended Citation
Schally, Andrew V.; Block, Norman L.; and Rick, Ferenc G., "New therapies for relapsed castration-resistant prostate cancer based on peptide analogs of hypothalamic hormones" (2015). HWCOM Faculty Publications. 40.
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New therapies for relapsed castration-resistant prostate cancer based on peptide analogs of hypothalamic hormones

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Asian Journal of Andrology (2015) 17, 1–4; doi: 10.4103/1008-682X.152819; published online: 26 June 2015
demonstrate the presence of high levels of receptors for LHRH, BN/GRP, and somatostatin, as well as mRNAs for their receptor subtypes, in human prostate cancer specimens.8–10,28 In experimental studies on human prostate cancer lines xenografted into nude mice, analogs of LHRH,10 analogs of somatostatin,29 and analogs of GRP30 each inhibited prostate tumors growth and in vitro reduced their proliferation.4,8–10 In vitro effects demonstrated a direct effect of these analogs on tumors.31 Following the example on Estracyt (estramustine) consisting of nitrogen mustard coupled to carrier estrogen, we developed cytotoxic analogs of LHRH, somatostatin, and GRP which actively target respective receptors on prostate cancers.18,20,31–37 Thus, we have synthesized a targeted cytotoxic LHRH analog, denoted AN‑152 (commercially AEZS‑108, zoptarelain‑doxorubicin), which combines a D‑Lys‑6 LHRH agonist moiety (necessary for binding to LHRH receptors on cancer cell surfaces) with the cytotoxic doxorubicin.19 This analog delivers doxorubicin to only those cells with LHRH receptors on the cell membrane, thus avoiding cytotoxic side effects in normal cells. We found that after binding to LHRH receptors, AN‑152 (AEZS‑108) is internalized into the tumor cells.38,39,52–57 AN‑152 (AEZS‑108) was extensively tested in vitro and also in vivo in nude mice with xenografted human cancer lines expressing LHRH receptors.8,9,37 This drug inhibited the growth of a wide range of carcinomas (including kidney, prostate, urothelium) and sarcomas. These included DU‑145 human androgen‑independent prostate cancer as well as HT‑1376, J82, RT‑4 and HT‑1197 bladder cancer lines.39,37–39 The administration of AN‑152 (AEZS‑108) produced a powerful inhibition of tumor growth, greater than that induced by doxorubicin alone. The hybrid was found to be more efficacious and less toxic than doxorubicin.57 These studies were followed by Phase I and II human trials in women with endometrial and ovarian cancer expressing LHRH receptors.30,31,34 Dose escalation studies established that the maximum tolerated dose of AEZS‑108 is 267 mg m−2. Dose‑limiting leukopenia and neutropenia were observed at the highest dose.40 Liu, Pinski et al. also subjected AN‑152 (AEZS‑108) to Phase II trials in patients with CRPC resistant to taxane.32 AEZS‑108 is currently in Phase III trials in USA and Europe in women with endometrial cancer. We have great expectations for it.

Another class of new and important antitumor peptides that could inhibit CRPC consists of antagonists of GHRH.43–46 The story behind these compounds is most interesting. One of us (AVS) was among the investigators who discovered GHRH in hypothalami of animals in the 1960s.61 Because only extremely small quantities of GHRH are present in the hypothalamus, it was not possible to characterize GHRH structurally until the early 1980s.49 At that time, the clinicians became aware of cases of paraneoplastic acromegaly in some patients with pancreatic carcinoma. These tumors were actually producing GHRH, which then induced GH release from the pituitary. Thus, GHRH can be produced by tumors themselves, and it thus functions in an autocrine/paracrine fashion as a growth factor. Samples of these tumors were used for the isolation and structural elucidation of GHRH, which was then synthesized.43–46 Over the past 30 years, we have been investigating the role of GHRH in tumor growth and found that many tumors produced GHRH and had GHRH receptors.43–46 We determined that human prostate cancer specimens and human prostatic cell lines express GHRH and GHRH receptors.55 We also demonstrated the expression of splice variants of these receptors.37–49 This presence of GHRH receptors provides the basis for a new approach to the treatment of CRPC based on antagonists of GHRH.53,54 Thus, over the past 20 years we produced nearly 2000 synthetic antagonistic analogs of GHRH, with each step improving their potency and half‑life.43–46,50 We substituted some of the natural (coded) L‑amino acids in the N‑terminal 29 amino acid sequence of GHRH that has all the biological activity either with their “D” isomers or with totally synthetic amino acids.43–46,50 The structure of one of our GHRH antagonists, MIA‑602, the one we have chosen for clinical development, is shown in Table 1. We have found that these GHRH antagonists can block the growth of over 20 different human tumor types, as exemplified by over 60 human cancer cell lines xenografted into nude mice.43–46,31–40 We showed that MIA‑602 and our other GHRH antagonists inhibited growth of PC‑3 and 22Rv1 human androgen‑independent prostate cancer cell lines and also hormone‑dependent prostate cancer lines.36–62 Our GHRH antagonists also suppressed prostate, kidney, urothelial, breast, triple‑negative breast, ovary, astrocytoma, melanoma, ENT tumors, esophagus, stomach, colon, lung, adrenal cortical, pheochromocytoma, uterus, osteosarcomas and multiple lymphoma types. In addition to their inherent effects on cancer, we found that the GHRH antagonists also potentiated the effects of cytotoxic chemotherapy without enhancing the toxicity.59

The side effect/toxicity profile of GHRH analogs is minimal. Similarly, LHRH agonists and antagonists also have little or no toxicity, and it is really their anti‑androgenic effect, not the drugs themselves that cause some adverse effects.71,72

PERSPECTIVES FOR THE IMPROVEMENT OF THERAPY FOR CASTRATION‑RESISTANT PROSTATE CANCER

Novel drugs are required for the treatment of CRPC. The best option may not be the agents that target androgen receptors or compounds which inhibit enzymes involved in androgen biosynthesis. This is because the androgen deprivation created by these compounds can be overcome by mutations in androgen receptors, the appearance of splice variants of these receptors or alternate biochemical pathways.

The use of currently available cytotoxic analogs of LHRH, or somatostatin that can be targeted to prostate cancers may lead to an improvement in the treatment of CRPC and an increase in the survival rate. A new modality based on GHRH antagonists also appears to be useful for the treatment of metastatic CRPC.

ACKNOWLEDGMENTS

This material is based upon work supported in part by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development of the Miami VA Healthcare System; by the Departments of Pathology and Medicine, Sylvester Comprehensive Cancer Center; and Division of Hematology/Oncology of the Miller Medical School, Department of the Miller School of Medicine, University of Miami; by the South Florida Veterans Affairs Foundation for Research and Education (all to AVS); and by the L. Austin Weeks Endowment for Urologic Research (NLB).

**Table 1: Structure of growth hormone‑releasing hormone antagonist, MIA‑602**

<table>
<thead>
<tr>
<th>Chemical structure of MIA‑602</th>
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<tbody>
<tr>
<td>MIA‑602 (PhAc‑Ada)‑D‑Arg, Phe (F)6, Ala8, H‑Arg, Tyr (Me)16, His112, Orn12, Abu15, His50, Orn23, Nle27, D‑Arg28, H‑Arg31</td>
</tr>
</tbody>
</table>

Abu: alpha‑aminobutyric acid; Ada: 12‑aminododecanoyl; Har: homoarginine; Nle: norleucine; Orn: ornithine; PhAc: phenylacetyl; Tyr (Me): O‑methyltyrosine; Ac: acetyl; Agm: agmatine; Amb: B‑aminocaprylyl; Amp: para‑amidino‑phenylalanine; Oct: octyl; Tyr (E): O‑ethytyrosine; Ish: isobutyryl
FGR received support from the Urology Care Foundation Research Scholars Program and the AUA Southeastern Section. The contents of this work do not represent the views of the Department of Veterans Affairs or the United States Government.

REFERENCES


