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REVIEW

Biological effect of neoadjuvant androgen-deprivation therapy assessed on specimens from radical prostatectomy: a systematic review

Alessandro ANTONELLI [1] *, Carlotta PALUMBO [1], Alessandro VECCIA [1], Salvatore GRISANTI [2], Luca TRIGGIANI [3], Stefania ZAMBONI [1], Maria FURLAN [1], Claudio SIMEONE [1], Stefano MAGRINI [3], Alfredo BERRUTI [2]

[1]Unit of Urology, ASST Spedali Civili, University of Brescia, Brescia, Italy; [2]Unit of Medical Oncology, ASST Spedali Civili, University of Brescia, Brescia, Italy; [3]Unit of Radiation Oncology, ASST Spedali Civili, University of Brescia, Brescia, Italy

*Corresponding author: Alessandro Antonelli, ASST Spedali Civili di Brescia, Piazzale Spedali Civili 1, Brescia, Italy.
E-mail: alessandro_antonelli@me.com

ABSTRACT

INTRODUCTION: Androgen-deprivation therapy (ADT) administered in neoadjuvant setting before radical prostatectomy (RP) represents an ideal *in vivo* human model to test the efficacy of hormonal treatments in prostate cancer (PCa). This review summarizes the findings from published studies specifically focused on the biological effects of ADT assessed on specimens from RP. The aim is to provide a base of knowledge that might be used to design future studies on neoadjuvant therapy for PCa.

EVIDENCE ACQUISITION: A systematic review of the literature was performed according to the PRISMA statements. Search protocol identified published studies including a detailed analysis on specimen from RP to assess the biological effects of neoadjuvant ADT. In November 2017, Medline, Embase, and Scopus databases were searched using the terms "neoadjuvant" AND ("hormone therapy" OR "androgen deprivation therapy") AND "prostate cancer" in the "Title/Abstract" fields. Effects of ADT were classified according to four pathways — suppression of cellular proliferation, induction of apoptosis, alteration of immune response and onset of hormonal refractoriness — and relative markers of response were identified.

EVIDENCE SYNTHESIS: From 1856 papers initially retrieved, 19 studies were finally selected and included into the present review. ADT was constituted by luteinizing hormone-releasing hormone (LH-RH) agonist alone in two, peripheral anti-androgen alone in one, both in 10, abiraterone acetate in one, unspecified in five. According to the above-mentioned four pathways, the following markers of response were identified: transcription of the oncogene TMPRSS2:ERG, translation of Aurora-A, coding of β1C integrin gene, translation of Ki-67, expression of nerve growth factors TrkA and p75NGFR, anti-angiogenic activity and micro-vessel density were involved into suppression of proliferation; mRNA transcription of bcl-2, expression of cleaved caspase-3 and translation of insulin growth factor binding protein 3, into induction of apoptosis; expression of IL-7 gene, programmed death-ligand 1, and increase of intra-prostatic T-cell population were related to alteration of immune response; finally, expression of heat shock protein 27 and de-differentiation of PCa to neuroendocrine cells, influenced the onset of hormonal refractoriness.

CONCLUSIONS: Despite a potential high interest, unexpectedly, only 19 heterogeneous studies investigated the effects of ADT through the analysis of specimens from RP. The present review summarizes the available evidences on this topic showing that ADT interferes on PCa at different levels that can be investigated by specific biological markers.

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KEY WORDS: Prostatic neoplasms - Neoadjuvant therapy - Prostatectomy - Biological assay.

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Introduction

Neoadjuvant regimens, *i.e.* systemic therapy administered to prepare local treatments, is a well-recognized strategy for several solid tumors as breast, bladder, rectal and esophageal cancers.[1-5] Concerning prostate cancer (PCa), androgen-deprivation therapy (ADT) before radiotherapy has grade 1 recommendation for locally advanced disease, because of significant survival benefit through a reduction of tumor burden, control of occult micrometatasis and increased cell sensitivity to ionizing radiation.[6-8] Conversely, ADT before radical prostatectomy (RP), is not recommended by international Guidelines out of individualized strategy because it doesn't provide any advantage in cancer-specific and overall survival.[9, 10] Accordingly, the use of ADT prior to surgery is progressively declined since the 1980's.[11]

Despite its limited clinical role, concerning research purposes, neoadjuvant setting before RP represents an optimal *in-vivo* human model to test biological effects of ADT on PCa. Indeed, this context gives the possibility to analyze both normal and neoplastic tissues from the entire prostatic gland and observe how they are affected by ADT. This assessment could provide findings of quality and reliability higher than what can be obtained from prostatic biopsies, cellular cultures or animal models.[12]

A major point to be addressed to design a trial on ADT in neoadjuvant setting is the identification of a measure of outcome, *i.e.* a marker of response represented by a cellular component which function is key in PCa, that is impaired due to the effect of treatments. Morphological effects of ADT on cellular and stromal components of PCa and surrounding benign tissues have been precisely described as intense involutional changes with loss of glandular architecture, cytoplasmic vacuolization, and nuclear pyknosis.[13] However, besides this typical histological picture, neoadjuvant ADT induces other several complex proteomic and genomic changes that have been less investigated.

The aim of the present review is a thorough insight into the literature that specifically investigated the consequences of neoadjuvant ADT on RP's specimens, with the aim to orientate future studies, standardize methodology and favor reproducibility of results.

Evidence acquisition

A systematic review of the literature concerning the effects of neoadjuvant ADT assessed on specimens from RP was performed in November 2017, according to the "Preferred reporting items for systematic reviews and meta-analyses" (PRISMA) statements.[14]

Medline, Embase and Scopus databases were searched without any time span limitation. A searching protocol with the MeSH terms "neoadjuvant" AND ("hormone therapy" OR "androgen deprivation therapy") AND "prostate cancer" in the "Title/Abstract" fields was performed; only the items with simultaneous presence of all terms were retrieved. Research was restricted to citations with available abstract and full text, human studies and English language; abstracts and meeting's reports were excluded; references sections were consulted to identify further studies. Two authors independently reviewed title and abstracts of the records retrieved and selected the studies specifically focused on the topic of the review. Then, all authors read the full text of these papers and reached an agreement on which ones to include into the present review. From each one, data on study design, size of cohort, type and regimen of ADT, investigative methodology, and main findings were then extracted. We considered as indicators of response to ADT proteomic (modifications in structure or activity of intracytoplasmatic proteins, cell-membrane receptors, components in prostatic stroma) or genomic (variation in DNA or RNA sequences, replication or transcription regulators) changes. Variation of serum markers (as PSA, neuron specific enolase, chromogranin, etc.), morphology or loco-regional staging were not reported because already discussed elsewhere.[15-17] The biological effects of ADT on PCa were summarized according to 4 main pathways: suppression of cellular proliferation, induction of apoptosis, alteration of immune response and onset of hormonal refractoriness. Search strategy is described in Supplementary Digital Material 1 (Supplementary Text File 1).

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TABLE I.—*Summary of papers' results and findings.*[18-36]

Study	Study design	Cohort size	Drug used	Duration of NHT	Investigation methodology
Calagua *et al.*, (2017)[18]	Prospective, matched-pair	88 44 with NHT 44 without NHT	Abiraterone acetate plus prednisone and leuprolide	3 months	Tissue pathology Immunohistochemistry
Miyata *et al.* (2015)[19]	Prospective, control group	108 48 with NHT 60 without NHT	Bicalutamide or LHRHa or both	3 months	Tissue pathology Immunohistochemistry Marker's response: semiquantitative
Lehmusvaara *et al.* (2013)[20]	RCT	28 8 goserelin 9 bicalutamide 11 no treatment	Goserelin *vs.* bicalutamide *vs.* no treatment	3 months	Hematoxylin and eosin Microarray hybridization
Lehmusvaara *et al.* (2012)[21]	RCT	28 8 goserelin 9 bicalutamide 11 no treatment	Goserelin *vs.* Bicalutamide *vs.* no treatment	3 months	Microarray hybridization
Sorrentino *et al.* (2011)[22]	Prospective, control group	126 76 with NHT 50 without NHT	Flutamide + leuprolide acetate *vs.* no treatment	3 months	Immunofluorescence Real-time reverse transcriptase (RT)-PCR
Fuzio *et al.* (2011)[23]	Prospective, control group	39 18 with NHT 21 without NHT	Goserelin + bicalutamide *vs.* no treatment	1 to 6 months	Northern and Western blot analysis Immunohistochemistry
Watanabe *et al.* (2010)[24]	Retrospective	83 40 with NHT 43 without NHT	Bicalutamide or LHRHa or both	8 months	Immunohistochemistry *In-situ* labeling for apoptosis
Fuzio *et al.* (2009)[25]	Prospective, control group	22 10 with NHT 12 without NHT	Goserelin + bicalutamide *vs.* no treatment	1 month	Northern hybridization experiments Nuclear run-on assays
Chavin *et al.* (2009)[26]	Retrospective	276 148 with NHT 127 without NHT	GnRH agonist	3 months	Tissue pathology Immunohistochemistry
Furukawa *et al.* (2007)[27]	Prospective	97 Before and after NHT	LHRHa (goserelin acetate or leuprorelin acetate) + bicalutamide or flutamide	3 months	Monoclonal antibodies
Festuccia *et al.* (2007)[28]	Prospective	102 41 with NHT 61 without NHT	Bicalutamide *vs.* no treatment	3 months	Hematoxylin and eosin Antibodies
Shimizu *et al.* (2007)[29]	Prospective	122 52 with NHT 70 without NHT	LHRHa + bicalutamide	4 to 12 months	Immunohistochemistry (chromogranin A antibody)

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Marker(s)	Biological role of marker(s)	Summary of results
PD-L1 expression Tumor-infiltrating CD8+ cells	Programmed death-ligand 1 (PD-L1) is transmembrane protein that plays a major role in suppressing the immune system. Upregulation of PD-L1 may allow cancers to evade the host immune system	NHT-treated tumors had decreased PD-L1 positivity. Treated tumors also harbored significantly fewer tumor-infiltrating CD8+ cells
Microvessel density (CD31-, CD34-, CD105-) Expression of (VEGF)-A and (TSP)-1	Microvessel density is used for the evaluation of angiogenesis is one of the most useful prognostic markers for tumor progression and survival. (VEGF)-A and (TSP)-1 regulate angiogenesis in prostate cancer	High CD105-MVD was correlated with high VEGF-A expression and low TSP-1 expression in NHT treated patients. CD105-MVD as a significant and independent predictor of BCR in PCa patients who underwent RP with NHT. NHT stimulates anti-angiogenic activity in prostate cancer tissues
TMPRSS2:ERG gene fusion miRNA expression (miR-125b, miR-21, and miR-32) Gene expression patterns induced by NHT	TMPRSS2:ERG is an androgen-receptor target gene and has a role in both the initiation and progression of PCa. Some miRNAs have been shown to be directly androgen- regulated in cell line models	TMPRSS2:ERG fusion positive and negative cases showed differential expression of miRNAs, and the difference was diminished by androgen ablation Significantly different effects of an anti-androgen and a GnRH agonist on gene expression in prostate cancer cells
Cytokine/chemokine gene expression levels	The lack of constitutive interleukin-7 (IL-7) gene expression in PCa, and related lymphocyte depletion, is a mechanism whereby PCa evades immunosurveillance	NHT upregulates IL-7 gene expression in the normal prostate epithelium and stroma and increases the intraprostatic T-cell population consisting of both cytotoxic-effector and regulatory T lymphocytes
Expression of BCL-2	BCL-2 is an integral protein of the external mitochondrial membrane that inhibits cell apoptotic death	Short-term administration of ADT interferes with BCL-2 expression, suggesting that androgen-mediated mechanisms may act through BCL-2-mediated apoptotic pathways, probably acting at the post-transcriptional level
Expression of X-linked inhibitor of apoptosis (XIAP) and cleaved caspase-3	Caspase- 3 is the most important apoptosis-related molecule. XIAP has the highest affinity and the most potent direct inhibitory activity for caspases	In the NHT group, there was a significantly higher expression of Caspase-3, but not a downregulation of XIAP, suggesting that apoptosis after NHT can be regulated by pathway independent from caspase.
Expression of β1C mRNA	The β1C integrin is an alternatively spliced variant of the β1 integrin subfamily that inhibits cell prolife- ration in prostate cancer cells	A significant increase of β1C mRNA expression and of gene transcriptional activity in patients who received NHT was found.
B7-H3 ligand expression	Prostate cancer cells uniformly express the immune cell inhibitory B7-H3 ligand. Enhanced B7-H3 expression correlates with increased disease progression and cancer-specific death.	B7-H3 expression seems to remain stable (or may even increase) in response to hormone therapy
Aurora-A protein expression	If overexpressed, Aurora-A could function as an oncogene through the abnormal regulation of centrosome function	The expression of Aurora-A was significantly lower in RP specimens than in biopsy specimens before NHT
Neurotrophin tyrosine kinase receptor (tkrA) and P75 neutrophin receptors expression	Normal prostate epithelial cells express both trkA the p75NGFR, whereas primary and metastatic PCa express only trkA	TrkA levels were significantly upmodulated, whereas p75NTR seemed to be reduced by NHT
Frequency and numbers of neuroendocrine tumor cells	Neuroendocrine tumor cells in prostate cancer are thought to increase after hormonal therapy due to neuroendocrine differentiation of tumor cells	No difference was found. Hormonal therapy should not induce the neuroendocrine differentiation, but androgen-independent neuroendocrine cells already exist before therapy

(To be continued)

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TABLE I.—*Summary of papers' results and findings[18-36] (continues).*

Study	Study design	Cohort size	Drug used	Duration of NHT	Investigation methodology
Yasuda *et al.* (2007)[30]	Retrospective	50 Before and after NHT	LH-RHa (leuprolide or gocererin acetate) + flutamide or bicalutamide	3 months	Immunohistochemistry (HIF-1α antibodies)
Miyake *et al.* (2006)[31]	Prospective	97 Before and after NHT	LHRHa (goserelin acetate or leuprorelin acetate) + bicalutamide or flutamide	3 months	Immunohistochemistry (antibody anti HSP27)
Autorino *et al.* (2005)[32]	Prospective, control group	84 44 with NHT 40 without NHT	Leuprolide + bicalutamide	3 months	Hematoxylin and eosin Immunohistochemistry (chromogranin A antibody)
Miyata *et al.* (2004)[33]	Prospective	42 Before and after NHT	Bicalutamide or LHRHa or both	3 months	Immunohistochemistry (antibody anti IGFBP-3) In situ labeling for apoptosis
Köllermann *et al.* (2001)[34]	Retrospective	40 20 with NHT 20 without NHT	Leuprolide + flutamide or bicalutamide	3 months	Immunohistochemistry (chromogranin A antibody)
Ahlgren *et al.* (1999)[35]	RCT	103 50 with NHT 53 without NHT	LHRHa	3 months	Immunohistochemistry
Matsushima *et al.* (1999)[36]	Prospective, group	80 35 with NHT 45 without NHT	Flutamide + LHRHa *vs.* no treatment	3 months	Immunohistochemistry (MIB-1 and CD31) *In-situ* labeling for apoptosis

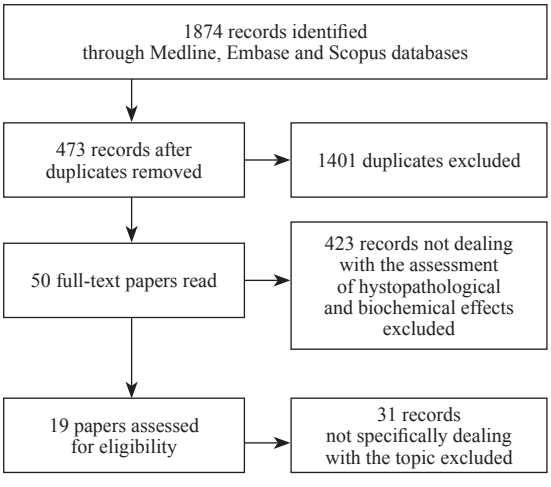

Figure 1.—PRISMA flowchart.

Evidence synthesis

Overall, the search algorithm retrieved 1856 papers; after first selection the full text of 47 was read by all authors and, finally, 19 studies published from 1999 to 2017 were in-depth examined since specifically investigated the effects of ADT on specimens from RP (Figure 1).

Table I and Table II show a summary of the findings presented by the 19 studies included.[18-36]

Overall 1615 patients were enrolled, for a mean size of cohorts of 85 (range 22-276). Regarding study's design, 3[27, 31, 33] were longitudinal case-control single-arm trials, comparing features of PCa before and after NHT on prostatic biopsy and RP specimens, respectively; two

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Marker(s)	Biological role of marker(s)	Summary of results
Expression and regulation of HIF-1α	In prostatic adenocarcinomas, the androgen up-regulates HIF-1α, and up- regulation of HIF-1α is considered to be an early event in prostate carcinogenesis	The hypoxic status was evaluated to be divided into two categories: weak (16 cases) or strong (34 cases). A significant difference in HIF-1α expression profiles were found in recurrent cases. NHT does not influence the expression of HIF-1α
Expression of heat shock protein 27 (HSP27)	HSPs are ubiquitous molecules. In PCa data suggest the involvement of HSPs in disease progression and resistance to conventional therapies	HSP27 expression in the RP specimens following NHT was significantly up-regulated compared with that in the corresponding needle biopsy specimens
Neuroendocrine differentiation (NE) after NHT	NE differentiation occurs in various degree in the majority of PCa and it has been correlated with tumor progression, poor prognosis and refractoriness to hormonal therapy	The neuroendocrine differentiation does not increase after NHT
Expression of insulin-like growth factor binding protein-3 (IGFBP-3) before and after NHT	IGFBP-3 has pro-apoptotic activity. Its expression correlates negatively with prostate cancer cell growth. Castration induces IGFBP-3 expression and apoptosis in the rat prostate	NHT resulted in a significant increase in IGFBP-3 expression compared with baseline
Neuroendocrine differentiation	NE differentiation lead to androgen independent growth	Short-term NHT does not induce relevant clonal propagation of NE cells
Proliferation index (PI) defined as the proportion of Ki-67-positive cells in a random cell count	Proliferation, apoptosis and angiogenesis are essential for cancerogenesis	There was no difference in tumor cell proliferation between the neoadjuvant group and the control group, neither in mean PI
Ki-67 labeling index (Ki-67 LI) The apoptotic index (AI) Intratumoral microvessel density (IMVD)	Proliferation, apoptosis and angiogenesis are essential for cancerogenesis	Correlations between proliferation, apoptosis, and angiogenesis in prostate carcinoma are altered significantly in association with androgen suppression

studies[20, 21] were 3-arms and compared no administration of ADT vs LHRH analogue *versus* peripheral anti-androgen; the remaining 14 studies[18, 19, 22-26, 28-30, 32-36] were two-arm and compared patients submitted or not to NHT (among these, three[20, 21, 35] were randomized controlled trials). Regarding treatment schedule, peripheral anti-androgens, luteinizing hormone-releasing hormone (LHRH) analogue, or combined in complete androgen blockade were used in 1,[28] 2,[26, 35] and 10 studies,[20, 21, 23, 25, 27-30, 32, 34] respectively. In five studies,[19-21, 24, 33] regimen was generically (either LHRH analogue or peripheral antiandrogen) with no other details. One study[18] accounted for "second generation" ADT with abiraterone acetate plus prednisone and LHRH analogue.

Several markers of response were adopted by studies and involved the 4 pathways above described. In detail, eight studies investigated how ADT could reduce proliferation, angiogenesis and metastatic potentiality by: 1) down-regulating the transcription of miRNAs related to TMPRSS2:ERG, an oncogene targeted by the androgen-receptor;[20] 2) down-regulating the translation of Aurora-A, a protein kinase that favors proliferation;[27] 3) enhancing the coding of β1C integrin gene, a membrane protein that inhibits proliferation usually under-expressed in PCa cells;[25] 4) decreasing the translation of Ki-67, a nuclear protein regulating the cellular cycle;[35, 36] 5) altering the balance between membrane-receptors for nerve growth factors TrkA

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and p75NGFR, that finally changes signal transduction from proliferative to anti-proliferative;[28] 6) stimulating anti-angiogenic activity and lowering micro-vessel density.[19, 36] Conversely, one study[30] reported that ADT did not impair PCa proliferation, showing that the expression of subunit 1a of HIF-1α (hypoxia-inducible factor), that contribute to the progression of PCa and is usually up-regulated by androgenic stimulus, was unchanged. Four studies[23, 24, 33, 36] found that ADT induced apoptosis of PCa. This happened by: 1) increasing mRNA expression and protein translation of bcl-2;[23] 2) promoting the expression of cleaved caspase-3;[24] 3) increasing translation of insulin growth factor-binding protein 3, a potent mediator of anti-proliferative and apoptotic processes.[33] Three studies[18, 22, 26] showed that ADT modulates immune response by: 1) promoting the up-regulation of IL-7 gene;[22] 2) increasing intra-prostatic T-cell population;[22] 3) decreasing programmed death-ligand 1 (PD-L1) expression.[18] Only one study[26] showed that ADT was not correlated to the expression of B7-H3, an immune cell inhibitory ligand whose overexpression correlates with progression. Finally, four studies[29, 31, 32, 34] documented that ADT reduced the onset of hormone-refractoriness by: 1) retarding de-differentiation of PCa to neuroendocrine components;[29, 32, 34] 2) promoting the up-regulation of expression of heat shock protein 27 (HSP27).[31]

A summary of these effects is reported in Figure 2.

Discussion

The pioneers Huggins and Hodge[37] first showed in 1941 that PCa is dependent on androgen stimulation, paving the way for the introduction in clinical practice of ADT. Neoadjuvant ADT provokes several well codified involutional changes to the architecture of PCa glands, manifested as cytoplasmic shrinkage and vacuolation, nuclear pyknosis, gland shrinkage, mucinous breakdown, and the presence of collagenous stroma.[38] Some randomized trials investigated the clinical impact of neoadjuvant ADT before RP analyzing several pathological outcomes adopted as indicators of clinical response. These studies reported that ADT could achieve downstaging, reduction of positive margins and lymph nodal invasion.[16, 17] Since none of these effects translated into advantages in survival, currently there is no suggestion in favor of neoadjuvant ADT by international Guidelines, at least out of personalized indications.

In recent years the knowledge of molecular pathways that drive the development and progression of PCa rapidly increased.[39, 40] Some of these pathways could be targeted by hormonal therapy and therefore clinicians and researchers should maintain a strong interest for studies on neoadjuvant ADT. Indeed, within this setting the deep interactions between ADT and PCa metabolism could be reliably assessed processing the whole prostate gland. Nevertheless, we unexpectedly retrieved only 19 studies specifically dealing with this issue. The design of trials on neoadjuvant ADT presents several difficulties concerning the identification of objective measures of outcome to report the effects of treatments. The ideal outcome should be the complete regression of viable PCa — complete pathological response — but this is unusual for PCa. Indeed, published trials showed a rate of complete response almost null after courses of NHT up to 3 months and a very few studies reported sporadic cases of complete response after longer term courses. The recent study from Taplin and coll[41] in that sense is noteworthy because found 10% of complete response after 12 weeks of therapy with abiraterone.

Thus, other markers of response should be searched by a deep insight into the pathways that regulate PCa cells. Obviously, doing this, is mandatory to have a solid knowledge of existing literature concerning this issue, and this review was conceived with this purpose.

The findings of available studies as summarized by our work confirmed that ADT could impair the activity of PCa cells at several points. We attempted at rationalizing these observations, identifying four pathways on which ADT was active - tumor progression, apoptosis, interaction with the host immune system and onset of hormonal refractoriness. Several specific indicators of response with their respective analytic method were identified and reported by our review. Theoretically, with such a categorization,

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TABLE II.—*Summary of the findings on each specific metabolic issues investigates.*[18-20, 22-36]

Metabolic issue investigated	Marker of response	Drug	Effect of NHT	Study
Hormonal refractoriness	Neuroendocrine differentiation	AA+LHRHa	No	Shimizu *et al.*[29]
				Autorino *et al.*[32]
				Köllermann *et al.*[34]
	Heat-shock protein 27	AA+LHRHa	Yes	Miyake *et al.*[31]
Immune response	IL-7 gene	AA+LHRHa	Yes	Sorrentino *et al.*[22]
	B7-H3 ligand	LHRHa	No	Chavin *et al.*[26]
	PD-L1	AAP+LHRHa	Yes	Calagua *et al.*[18]
Proliferation, angiogenesis and metastatic potentiality	Microvessel density	AA±LHRHa	Yes	Miyata *et al.*[19, 36]
	VEGF-A, TSP-1	AA±LHRHa	Yes	Miyata *et al.*[19]
	TMPRSS2:ERG gene/miRNA	AA or LHRHa	Yes	Lehmusvaara *et al.*[20]
	Aurora-A	AA±LHRHa	Yes	Furukawa *et al.*[27]
	Neurotrophin receptors	AA	Yes	Festuccia *et al.*[28]
	HIF-1α	AA+LHRHa	Yes	Yasuda *et al.*[30]
	B1C	AA+LHRHa	Yes	Fuzio *et al.*[25]
	Ki-67	LHRHa	No	Ahlgren *et al.*[35]
	Ki-67	AA+LHRHa	Yes	Matsushima *et al.*[36]
Apoptosis	XlAP, Caspase-3	AA±LHRHa	No	Watanabe *et al.*[24]
	IGFBP-3	AA±LHRHa	Yes	Miyata *et al.*[33]
	BCL-2	AA+LHRHa	Yes	Fuzio *et al.*[23]
	Apoptotic index	AA+LHRHa	Yes	Matsushima *et al.*[36]

NHT: neoadjuvant hormone therapy; AA: anti-androgen; AAP: abiraterone acetate plus prednisone; LHRHa: luteinizing hormone-releasing hormone agonist; PCa: prostate cancer.

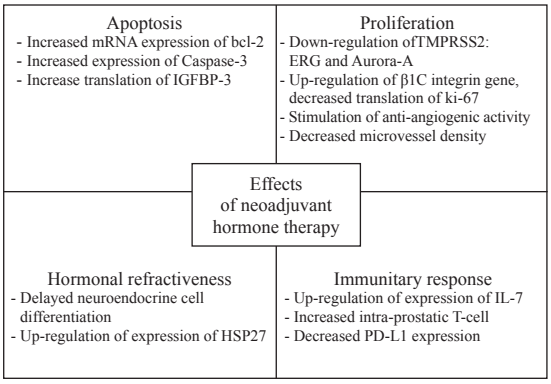

Figure 2.—Visual summary of the possible effects of neoadjuvant hormone therapy or prostate cancer cells biology.

future studies might be oriented to investigate the markers of response descriptive of a specific biological effect to assess if ADT could play a role for a specific clinical need, as prevention of local or metastatic diffusion, regression of the sites of disease or delay of the onset of castration-resistance.

Currently, "classical" ADT is probably raising a poor interest, because it is used in clinical practice since 4 decades; moreover, its adoption in neoadjuvant setting is discouraged by the lack of approved indications. Nevertheless, during recent years the therapeutic scenario of PCa has changed and the interest in studies on neoadjuvant treatments could be renewed. Indeed, the surgical indication for locally advanced[42] and even oligo-metastatic PCa,[43] within a multimodal strategy,[44, 45] is expanding and for these patients ADT prior to surgery is frequently practiced. Moreover, the advent of new hormonal molecules as degarelix, abiraterone, and enzalutamide stimulated the interest in studies in neoadjuvant setting. Indeed, three publications concerning these drugs were recently published[41, 46, 47] the measure of outcome was mainly histological — cytoplasm concentration of testosterone and complete pathological response — and were excluded from this review, accordingly to our search methodology, but future development are expected.

Conclusions

The evidence summarized by the present review showed that ADT interferes on PCa at different levels, each one investigable by several specific biological markers. These results might be a template on which future studies with available or new drugs could be designed.

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