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Review Article

Anticancer Drugs-Related Hypogonadism in Male Patients with Advanced Cancers on Active Treatment: A Systematic Review

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Abstract

Background: In male patients with cancer treated with antineoplastic drug, hypogonadism is a neglected cause of diminished quality of life. This condition may be cancer related as well as toxicity related. The role of antineoplastic drug in causing hypogonadism is poorly understood. The aim of this systematic review was to establish the prevalence, nature (primary/secondary), and impact of hypogonadism on quality of life in male patients with cancer on antineoplastic therapy.

Methods: The search strategy used PubMed, Embase, and Cochrane databases to select articles in English language that described hypogonadism in male patients with cancer. The search period was from January 1, 1945 to February 28, 2023. We included observational studies, case reports or case series and excluded studies concerning hematological malignancies, prostate cancer, female patients, and survivors.

Findings: Of 4488 records identified, 28 studies met inclusion criteria (17 observational studies, 11 case reports or case series). Anti-angiogenic drugs and crizotinib were found to have a role in the development of hypogonadism. Patients treated with immune checkpoint-inhibitors developed secondary hypogonadism due to immune-related hypophysitis or orchitis. As for active chemotherapy, platinum salts were often associated with hypogonadism, followed by antimetabolites and taxanes. Selected studies were heterogeneous for populations, interventions, and outcomes assessments. Thus, a generalization is difficult. Moreover, the role of concurrent etiologies cannot be excluded in most studies.

Conclusion: Our research emphasizes the importance of evaluating the gonadal axis before treatment in patients considered at risk and testing it at regular intervals or in case of clinical suspicion.

Key words: male hypogonadism; anti-cancer therapy toxicity; testosterone; chemotherapy; immunotherapy; targeted therapy.

Implications for Practice

This review highlights the occurrence of male hypogonadism as a possible anti-cancer treatment toxicity, even if the quality of evidence is still low. As such, it could be useful to develop trial to better understand this adverse event. In clinical practice, it could be useful to evaluate gonadal axis before treatment at risk and in case of typical symptoms, since testosterone replacement therapy may be beneficial in these patients.

Introduction

The improvement of anticancer strategies and the increasing number of therapeutic options such as chemotherapy, targeted therapies, and immune checkpoint-inhibitors, resulted in the last decade in an increased survival in patients with advanced or metastatic cancer.[1,2] There is a growing consensus that, in these patients, quality of life (QoL), together with survival, should be considered as clinical outcomes and that QoL can be influenced by both the disease and anticancer treatment effects. Male hypogonadism is a possible, though neglected, cause of diminished QoL associated with cancer and its treatments.[3,4] While this condition is prevalent in male

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patients with cancer, the role of antineoplastic pharmacological treatment in causing primary or secondary hypogonadism is poorly understood and there are poor standard indications for its investigation in clinical practice.[3,5]

Male hypogonadism is characterized by blood total testosterone (TT) levels lower than 231-350 ng/dL, free testosterone (FT) lower than 170-240 pmol/L, bioavailable testosterone (BT) lower than 100 ng/L, and associated clinical signs and symptoms.[5-8] Asthenia, sexual dysfunction, mood changes, and difficulties in concentration can be confused with cancer-related symptoms, also when combined with objective clinical findings such as anemia, muscle wasting, reduced bone mass, or mineral density and changes in cholesterol levels.[3]

The aim of this systematic literature review was to describe anticancer drugs-related hypogonadism in patients with male with advanced cancers.

Methods

This systematic literature review was performed at the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Italy between February and April 2023. The protocol of this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration code CRD42023410130). The systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The Participants-Intervention/Exposure-Comparison-Outcomes (PICO) structure was used to manage the review (Supplementary Appendix 1).

The aim of this review was to evaluate the prevalence of hypogonadism in patients with male treated with different medical therapies for advanced cancer, the nature of hypogonadism (primary/secondary), and the impact of hypogonadism on QoL.

Search Strategy and Selection Criteria

Literature searches were conducted, with a combination of descriptors identified using Medical Subject Headings (MeSH) terms and related terms, in the electronic databases PubMed (National Library of Medicine, NLM), Embase, and the Cochrane Library databases.

The period for the search was from January 1, 1945 to February 28, 2023, this wide interval was useful not to miss articles on chemotherapy, still in use in some contexts. The keywords and research strings are reported in Supplementary Appendix 1. Inclusion criteria were: prospective observational (PO) and retrospective observational (RO) studies, and case reports (CRs) or case series (CS), conducted in male adult patients and articles in English language only.

A few randomized clinical trials (RCT) were found which evaluated testosterone replacement therapy (TRT) in selected hypogonadal patients. Due to the different primary aim and to limited data reported in these RCTs regarding baseline or previous therapies, as well as other possible causes of hypogonadism in history, they were excluded from this review.

In addition, the search excluded studies that concerned only females (in studies with both sexes, only data concerning male sex were selected), hematological malignancies, prostate cancer, patients treated with surgery or radiotherapy involving gonads or hypophysis/hypothalamus. Thus, we focused this review on male hypogonadism because typical symptoms are similar to therapies adverse events or cancer-related symptoms. Moreover, male hypogonadism is more suitable to replacement therapy for palliative purpose than female hypogonadism, due to easier detection and treatment opportunities. We decided to exclude from this review hematological malignancies due to the different clinical history and treatments. We also excluded studies in advanced prostate cancer, where hypogonadism is a desired effect of therapy and testosterone replacement could increase the risk of recurrence, although evidence is conflicting.[9]

We also excluded studies on cancer survivors off therapy, while focusing on patients in active therapy. Additionally, articles citing hypogonadism without making prevalence or risk data available were also excluded.

The negative filters on databases were: only full text available studies, narrative or systematic reviews and meta-analyses that we used to complete the research with gray literature (also obtained from references of studies included in the research). Articles resulting from the search were screened and selected independently by 2 reviewers (G.M. and L.Z.). In case of doubt for eligibility between the reviewers, a consensus discussion was made: the uncertain articles were discussed in a team composed of 5 reviewers (G.M., L.Z., M.S., E.Z., A.C.). For non-selected articles, reviewers will keep track of the reason for the exclusion only for studies assessed in full text.

Data Extraction and Quality Assessment

Information extrapolated from the selected studies was collected in a Microsoft Excel spreadsheet (variables string in Supplementary Appendix 1), by the reviewers (G.M. and L.Z.). For each study, the risk of bias was independently assessed by G.M. and L.Z., according to the tool developed by Murad et al (for C.R.) and following the Newcastle-Ottawa scale (for observational studies).[10,11] G.T. helped in the descriptive analysis of the data and in the construction of the Forest plot.

There was no funding source for this study.

Results

Search Results

We screened 4488 articles from 3 databases: 2723 (PubMed), 1570 (Embase), 195 (Cochrane), and 14 were found by manual search within included articles and screened reviews and meta-analysis (Fig. 1). We selected 69 articles for a full text review; of these we excluded 41 (reasons listed in Fig. 1). Data extraction was performed in 28 articles, of these 11 were CR/CS, 17 observational studies, of which 13 PO and 4 RO. To reduce the heterogeneity of the results, we organized these articles according to drug categories (targeted therapy, immunotherapy, chemotherapy, and others). To summarize the treatments and cancers evaluated in all the studies, we developed Table 1. Moreover, to describe the prevalence of hypogonadism among patients evaluated in each study, we developed the Forest plot in Fig. 2. It must be noted that the data extracted from the study to elaborate the Forest plot however suffer of a high heterogeneity due to patient characteristics, treatments, study design, and methods for evaluating hypogonadism; thus not allowing to perform a meta-analysis.

The most important characteristics of the studies are listed in Tables 2-4.

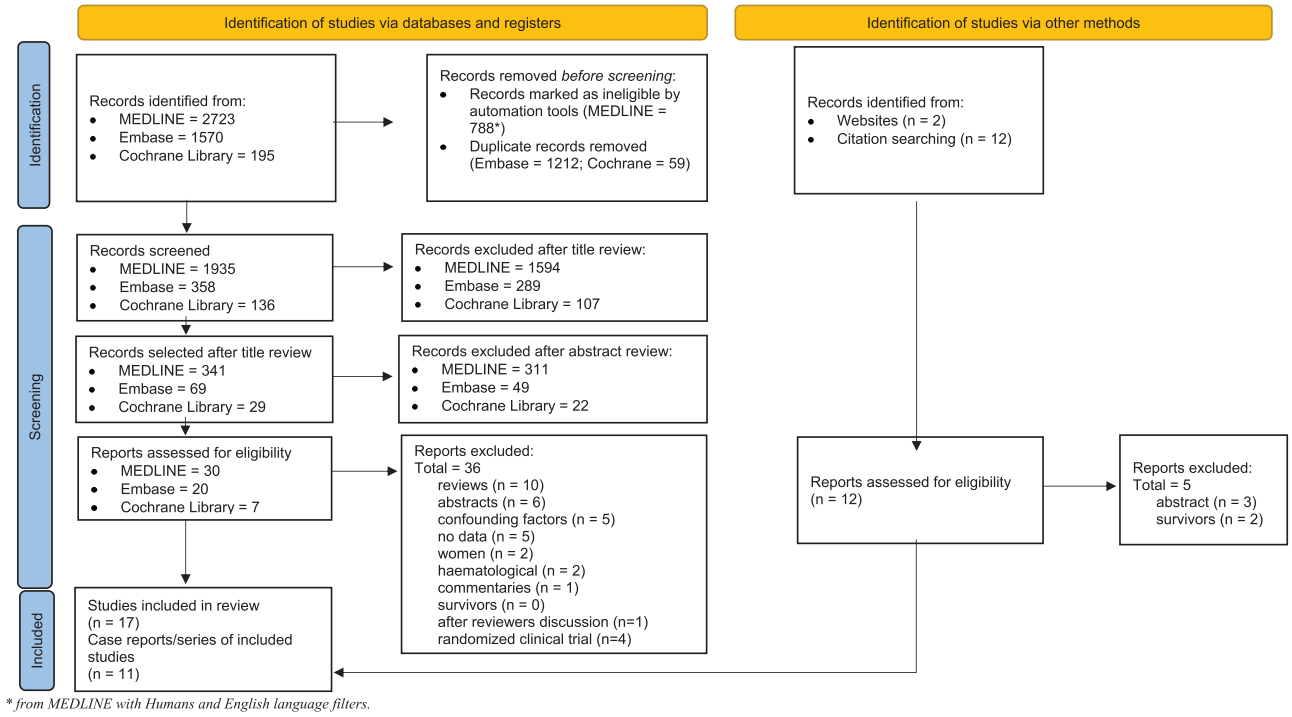

Figure 1. Search strategy flowchart. From: Page et al.[12] For more information, visit: http://www.prisma-statement.org/

Table 1. Histologies and therapies founded as associate with hypogonadism.

Histology	Targeted therapy (*n* male)	Immunotherapy (*n* male)	Chemotherapy (*n* male 463) no prevalence for individual chemotherapy	Others (*n* male)
Lung	Crizotinib (74)	Durvalumab, atezolizumab, nivolumab (8)	Platinum-based, paclitaxel, gemcitabine, 5-FU, capecitabine	
Thoracic others			Platinum-based, paclitaxel, gemcitabine, 5-FU, capecitabine	
Colo-rectal	Crizotinib (1)	anti-CTLA4 plus anti-PD-L1 (5)	Platinum-based, paclitaxel, gemcitabine, 5-FU, capecitabine	
Gastrointestinal others			Platinum-based, paclitaxel, gemcitabine, 5-FU, capecitabine	
Head & neck squamous		Nivolumab (1)	Platinum-based, paclitaxel, gemcitabine, 5-FU, capecitabine	
Thyroid	Vantedanib (25)			
Neuroendocrine		anti-CTLA4 plus anti-PD-L1 (5)		PRRT (38)
Melanoma		Ipilimumab, nivolumab, atezolizumab, pembrolizumab (393)		
Renal	Pazopanib, sunitinib, sorafenib, axitinib, temsirolimus, everolimus (231)			
Genitourinary others		Anti-CTLA4 plus Anti-PD-L1 (21)	Platinum-based, paclitaxel, gemcitabine, 5-FU, capecitabine	
Adrenal carcinoma		Ipilimumab-Nivolumab (1)		Mitotane (26)
GIST	Imatinib (2)			

Abbreviations: 5-FU, 5-fluorouracil; CTLA-4, cytotoxic T-lymphocyte antigen-4; GIST, gastrointestinal stromal tumors; PD-(L)1, programmed death-(Ligand)1; PRRT, peptide receptor radionuclide therapy.

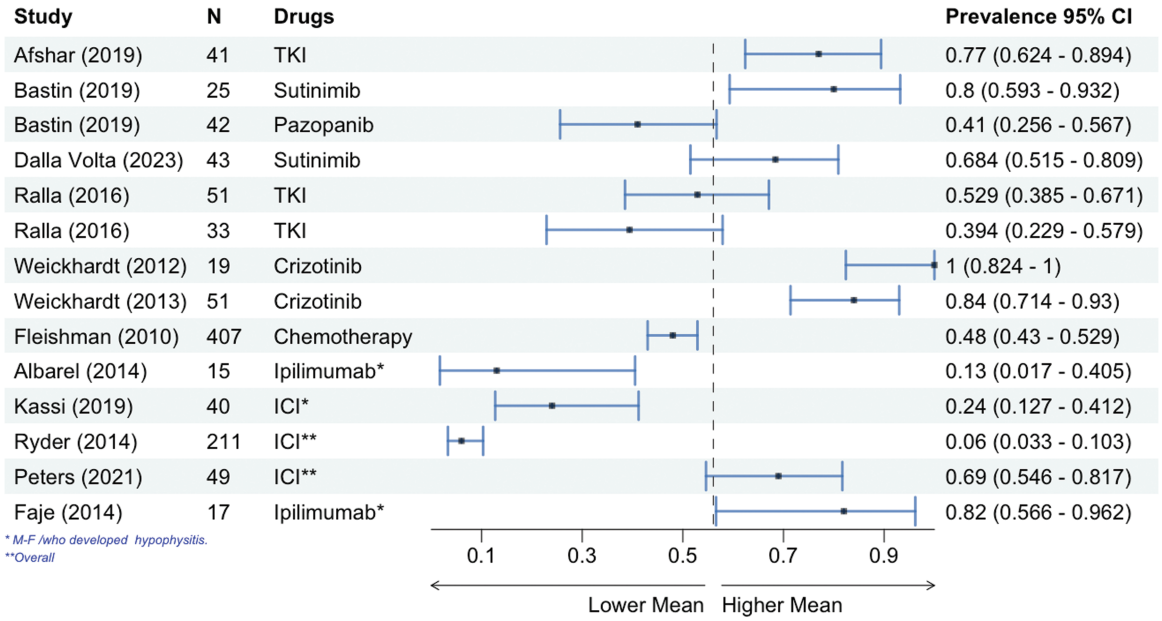

Figure 2. Search strategy flow-chart. Forest plot illustrating the prevalence of male hypogonadism during different anticancer drugs in selected observational studies. The dashed line represents the overall mean of the prevalence across the different studies. The extremes of the confidence interval (CI, 95%) around the prevalence were computed using the binomial test. ICI: immune-checkpoint-inhibitor. TKI: tyrosine kinase inhibitor.

Targeted Therapy

We selected 10 studies concerning targeted therapy, 3 CRs, 7 OS including overall 349 patients (Table 2).[13-22]

Afshar et al[13] found low TT in 77% of a population of patients affected by mRCC treated with TKI (100% of patients receiving pazopanib and none from the axitinib group). The majority of patients had secondary hypogonadism (86.3%).

In the Bastin et al[14] study, 80% of patients with mRCC on sunitinib were hypogonadal compared to less than half patients treated with pazopanib.

In another study[15] on 13 patients with mRCC 68% developed hypogonadism after sunitinib, which was secondary in 61%, primary in 15% and in subclinical 23% of cases.

Finally, Ralla et al[16] considering both patients affected by localized renal cell carcinoma (loRCC) and mRCC found a 52.9% of patients with hypogonadal in the mRCC and 39.4% in the loRCC group.

The effect of crizotinib was investigated for the first time in a prospective cohort of 38 patients with non-small cell lung cancer (NSCLC).[17] All patients had low TT after crizotinib compared with 32% in the control group. Furthermore, 50% of crizotinib-treated patients were symptomatic for fatigue. The nature of hypogonadism was suggested to be secondary.

A complementary, multicenter, PO was conducted by the same authors to relate TT and FT values to hypogonadism symptoms and to test TRT effectiveness.[18] Among crizotinib-treated patients 84% were hypogonadal, FT was low in most of cases. Using the Androgen Deficiency in Aging Males (ADAM) questionnaire almost 80% of patients with low TT or FT were symptomatic. Of these, 9 patients were treated with TRT, resulting in symptom improvement and recovered TT values within 2 months for 5 patients, whereas patients who had persistent low TT values did not show clinical benefit, suggesting possible underdosing of TRT.

Also, a CS describes hypogonadism in patients treated with crizotinib for NSCLC,[19] while 2 CRs described a symptomatic hypogonadism in patients affected by gastrointestinal stromal tumors (GIST) and treated with imatinib 400 mg/day.[20,21]

One study evaluated gonadal function in 25 males with thyroid cancer (differentiated and medullary) treated with vantedanib.[22] In these patients TT, bioavailable testosterone (BT), FSH, and SHBG were increased, while inhibin B was decreased. Thus, authors hypothesized that this could be due to a Sertoli cells failure, but confirmation is missing.

Immunotherapy

We found 12 studies (2 PO, 3 RO, 5 CRs, 2 CS) which described the occurrence of male hypogonadism during immune checkpoint-inhibitors therapy (Table 3).[23-34] All observational studies described secondary hypogonadism and focused attention on immune-related hypophysitis.[23-27]

In the 2 PO on overall 200 male patients, the prevalence of secondary hypogonadism was between 2% and 13% after anti-CTLA-4 or anti-PD-(L)1 (also in combination).[23,24] Low levels of TT during immunotherapy were also recorded in a retrospective analysis of different RCTs enrolling patients with metastatic melanoma.[25] In a group of 134 male treated with ipilimumab in different trials or expanded access programs, 6 patients were diagnosed with secondary hypogonadism due to hypophysitis and 9 with hypogonadism without hypophysitis.

In the study by Peters et al,[26] more than half of 49 patients with normal baseline TT, developed secondary hypogonadism after immunotherapy. Three patients were treated with TRT, resulting in a subjective improvement of fatigue. In another similar RO, 9% of patients had secondary hypogonadism.[27]

Table 2. Studies on targeted therapy-related hypogonadism.

Author, Year, Study design	Patients, (*n* M/F) and cancer prevalence	Primary outcome	Anticancer drugs	Study design for hypogonadism detection	Biochemical cut-off values for hypogonadism	Hypogonadism prevalence (%): total (primary/secondary)	QoL/symptoms assessment and correlation with hypogonadism	Correlation of hypogonadism with anticancer drug	Limitations
Afshar, 2019[13]	Patients: 41/0 Only mRCC	To assess a relation between targeted therapy and hypogonadism	Pazopanib 41.4% axitinib 34.1% sunitinib 19.5%	PO Comparison with normality data	TT <350 ng/dL	77% (13.6/86.3) None of patients on axitinib All patients on pazopanib were hypogonadal 5 patients treated with sunitinib	NA	Univariate analysis Correlation between time on targeted therapy and TT level	Sample size No pre-anticancer therapy measurements Blood sample timing No correction for confounding factors
Bastin, 2019[14]	Patients: 63/0 Only mRCC	To evaluate LH-TT relation during 1st and 2nd line targeted therapy	Sunitinib Pazopanib Everolimus	PO Comparison with baseline levels	TT <300 ng/dL	Sunitinib: 80% (10/90) Pazopanib: 41% (9/91)	NA	Univariate analysis indirect correlation between sunitinib, TT and LH levels Secondary hypogonadism was significantly less frequent during pazopanib than during sunitinib	Sample size Blood sample timing No correction for confounding factors
Dalla Volta, 2023[15]	Patients: In 30/0 cross sectional cohort 13 in prospective cohort Only mRCC	To assess gonadal function in patients with mRCC on first-line therapy with sunitinib	Sunitinib	PO Comparison with baseline levels (in prospective cohort)	TT <350 ng/dL FT <63 pg/mL	After 9 months 68.4% (15/7)	FACT-G only FT-QoL relation 6 patients treated with TRT had benefits on FACT-G global score (median improvement of 11.5 points)	Descriptive, pre- and post-therapy TT change	Sample size Blood sample timing No correction For confounding factors
Ralla, 2016[16]	Patients: 51/0 mRCC 33/0 loRCC mRCC loRCC	To investigate the prevalence of late onset hypogonadism in patients mRCC and loRCC, treated with targeted therapy	Sunitinib, Sorafenib, Pazopanib, Axitinb Everolimus, Temsirolimus	PO Comparison with normality data	EAU criteria: ≥2 symptoms + 2 separate measurements of TT <8 or 8 nmol/L < TT <12 nmol/L with FT <243 pmol/L HIM criteria; TT <300 ng/dL MMAS criteria ≥ 3 clinical symptoms + TT <200 ng/dL or TT >200 ng/dL with fT <8.91 ng/dL)	For mRCC vs loRCC: Using EAU criteria: 13.7% vs 15.2% Using HIM criteria: 52.9% vs 39.4% Using MMAS criteria: 47.1% vs 21.2% LH and FSH values were in range	ADAM, QLQ-C30, IIEF-5 A significant difference between these loRCC and mRCC was found for ADAM score, hip-to-waist ratio, and testicular volume	Multivariate analysis Sexual hormones levels had no significant difference in mRCC vs loRCC	Sample size Heterogeneity in anticancer treatments No pre-anticancer therapy measurements No correction for confounding factors
Weickhardt, 2012[17]	Patients: 19/0 patients in crizotinib group 19/0 patients in control group Only NSCLC	To evaluate hypogonadism prevalence, TRT effectiveness in crizotinib treated patients	Crizotinib	PO Case-control groups	TT <241 ng/dL FT <9 ng/dL	100% (NA) patients in crizotinib group had low TT and 90% had low FT 32% (NA) patients in control group had low TT, FT was not assessed in this group	50% of fatigue G1-2 (CTCAE) in crizotinib group No CTCAE available for the control group	Univariate analysis Correlation between crizotinib use decreased TT level In patients with low TT levels, there were no significant differences in FSH and LH between the 2 groups	Sample size Blood sample timing Hormone panel and ADAM questionnaire only in a subgroup Not patient-reported assessment of symptoms

Table 2. Continued

Author, Year, Study design	Patients, (*n* M/F) and cancer prevalence	Primary outcome	Anticancer drugs	Study design for hypogonadism detection	Biochemical cut-off values for hypogonadism	Hypogonadism prevalence (%): total (primary/secondary)	QoL/symptoms assessment and correlation with hypogonadism	Correlation of hypogonadism with anticancer drug	Limitations
Weickhardt, 2013[18]	Patients: 32/0 patients in crizotinib group 1 2 other groups as per Weickhardt 2012 Cancer prevalence (n): 50 NSCLC, 1 GI	To evaluate hypogonadism prevalence, SHBG and albumin levels, TRT effectiveness in crizotinib treated patients	Crizotinib	PO Case-control groups	TT below LNL in different assays	84% of patients in group 1 had low TT (NA)	ADAM questionnaire 79% of patients with low TT and 84% of patients with low FT had symptoms of androgen deficiency hypogonadism induced by crizotinib had a clinically significative effect TRT was used in 9 patients and 5/9 reported symptoms improvement	Univariate analysis Correlation between TT and crizotinib use	Sample size Blood sample timing Hormone panel and ADAM questionnaire only in a subgroup
Sargis, 2015[19]	Patients: 5/2 Only NSCLC	To describe the effects of crizotinib on multiple hormonal axes	Crizotinib	CS Comparison with normality data	TT <different thresholds, range 180-280 ng/dL FT <90 pg/mL	80% (75/25) of male 0% of female	NA	Descriptive	- Sample size - Blood sample timing No correction for confounding factors No baseline measurements
Tanriverdi, 2011[20]	Patient: 1/0 GIST	To describe a case of hypogonadism associated with gynecomastia and testicular hydrocele in patient treated with imatinib	Imatinib	CR Comparison with normality data	TT 240 ng/dL Estrogen 59.6 pg/mL, above normal limits LH and FSH in range	Normogonadotropic hypogonadism	No tools were mentioned, gynecomastia, and unilateral hydrocele After discontinuing imatinib there was a partial regression of symptoms	Descriptive After discontinuing imatinib there was an increase in TT	Not clear follow-up Blood sample timing No baseline measurements Lack of challenge/rechallenge phenomenon Not discussed confounding factors
Kim, 2005[21]	Patient: 1/0 GIST	To describe a case of hypogonadism associated with gynecomastia and testicular hydrocele in patient treated with imatinib	Imatinib	CR Comparison with normality data	TT 230 ng/dL LH in range and FSH 14.1 IU/L, above the threshold	Possible secondary hypogonadism	No tools were mentioned, gynecomastia, and unilateral hydrocele Decrease libido and impotence were noted Gynecomastia improved after using TRT	Descriptive	Not clear follow-up Blood sample timing No baseline measurements
Brassard, 2011[22]	Patients: 25/14 Post hoc analysis of 2 RCT Only thyroid cancer	To assess the endocrine effects of vandetanib in patients with thyroid cancer	Vantedanib	PO Comparison with normality data, patients treated with only placebo were few to be defined as a control group	Tested TT, BT, SHBG, LH and FSH	No prevalence of hypogonadism Increase in TT (+ 76 ng/dl) and BT (+ 47 ng/dl) in patients treated with vandetanib SHBG increased after vantedanib	NA	Univariate, analysis Correlation between vantedanib use and TT, BT, SHBG, FSH (increased) and inhibin (decreased) levels	Sample size No prevalence of hypogonadism No correction for confounding factors

Abbreviations: ADAM, Androgen Deficiency in Aging Males questionnaire; BT, bioavailable testosterone; CR, case report; CS, case series; CTCAE, common terminology criteria for adverse events; EAU, European association of urology; FSH, follicle stimulating hormone; FT, free testosterone; GI, gastrointestinal; GIST, gastrointestinal stromal tumors; HIM, hypogonadism in male study (criteria); IIEF-5, International Index of Erectile Function Questionnaire-5; LH, luteinizing hormone; LNL, lower normal limit; loRCC, localized renal cell carcinoma; MMAS, Massachusetts male aging study (criteria); mRCC, metastatic renal cell carcinoma; NA, not assessed; NSCLC, non-small cell lung cancer; PO, prospective observational; QLQ-C30, Quality of Life questionnaire-C30; SHBG, sex hormone binding globulin; TRT, testosterone replacement therapy; TT, total testosterone.

Table 3. Studies on immunotherapy-related hypogonadism.

Author, Year, Study design	Patients, (*n* M/F) and Cancer prevalence	Primary outcome	Anticancer drugs	Study design for hypogonadism detection	Biochemical cut-off values for hypogonadism	Hypogonadism prevalence (%): total (primary/secondary)	QoL/symptoms assessment and correlation with hypogonadism	Correlation of hypogonadism with anticancer drug	Limitations
Albarel, 2014[23]	Patients: 15 of 131 treated patients developed hypophysitis, of these 10/5 were studied with hormonal panels Only Melanoma	To analyze the clinical, biological, and radiological characteristics of autoimmune hypophysitis	Ipilimumab	PO Comparison with baseline levels	NA	13% (0/100) of patients with hypophysitis	No tools used to define symptoms 100% of patients showed hypophysitis symptoms 1 patients received TRT. No outcomes were reported	Descriptive	Sample size Blood sample timing No correction for confounding factors
Kassi, 2019[24]	Patients: 195/144 Only Melanoma	To describe irAEs in patients treated with anti-CTLA4 and anti-PD(L)1, either as monotherapy, combination, or sequential treatment	pembrolizumab, ipilimumab, nivolumab, atezolizumab, ipilimumab-nivolumab	PO Comparison with baseline levels	NA	2% (0/100) of total and 24% of patients with anterior hypophysitis	NA	Descriptive regarding hypogonadism	- No correction for confounding factors
Ryder, 2014[25]	Patients: 211 (134/77) studied for hypophysitis 9% of 211 had hypophysitis Only Melanoma	To evaluate the prevalence of immune related adverse events (irAEs)	Anti-CTLA-4 alone or association with anti-PD-1 (ipilimumab; ipilimumab-nivolumab)	RO Comparison with baseline levels	TT <62.8 pmol/L	2% (NA) of patients developed a clear hypophysitis associated hypogonadism 4% (NA) patients had low-testosterone levels without hypophysitis	NA	Descriptive	TT cut-off too low vs guidelines Poor hormonal panel (no LH/FSH) Blood sample timing No correction for confounding factors No/short duration of follow-up
Peters, 2021[26]	Patients: 49/0 Cancer prevalence: Prostate 30% Basal cell carcinoma 20% Bladder 10% CRC 10% Lymphoma 10% NET 10%	To describe low TT in men treated with immunotherapy and benefits after TRT	Pembrolizumab, ipilimumab, nivolumab	RO Comparison with baseline levels	TT <300 ng/dL 24% of patients had low TT at baseline	69% (0/100)	No tools used to define symptoms 100% of patients reported fatigue Only 3 patients started TRT. They reported increased energy levels Obesity, enrollment in a clinical trial, adrenal/thyroid dysfunctions were associated with lower TT levels	Multivariable analysis No association between low TT levels and Ipilimumab, Pembrolizumab, or Nivolumab treatment	Sample size Blood sample timing 30% of patients had prostate carcinoma Few details about follow-up
Faje, 2014[27]	Patients: 51/103 Only Melanoma	To evaluate the prevalence of autoimmune hypophysitis	Ipilimumab	RO Comparison with normality data	NA	9% (0/100) in 7 patients TT was undetectable, in 6 TT <129 ng/dL, 1 TT 201 ng/dL in hypogonadal patients LH was <2.2 IU/L, and FSH was <6.5 mIU/mL	NA	Descriptive regarding hypogonadism	No baseline measurements (for TT) Blood sample timing No correction for confounding factors
Brunet-Possenti, 2017[28]	Patient: 1/0 Melanoma	To describe a case of hypogonadism associated with orchitis	Ipilimumab-nivolumab	CR Comparison with normality data	TT <14 ng/dL	100% (100/0)	No tools were mentioned	Descriptive	No baseline measurements Blood sample timing No correction for confounding factors

Table 3. Continued

Author, Year, Study design	Patients, (*n* M/F) and Cancer prevalence	Primary outcome	Anticancer drugs	Study design for hypogonadism detection	Biochemical cut-off values for hypogonadism	Hypogonadism prevalence (%): total (primary/secondary)	QoL/symptoms assessment and correlation with hypogonadism	Correlation of hypogonadism with anticancer drug	Limitations
Nevgi, 2020[29]	Patient: 1/0 adrenocortical carcinoma	To describe a case of autoimmune polyendocrine syndrome	Ipilimumab-nivolumab	CR Comparison with normality data	TT 2.3 nmol/L or 66 ng/dL	100% (100/0)	No tools were mentioned TRT was started resulting in improvements in energy and libido	Descriptive	No baseline measurements Blood sample timing No correction for confounding factors
Davies, 2019[30]	Patient: 1/0 NSCLC	To describe a symptomatic hypogonadism	Durvalumab	CR Comparison with normality data	TT <80 ng/dL	100% (0/100)	No tools were mentioned Profound fatigue, hot and cold flushes, excessive sweating, and a decline in ECOG PS) Testosterone proprionate was started resulting in the resolution of symptoms within few weeks	Descriptive	No baseline measurements Blood sample timing No correction for confounding factors
Lin, 2019[31]	Patients: 4/3 Cancer prevalence (*n*): Lung 3, Periampullary adenocarcinoma 1 Cervix 1 Urothelial 1, Melanoma 1	To describe cases of autoimmune hypophysitis	Pembrolizumab, nivolumab, anti-CTLA4 plus anti-PD-L1	CS Comparison with normality data	NA	28% (0/100), Both patients had very low TT (<0.20 ng/dL)	No tools used to define symptoms 50% anorexia and lethargy Only one patient started topical testosterone gel. No outcome reported	Descriptive	No baseline measurements Blood sample timing No correction for confounding factors
Lupi, 2019[32]	Patients: 3/1 Only NSCLC	To describe cases of autoimmune hypophysitis	Atezolizumab, nivolumab	CS Comparison with normality data	TT <1.75 µg/L	50% (0/100)	No tools used to define symptoms Patients had also adrenal insufficiency (confounding factor)	Descriptive	Unusual cut-off for low TT No baseline measurements Blood sample timing No correction for confounding factors
Lanzolla, 2019[33]	Patient: 1/0 NSCLC	To describe a case of autoimmune polyendocrine syndrome	Atezolizumab	CR Comparison with normality data	TT 1.5 ug/L	100% (0/100)	No tools used to define symptoms Patients had also autoimmune polyendocrine syndrome (confounding factor)	Descriptive	No baseline measurements Blood sample timing Presence of a confounding factor
Fosci, 2021[34]	Patient: 1/0 Hypopharyngeal carcinoma with antero-hypophyseal metastasis (confounding factor)	To describe cases of autoimmune hypophysitis	Nivolumab	CR Comparison with normality data	TT 0.5 nmol/L or 14 ng/dL	100% (0/100)	No tools used to define symptoms	Descriptive	No baseline measurements Blood sample timing No correction for confounding factors

Abbreviations, CR, case report; CS, case series; CRC, colorectal cancer; CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG-PS, eastern cooperative oncology group performance status; FSH, follicle stimulating hormone; irAEs, immune-related adverse events; LH, luteinizing hormone; NA, not assessed; NET, neuroendocrine tumor; NSCLC, non-small cell lung cancer; PD-(L)1, programmed death-(Ligand)1; PO, prospective observational; RO, retrospective observational; TRT, testosterone replacement therapy; TT, total testosterone.

Table 4. Studies on chemotherapy and other anticancer drugs-related hypogonadism.

Author, year, study design	Patients number (M/F) and cancer prevalence	Primary outcome	Anticancer drugs	Study design for hypogonadism detection	Biochemical cut-off values for hypogonadism	Hypogonadism prevalence (%): total (primary/secondary)	QoL/symptoms assessment and correlation with hypogonadism	Correlation of hypogonadism with anticancer drug	Limitations
Chemotherapy									
Garcia, 2006[35]	Patients: 31/0 cancer patients 25/0 controls Cancer prevalence: lung 59%, CRC 13%, CUP 6%, others 23%	To evaluate the correlation between TT, FT, BT, SHBG, LH and TNF-α, IL-6, IGF-1, and ghrelin.	CT at any time 58% platinum-based 32% only mentioned gefitinib and interferon CT within 1 year 26%	PO Case-control groups	NA	Prevalence not assessed. Hormonal levels lower in cancer than in control group: TT 11.8/13.41 nmol/L FT 0.08/0.14 nmol/L BT 1.4/3 nmol/L LH 20.45/5.69 IU/L	ESAS-VAS for appetite (mean value cancer/control: 3/4.9) Direct correlation between FT and appetite	Univariate analysis No correlation between opioids and sex hormones levels	Sample size No prevalence of hypogonadism Few details about CT Blood sample timing No correction for confounding factors Short duration of follow-up
Fleishman, 2010[36]	Patients: 407/0 Cancer prevalence: thoracic 17% GI 39% GU 7% -hemato 25% H&N 10% -others 1%	To evaluate hypogonadism prevalence and its correlation with functional status and QoL	Platinum based 43% Paclitaxel 16% Gemcitabine 10% 5-FU 22% Capecitabine 6%	PO Comparison with normality data	TT <300 ng/dL FT <52 pg/dL BT <95 ng/dL	48% (NA)	FACTP (NA) The overall QoL and sexual function scores were significantly reduced in hypogonadal patients Correlation between obesity, opioid, white ethnicity, and the sexual function subscale on the FACTP	Multivariate analysis No correlation between chemotherapy opioids and sex hormones levels	Poor hormonal panel (no LH/FSH) No preCT measurements No details about time on therapy No correction for confounding factors No/short duration of follow-up
Other therapies									
Elston, 2021[37]	Patients: 23/11 patients in PRRT group 15/17 patients in control group Only NET	To assess the prevalence of clinically significant hypopituitarism a minimum of 2 years following PRRT for NET	PRRT	PO Case-control groups	NA	47% of men in PRRT group (45/55). 80% of patients with primary hypogonadism had received prior CT 33% of men in control group (40/60) Median time from PRRT to secondary hypogonadism was 96 months vs 68 months for primary hypogonadism	NA	Univariate analysis No significative differences in secondary hypogonadism between the PRRT and non-PRRT groups	Sample size (but rare cancer) No details about symptoms No hormonal panel before PRRT (but control group)
Nader, 2006[38]	Patients: 10/0 Only recurrent adrenal carcinoma	To understand the mechanism by which mitotane increases steroid-binding proteins concentration	Mitotane	PO Comparison with normality data	TT <300 ng/d Non-SHBG bound T <130 ng/dl	40% (NA) Low non SHBG bound T in 70% Increased SHBG and CBG in 80% and 90% of patients, respectively	NA	Multivariate analysis Correlation between mitotane use and SHBG (increase)	Sample size (but rare cancer) Few details about patients' history and confounding factors Poor hormonal panel (no LH/FSH) No baseline measurements
Vikner, 2021[39]	Patients: 15/35 Local adrenal carcinoma 52% Advanced adrenal carcinoma 48%	To define the hormonal and metabolic toxicity of mitotane and how to manage it	Mitotane	RO Comparison with normality data	NA	Prevalence not assessed estrogen, TT, LH and SHBG increased 6 months, FT levels did not increase. SHBG levels decrease after mitotane cessation, while sex hormones did not change after mitotane discontinuation	No tools used to define symptoms 4 patients presented hypogonadal symptoms. After initiation of TRT, 3 had no benefit, while 1 had improvement in sexual function, but increased gynecomastia	Univariate analysis Correlation between mitotane use and SHBG, LH (increased). These changes were linked to an increase of TT levels	Sample size Few details about other anticancer therapies Blood sample timing No correction for confounding factors No baseline measurements No details about TRT and follow-up

Table 4. Continued

Author, year, study design	Patients number (M/F) and cancer prevalence	Primary outcome	Anticancer drugs	Study design for hypogonadism detection	Biochemical cut-off values for hypogonadism	Hypogonadism prevalence (%): total (primary/secondary)	QoL/symptoms assessment and correlation with hypogonadism	Correlation of hypogonadism with anticancer drug	Limitations
Sparagana, 2008[40]	Patient: 1/0 Ectopic ACTH syndrome of unknown primary origin	To describe a case of symptomatic hypogonadism associated to mitotane	Mitotane	CR Comparison with normality data	TT <400 ng/dl	Primary hypogonadism (TT 220 ng/dl, LH and FSH increased)	No tools used to define symptoms Impotency, reduced testes size TRT used with an improvement in libido	Descriptive	Blood sample timing No baseline measurements phenomenon Not discussed confounding factors

Abbreviations, 5-FU, 5-fluorouracil. ACTH, adrenocorticotropic hormone. BT, bioavailable testosterone. CBG, corticosteroid binding globulin. CR, case report. CRC, colorectal cancers. CT, chemotherapy. CUP, cancer of unknown primary. ESAS, Edmonton symptom assessment system. FACT-P, Functional Assessment of Cancer Therapy-Prostate score. FSH, follicle stimulating hormone. FT, free testosterone. GI, gastrointestinal. GU, genitourinary. H&N, head and neck. IGF-1, insulin-like growth factor-1. IL-6, interleukin-6. LH, luteinizing hormone. NA, not assessed. NET, neuroendocrine tumor. PO, prospective observational. PRRT, peptide receptor radionuclide therapy. QoL, quality of life. RO, retrospective observational. SHBG, sex hormone binding globulin. TNF-α, tumor necrosis factor-α. TRT, testosterone replacement therapy. TT, total testosterone. VAS, visual analog scale.

Two CRs described immune-related primary hypogonadism. In particular, Brunet-Possenti et al[28] reported a case of primary hypogonadism due to an acute bilateral orchitis during ipilimumab plus nivolumab combination therapy for a metastatic melanoma. Nevgi et al[29] described a patient with metastatic adrenocortical carcinoma who developed, during a treatment with an anti-PD-L1, a multiorgan autoimmunity during (hepatitis, adrenalitis, and thyroiditis) with immune-related primary hypogonadism without clinical signs of orchitis. It is important to note that the last patient was taking high doses of opioids and underwent high doses of corticosteroids.

Other CR and CS[30-34] showed cases of secondary hypogonadism, some with the subsequent use of TRT, and symptoms improvement.[30]

Chemotherapy

Only 2 PO studies reported hypogonadism in male patients during an active chemotherapy (CT; Table 4).[35,36]

The single-center, cross-sectional study from Garcia et al[35] included 31 male cancer patients undergoing both CT and targeted therapy (only mentioned) and 25 male controls. A statistically significant decrease in FT level was the main result, while the prevalence of hypogonadism was not mentioned. LH levels were higher in patients with cancer and in those treated with platinum-based drugs; however, this finding was not statistically significant. Overall, previous CT, type of therapy, histology, stage, and the presence or absence of opioid therapy did not correlate with hormone values.

Fleishman et al[36] conducted a multicenter study evaluating TT and FT on 407 patients. Patients treated with platinum salts were most represented among the hypogonadal, followed by patient treated with antimetabolites (5-fluorouracil), capecitabine, gemcitabine, and paclitaxel. The prevalence of hypogonadism was 48%, with a mean TT of 176 ng/dL. Finally, the total QoL score, and the items dedicated to sexual function decreased significantly in hypogonadal patients.

Other Therapies

Peptide Receptor Radionuclide Therapy

A multicenter cohort study was conducted to evaluate the use of PRRT in 23 male patients with neuroendocrine tumors in comparison with 15 male patients in the control group (Table 4).[37] Patients with known pituitary problems were excluded, but a baseline hormone levels' evaluation was absent. Seven patients had primary hypogonadism (5 from the PRRT group and 2 in control group) and 9 had secondary hypogonadism (6 from PRRT and 3 from control group).

Mitotane

Mitotane-induced hypogonadism was considered in 2 PO and 1 CR (Table 4).[38-40] Nader et al[38] included 10 males affected by recurrent adrenal carcinoma receiving mitotane for at least 6 months. Of these, the 40% developed low TT levels.

The study by Vikner et al[39] evaluated different hormonal axes and metabolic profiles during the first year of therapy in 15 male patients. Mitotane was associated with a SHBG, LH, estrogens, and TT *increase* (53%), while FT did not change significantly. Mitotane discontinuation lowered SHBG values but did not significantly change hormone levels. TRT was initiated in 4 symptomatic patients. The authors hypothesized

symptoms were due to a decreased dihydrotestosterone production, led by a mitotane inhibition of 5-α-reductase, and an association with an increase of estrogens and SHBG values. Patients had no improvements in symptoms except for one patient who experienced gynecomastia and it was necessary to associate letrozole to TRT, for symptoms relief.

Sparagana[40] published a case of primary hypogonadism in a patient with an ectopic ACTH production treated with mitotane. The patient developed impotence and reduction of testicular volume. The start of a TRT led to a benefit on libido and impotence.

Discussion

To the best of our knowledge, this is the first systematic literature review on the role of an active anti-cancer drugs in the development of male hypogonadism in advanced patients with cancer. Relating testosterone only to sexual function and the stigma accompanying this molecule, often associated with doping purposes, could have contributed to this neglect.

While male hypogonadism is a non-negligible adverse event of tyrosine kinase inhibitors, immune checkpoint inhibitors, and chemotherapy, as well as other anticancer drugs it is seldom considered in clinical practice and poorly studied (Table 1). Hypogonadism due to the overall psychophysiological impact of cancer and its therapies can contribute to symptoms (fatigue, loss of appetite, weight loss, lowered libido, and mood) which can induce clinicians to modify a patient therapeutic strategy.[3,4] Hence, the importance of considering this condition and of producing studies on replacement therapy. Male hypogonadism induced by targeted therapies was primarily investigated during anti-angiogenic treatment for mRCC (Table 2). Studies on sunitinib, pazopanib, and axitinib in mRCC were inconsistent with respect to the nature of hypogonadism, and it is not possible to define specific association of individual drugs with hypogonadism.[13-16]

The only targeted therapy studied as a risk factor in patients with advanced NSCLC was crizotinib although evidence was limited to 70 patients in 2 complementary studies and a in third study with a very small sample size (Table 2).[17-19] Two CRs described hypogonadism in patients treated with imatinib for GIST.[20,21]

Literature regarding TT in patients with thyroid cancer treated with vantedanib and in patients treated with mitotane for adrenal carcinoma was limited and with several bias, thus further investigations are needed.[22,38-40] The pharmacodynamic mechanism implicated in this toxicity from targeted therapy is not well understood, but probably related to an inhibition of neuroendocrine pathways regulating hormone production (in the hypothalamus, pituitary, or gonads) or to an alteration of the glandular microcirculation eventually induced by antiangiogenetics.

Immune-induced male hypogonadism has been described with several immune-checkpoint inhibitors, most often with anti-CTLA-4 or during combination schemes, but anti-PD(L)1s are also associated with hypogonadism (Table 3).[24,26,30-34]

A greater number of studies reported male secondary hypogonadism as an immune-related adverse event, due to autoimmune hypophysitis.[23-27,31,32,34] Hypophysitis is a known toxicity of immunotherapy, it is not always related to damage to gonadotropic cells, but their axis must be evaluated.[41] It should also be noted that there are cases of primary hypogonadism (due to orchitis or gonadal dysfunction without inflammation) or of an unknown nature.[28-30,33]

Only 2 PO studies evaluated blood testosterone levels in patients undergoing chemotherapy for advanced cancers (Table 4).[35,36] and these studies the specific role of individual chemotherapeutic agents was not assessed. Hypogonadism during chemotherapy is poorly documented. Instead, this condition is well studied as a chronic toxicity in cancer survivors, especially patients with pediatric or testicular cancers.[42-47]

The mechanism that concerns hypogonadism after PRRT depends on the therapy mechanism of action, in fact the radiopharmaceutical binds to the cells having somatostatin receptors, which are present in the gonadotropic cells of the pituitary gland. In the only study on PRRT, this therapy was not a predictor of male hypogonadism (Table 4).[37]

Only few patients with cancer in the reported literature were treated with TRT for male hypogonadism, even if international guidelines do not pose contraindications in this population.[5-7,48-50] Most of the patients receiving TRT showed improved symptoms; meanwhile lack of benefit from TRT was often associated with persistent low TT levels.[15,17,18,21,23,26,29,39,40] Thus, it is possible that some patients received an under-dosed therapy. It is still to be defined if transdermal or intra-muscular formulation, and eventually which ester, is to be preferred in this indication. Available data derive only from anecdotal experience, and observational studies and this question it is not answered also by the available RCTs.

We selected 4 RCTs designed to evaluate TRT in patients with cancer on active chemotherapy or targeted therapy. TRT appeared active on symptoms in 3 out of 4 RCTs.[51-54] However, we did not consider the RCTs in this review because they did not show clearly therapies and patients' characteristics, that could have an impact on the development of hypogonadism. Furthermore, our systematic review was descriptive and the great heterogeneity in population, intervention, and outcomes evaluation did not allow a meta-analysis.

The selected studies have several limitations (Tables 2-4, last column). Studies results are difficult to compare because the populations are very heterogeneous, even within the same pharmacological groups, considering both treatment and patient characteristics. The definitions of hypogonadism used are also different and, sometimes, they do not comply with the guidelines of endocrinological societies.[5-8,48-50] In many studies, a hormonal panel at baseline was absent, blood sampling was carried out at different times, and not in the morning. This bias in some studies was balanced by using a control group. Several studies did not indicate the prevalence of primary/secondary hypogonadism because the hormonal panel was not designed for studying the gonads-pituitary-hypothalamus axis. Moreover, in many studies the blood test was unique, or the follow-up was short.

A major limitation is that the role of concurrent etiologies of hypogonadism cannot be excluded in most studies because other causes of hypogonadism at baseline were not considered, such as complications of advanced cancer, comorbidities, or symptomatic drugs (eg, antidepressants and opioids).[3,4]

Conclusions

This review aims to bring attention to the problem of male hypogonadism in daily oncology practice. The available evidence supports the suggestion that hypogonadism and its

management have an impact on symptom burden and the quality of life of patients with cancer. Replacement therapy may be helpful; however, larger, generalizable randomized trials are needed to define the benefit of TRT. From our review, some conditions listed in Table 1 can be considered at risk and support the evaluation of this hormonal axis before treatment. Our results also highlight that more evidence is needed to identify and assess the multiple clinical factors that are likely to contribute to the risk of hypogonadism in these patients and to support better guidelines for assessment and management.

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Author Contributions

G.M. and L.Z. were responsible for study concept and design. G.M., L.Z. performed the literature search, screening, and selection of papers; they also wrote the original draft. G.M., L.Z., and E.Z. handled data extraction. E.Z. supervised all stages of this study and made quality assessment. E.Z., M.S., G.T., and A.C. revised the manuscript; they also reviewed and edited the manuscript. All authors approved the final version to be published.

Conflict of Interest

G.M., L.Z., M.S., and G.T. declare no competing interests. E.Z. has received honoraria from Amgen. A.C. has received honoraria from Angelini, Shionogi, Kyowa Kirin, Molteni, Pfizer/Eli Lilly Italia SPA.

Data Availability

No new data were generated or analyzed in support of this research.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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