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Perspectives on the co-treatment with GnRHa in female patients undergoing hematopoietic stem cell transplantation

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Abstract

Outcomes after hematopoietic stem cell transplantation (HSCT) for patients with both malignant and nonmalignant diseases have improved significantly in recent years. However, the endocrine system is highly susceptible to damage by the high-dose chemotherapy and/or irradiation used in the conditioning regimen before HSCT. Ovarian failure and subsequent infertility are frequent complications that long-term HSCT survivors and their partners face with a negative impact on their QoL. Several meta-analyses of randomized clinical trials showed that gonadotropin-releasing hormone agonist (GnRHa) administration in advance of starting standard chemotherapy decreases the risk of gonadal dysfunction and infertility in cancer patients, but GnRHa use for ovarian protection in HSCT patients is not fully determined. In this review, we are discussing the potential preservation of ovarian function and fertility in pubertal girls/premenopausal women who undergo HSCT using GnRHa in parallel with conditioning chemotherapy, focusing on the current data available and making some special remarks regarding the use of GnRHa.

Key Words
- hematopoietic stem cell transplantation
- GnRHa
- gonadal function
- fertility preservation

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Introduction

Hematopoietic stem cell transplantation (HSCT) is increasingly used for the treatment of both malignant and nonmalignant diseases. Survival after autologous/allogeneic HSCT is no longer the highest concern, as many patients survive the acute complications of the procedure and remain free of their original disease. Instead, long-term side effects are important to recognize and treat (1, 2, 3) to maintain a good quality of life (QoL) for HSCT recipients (4, 5). Gonadal insufficiency and subsequent infertility are frequent problems that long-term HSCT survivors and their partners face with a negative impact on their QoL (4, 5). Beside infertility, premature ovarian failure (POF) can have a significant impact on QoL (6), including hot flashes, risk for osteoporosis and mood lability (7).

Total body irradiation, even low-dose regimen, as well as the chemotherapeutic agents used in the conditioning regimen for HSCT, and the deleterious effects of chronic graft vs host disease implies a risk of consequent gonadotoxicity (8, 9, 10). A review of the literature on gonadal toxicity of HSCT clearly stated that the risk of ovarian damage and POF is very high in HSCT recipients (11). Gonadal damage following HSCT results in a spectrum of gonadal function with varied clinical outcomes (5). Ovarian failure after HSCT has been observed in 65–84% of transplant recipients (5, 12, 13, 14). In patients performing HSCT for hematological malignancies, the incidence of POF is even higher than 90% (15). More than 80% of HSCT recipients present permanent amenorrhea following

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conditioning regimen with cyclophosphamide/total body irradiation (TBI) or cyclophosphamide/busulfan (8, 16). While ovarian dysfunction is nearly universal following myeloablative (MA) conditioning, the risk is unclear after reduced-intensity conditioning (RIC) (7, 17). However, analysis of the contribution of conditioning regimens to gonadotoxicity may be confounded by the disease itself or prior exposure to cytotoxic agents. In addition, there is a considerable difference between prepubertal/postpubertal girls undergoing HSCT (7, 18). When HSCT is performed in prepubertal girls, the risk for future gonadal insufficiency is approximately 50% (19). A half of the prepubertal girls treated with chemotherapy and hyper-fractionated TBI retain adequate ovarian function to enter puberty and menstruate regularly after transplantation (20). Therefore, creating a 'prepubertal milieu' using GnRHa can be regarded as an option for preserving normal gonadal function in young women performing HSCT (8, 21). Although human primordial follicles are not directly under gonadotrophin influence it seems that GnRH co-treatment offers a degree of protection to follicle reserves by decreasing ovarian perfusion and thus minimizing penetration of gonadotoxic agents to the primordial follicles, which leads to the protection of undifferentiated germ-line stem cells and the upregulation of antiapoptotic molecules (21, 22).

It has been demonstrated by several meta-analyses of clinical randomized studies that the use of GnRHa before/during starting standard chemotherapy decreases the risk of gonadal dysfunction and infertility in patients with different types of cancer (23, 24). Still, the possible utility of this technique of preserving normal ovarian function and fertility in HSCT recipients has not yet been established (25).

Methods

This is a literature review from reliable electronic databases conducted between October 2016 and April 2017 using the following key words related to the topic: 'gonadotropin-releasing hormone analogues', 'GnRHa', 'luteinizing hormone-releasing hormone agonist', 'LHRHa', 'gonadal function', 'ovarian failure', 'fertility', 'fertility preservation', 'pregnancy', 'hematopoietic', 'transplantation', 'chemotherapy', 'cancer'. Only articles published in the last five years and several articles of great scientific importance were selected and commented in this review.

The first part of the present review aims at describing the effectiveness of GnRHa co-administration during standard chemotherapy for preservation of normal gonadal function and fertility in young patients with cancer. In the second part, which represents the aim of the present paper, we are discussing the potential preservation of ovarian function and fertility in pubertal girls/premenopausal women who undergo HSCT using GnRHa in parallel with conditioning chemotherapy. In the last part of the review, we make some special remarks regarding the use of GnRHa.

Critical analysis of selected studies

The efficacy of GnRHa co-treatment before/during standard chemotherapy in young cancer patients

GnRHa co-treatment in terms of ovarian protection in cancer patients The role of temporary ovarian suppression with GnRHa before/during chemotherapy in preserving ovarian function and fertility is not unequivocally accepted. Several systematic reviews and meta-analyses of randomized clinical trials (RCT) assessing the efficacy of GnRHa co-treatment (Table 1) showed that GnRHa co-treatment reduces POF and increases the pregnancy rate (PR) in survivors (Table 2) (23, 24, 26, 27, 28, 29, 30, 31). However, other meta-analyses have found that GnRHa given with chemotherapy was associated with increased rates of recovery of regular menses, but the evidence was insufficient to assess outcomes related to GnRHa and ovarian function and fertility pointing to the fact that further investigations are needed (32, 33).

The largest meta-analysis that provides convincing evidence of the protective role of GnRHa in young cancer patients is the one performed by Lambertini and coworkers in breast cancer patients (23), which showed a significant reduced risk of POF and increased number of patients achieving pregnancy in patients receiving GnRHa co-treatment (Table 2). Additionally, the study of Moore and coworkers demonstrated a more favorable disease-free survival (P=0.04) and overall survival rates (P=0.05) alongside with preserving the ovarian function (POF rate at 2 years was 8% in the GnRH arm vs 22% in the standard chemotherapy arm, OR: 0.30, P=0.04) and improved fertility in the GnRHa arm (21% in the GnRHa arm vs 11% in the chemotherapy-alone group, P=0.03) (34).

In 2014, Blumenfeld and coworkers summarized in a meta-analysis that included 1837 patients (1059 in the

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Table 1 Summary of the meta-analyses of RCT assessing the efficacy of GnRHa given before and during chemotherapy in cancer patients.

Reference	No. of patients included	Patient population	Endpoint
Pro			
Lambertini, 2015	1231	BC	POF, PR
Shen, 2015	1062	BC	POF, PR
Del Mastro, 2014	765	BC, HL, ovarian cancer	POF
Sun, 2014	621	BC, HL, ovarian cancer	POF
Yang, 2013	528	BC	Resumption of menses, spontaneous ovulation, PR
Wang, 2013	677	BC	Resumption of menses
Bedaiwy, 2011	340	BC, HL, ovarian cancer	Resumption of menses, spontaneous ovulation
Chen, 2011		Various	Resumption of menses, spontaneous ovulation, PR
Munhoz, 2016	856	BC	Resumption of regular menses, PR
Contra			
Elgindy, 2015	907	Various	Resumption of menstruation, ovarian reserve, PR

BC, breast cancer; HL, Hodgkin lymphoma; POF, premature ovarian failure; PR, pregnancy rate; RCT, randomized clinical trials.

RCT), the pros and cons of using GnRHa to minimize the gonadotoxic effect of chemotherapy and preserve fertility in patients with different types of oncological/autoimmune disorders. The concept underlined was that preventing POF is preferable to treating it, following the dictum 'an ounce of prevention is worth a pound of cure' (35).

Summary of the studies assessing the efficacy of GnRHa in cancer patients in terms of fertility preservation Temporary ovarian suppression with GnRHa during chemotherapy has been studied as a strategy to preserve ovarian function rather than as an option for fertility preservation (36) considering that the recovery of cyclic ovarian function after chemotherapy does not always

Table 2 The results of the meta-analyses of RCT assessing the efficacy of GnRHa given before/during chemotherapy.

Reference	Endpoint	No. of patients	Results GnRHa vs control	*P* value
Pro				
Lambertini, 2015	POF	1231	18.5% vs 33.5%, OR = 0.36	<0.001
	1-year Amenorrhea	882	31% vs 42.9%, OR = 0.55	<0.001
	PR	706	33 vs 9, OR = 1.83	0.041
	DFS	626	19.5% vs 18.8%, HR = 1.00	0.939
Shen, 2015	POF	1064	OR 2.57, 95% CI 1.65–4.01	0.0001
	PR		OR 0.177; 95% CI = 0.92, 1.40	0.09
Del Mastro, 2014	POF	765	OR = 0.43; 95% CI: 0.22–0.84	0.013
Sun, 2014	POF	621	9.66% vs 26.67%, RR of 0.45, 95% CI 0.22–0.92	0.02
Yang, 2013	POF	528	RR of 0.40, 95% CI 0.21–0.75	
	RM		RR = 1.31, 95% CI 0.93–1.85	
	PR		RR = 0.96, 95% CI 0.20–4.56	
Wang, 2013	RM	677	OR 2.681; 95% CI, 1.169–6.146	
Chen, 2011	RM		RR 1.90, 95% CI 1.30–2.79	
	Amenorrhea		RR 0.08, 95% CI 0.01–0.58	
	Ovulation		RR 2.70, 95% CI 1.52–4.79	
	PR		RR 0.21, 95% CI 0.01–4.09	
Bedaiwy, 2011	RM	340	57.22% vs 35.22%	0.03
			OR 3.46; 95% CI, 1.13–10.57	
	Spontaneous Ovulation	98	60.41% vs 22%	0.0002
			OR 5.70; 95% CI, 2.29–14.20	
Munhoz, 2016	RM 6 months	856	OR = 2.41; 95% CI 1.40–4.15	0.002
	RM 12 months	778	OR 1.85; 95% CI 1.33–2.59	0.0003
	PR	218	OR 1.85; 95% CI 1.02–3.36	0.04
Contra				
Elgindy, 2015	RM	907	68.4% vs 59.9%, RR 1.12, 95% CI 0.99–1.27	0.7
	PR		RR 1.63, 95% CI 0.94–2.82	

CI, confidence interval; DFS, disease-free survival; OR, odds ratio; POF, premature ovarian failure; PR, pregnancy rate; RCT, randomized clinical trials; RM, resumption of menses; RR, relative risk.

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imply fertility restoration (36). A prospective observational study performed by Huser and coworkers involving 108 females newly diagnosed with HL who were treated with different types of chemotherapy while receiving GnRHa to preserve ovarian function demonstrated significantly better fertility outcomes among HL patients receiving less gonadotoxic chemotherapy (34.1% in HL patients receiving less gonadotoxic chemotherapy vs 3.1% in the most gonadotoxic chemotherapy group) (37). However, the limitation of the study is that all patients in the trial received GnRHa in addition to different regimens of chemotherapy. Therefore, the protection of GnRHa on ovarian function and fertility preservation could not be appropriately assessed in the lack of a control group not receiving GnRHa. The results of a prospective RCT performed by Demesteere and coworkers also point to the fact that GnRHa co-treatment might have a protective role on fertility outcome (38). The long-term follow-up of patients included in this study (67 of the initial 129 patients) revealed that 53.1% (17/32 patients) and 42.8% (15/35) patients achieved pregnancy in the GnRHa and control groups, respectively (P=0.467). Furthermore, five pregnancies (two in the GnRHa group and three in the control group) occurred in patients with protocol-defined POF (38). However, the authors concluded that triptorelin was not effective in improving fertility considering the high PR observed in both groups (38). The issue of fertility preservation by GnRHa co-treatment was also addressed by Blumenfeld and coworkers in a large retrospective study, which demonstrated a high PR in the GnRHa group (69.7% vs 42.4% in the control group, P=0.0003) (21). Spontaneous pregnancies occurred in 80 women (65.6%) in the GnRHa group in comparison to 25 (37.9%) in the control group (OR=3.12; P=0.0004) (21). In addition, the age for those who spontaneously conceived was 14–38 years in the GnRHa arm compared to 14–30 years in control group suggesting a possible prolongation of the fertile window by almost 10 years (21). After publishing the results of his study, Del Mastro & Lambertini concluded that the data presented are very encouraging, supporting the idea of administering GnRHa before and during gonadotoxic therapy not only for recovery of cyclic ovarian function after chemotherapy, but also for fertility restoration (36). Del Mastro pointed out to the fact that the studies evaluating the efficacy of GnRHa therapy report a very high PR: 61% by Blumenfeld and coworkers (21), 71% by Wong and coworkers (39), 88% by Moore and coworkers (34), suggesting that the temporary suppression with GnRHa during chemotherapy may not be a strategy only for fertility preservation, but also to increase the likelihood of achieving a pregnancy (36).

The potential protective role of GnRHa co-treatment during chemotherapy in young female patients undergoing HSCT

As recommended by major international guidelines, it is of critical importance to discuss with all patients at diagnosis regarding late side effects of therapy and the options for preservation of normal gonadal function and the possibility for future fertility (5, 40, 41). In vitro fertilization (IVF) and embryo cryopreservation, oocyte cryopreservation and ovarian tissue banking are accepted methods for fertility (5). Other options such as temporary ovarian suppression with gonadotropin-releasing hormone analogues (GnRHa) during chemotherapy are still considered experimental (5, 42).

Summary of the studies assessing the efficacy of GnRHa in HSCT recipients in terms of ovarian protection To date, only a few studies have addressed the issue of GnRHa efficacy in terms of ovarian protection in HSCT patients (Tables 3 and 4). Blumenfeld and coworkers compared in a prospective, non-randomized study the rate of POF after HSCT in young women receiving GnRHa in conjunction with gonadotoxic chemotherapy vs chemotherapy alone (21). Eighty-three women undergoing

Table 3 Summary of the studies assessing the efficacy of GnRHa given before and during chemotherapy in HSCT recipients in terms of ovarian function and fertility preservation.

Reference	Type of study	No of patients	Endpoint
Blumenfeld, 2012	Prospective, nonrandomized study	83	COF
Cheng, 2012	Prospective, phase II study	44	COF
Pup, 2014	Retrospective study	17	PR
Phelan, 2016	Prospective study	17	POF
Demesteere, 2016	Prospective randomized study	10	POF
			COF, ovarian reserve (AMH level), DFS

AMH, anti-Mullerian hormone; COF, cyclic ovarian function; DFS, disease-free survival; POF, premature ovarian failure.

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Table 4 Results of the studies assessing the efficacy of GnRHa given before and during chemotherapy in HSCT recipients in terms of ovarian function and fertility preservation.

Reference	No of patients	Previous Cxt	Type of HSCT	Type of disease	Results
Blumenfeld, 2012	83		Allo/auto	Various	18/47 in GnRHa group vs 4/36 in control group
	33		Auto	Lymphoma	14/21 in GnRHa group vs 2/11 in control group
Cheng, 2012	44	Yes (42/44)	Allo/auto	Various	7/44
	29		Allo	Allo HSCT	2/29, $P=0.04$
	15			Auto HSCT	5/15
Pup, 2014	17		Auto	Lymphoma	5/17
Phelan, 2016	17 (7 received GnRHa)	Yes	Auto/allo	Various	3/7
Demesteere, 2016	10 (3 received GnRHa)	No	Auto	Lymphoma	2/3 in GnRHa group vs 4/7 in control group

HSCT, hematopoietic stem cell transplantation.

HSCT for malignant diseases were enrolled in the study and fifty women chose to receive GnRHa within 10–14 days to chemotherapy. POF was defined as amenorrhea associated with a FSH level above 40 IU/mL (25). The study found that GnRHa co-treatment in parallel with conditioning chemotherapy before HSCT may significantly decrease the POF rate from 82% to 33% in lymphoma patients. Furthermore, cyclic ovarian function (COF) defined as resumption of menses for at least 6 months following HSCT, ultrasonographic evidence of ovarian follicles or corpus luteum and normal FSH and LH levels or pregnancy, was present in 38.3% women who received the GnRHa in comparison with 11.1% in the chemotherapy-alone group. In lymphoma patients, the COF returned in 66.7% women in the GnRH arm vs 18.2% for control. The authors concluded that GnRHa use may be beneficial in women undergoing HSCT, especially for lymphoma (25).

Also, Cheng and coworkers analyzed in a phase II prospective study the effectiveness of GnRHa use in HSCT recipients (43). Among the 44 patients evaluated in the study who performed HSCT, 33 women received MA regimens and 11 non-MA regimens. The median age of the patients was 25 years with a median follow-up period of 355 days. The study found that a total of 16% (7/44) women restored normal ovarian function, 18% (6/33) in the MA group and 9% (1/11) in the non-MA, respectively ($P=0.66$). A third of the patients who performed autologous transplantation (33%) resumed COF compared with 7% of patients who underwent allogeneic transplantation ($P=0.04$). Five of the seven patients that restored COF had HL. The authors concluded that leuprolide was not able to preserve the ovarian function in patients who underwent HSCT using either MA or non-MA regimens (43). Their work was criticized by colleagues in the medical field for several reasons. First, GnRH-a was administered before the conditioning chemotherapy preceding HSCT, not before patient's first exposure to chemotherapeutic agents (almost all patients received at least one prior chemotherapy regimen and 12 patients also received prior local radiation) (44). Secondly, the dosage of GnRHa was twice the dose of triptorelin/leuprolide used in previous studies, which led to 9 patients dropout because of the high rate of side effects (44).

In another study, Phelan and coworkers investigated the impact of leuprolide on ovarian function after MA conditioning (intervention group) and monitored ovarian function after RIC in a descriptive pilot study (observational group) that included 7 evaluable patients in the interventional arm (that received GnRHa) and 10 patients in the observational group (7). The patients in the first group underwent both autologous and allogeneic HSCT, while the women in the observational arm received allogeneic RIC. The authors used a combination of long-acting and short-acting leuprolide. FSH was measured at baseline, days 100 and 180, and at 1 and 2 years following HSCT, and the POF was defined as an FSH level over 40 IU/mL. The incidence of POF in the intervention group was 43% (3 out of 7 subjects) at a median of 703 days post-transplant (range, 206–754 days), lower than the incidence reported in the literature (5, 12, 13, 14), suggesting a protective role of GnRH co-administration (7). However, as the author commented, the period of follow-up was rather short (median of 703 days post transplant), and it is possible that some of the women in the interventional group with preserved ovarian function may develop POF over time (7). In the observational group that received RIC, the incidence of POF was 10% (the single patient in this group with POF received a second transplant). Still, most of the patients in the observational group were treated for nonmalignant conditions and

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only two of them were exposed to significant amounts of gonadotoxic chemotherapy (alkylating agents) prior to their conditioning regimen for the HSCT (7).

Fertility impairment after HSCT Prevention of ovarian failure is an important endpoint when evaluating the use of GnRHa (7). However, even where gonadal recovery and pregnancy occur, it is important that the patient be aware that their ovarian reserve may be reduced by conditioning or pre-HCT chemoradiotherapy and that POF remains probable (5). In recent years, because of improvement in the prognosis of HSCT survivors, fertility issues have received increased attention. Studies have shown that most survivors of pediatric HSCT express the desire to have children in the future (8). Although both the patients and their parents are focused on survival at the time of diagnosis, for the majority, fertility becomes a secondary issue. Because of these concerns, fertility preservation options should be discussed with all patients having to undergo HSCT (8, 45).

Fertility rate is severely affected following HSCT with a conception rate <1% (8, 46, 47). Only 0.6% of patients (232 patients) conceived after one autologous or allogeneic BMT, according to an extensive survey, involving 19,412 allogeneic and 17,950 autologous transplanted patients (46). Similarly, in another study, only 3% female patients conceived after HSCT (12). The same results came from the study of Sanders and coworkers performed on 708 pre- and postpubertal survivors of HSCT, which reported a PR of 4.5% (32 patients) (13). However, it is important to recognize that these studies assessing fertility after HCT are limited by the fact that they have not accounted for whether patients were actually trying to conceive (5). A recent publication by Dyer and coworkers that investigated the impact of allogeneic HSCT on fertility reported that 22% survivors tried to conceive, with 10.3% PR (48). Although RIC with exposure to no or reduced dose TBI appear to be less deleterious to reproductive function (5, 7), more research is needed to determine whether these regimens result in better pregnancy outcomes.

Hormonal therapies such as the use of or GnRHa to suppress ovarian function during cancer treatment are one of the simplest means of preserving fertility. However, its efficacy is not well studied in HSCT recipients (5). There is one report in the literature of a postpubertal lymphoma patient that had two spontaneous pregnancies and successful deliveries after repeated autologous transplantation and GnRHa co-treatment (49). The author suggested that the prepubertal milieu induced by the GnRHa might have contributed to the preserved fertility, despite repeated HSCT (49). Also, during the long-term follow-up of 67 HL patients in a RCT, one pregnancy was reported after egg donation in a patient from the GnRHa group, who was treated with the HSCT conditioning regimen (38).

In addition, a retrospective study performed by Pup and coworkers including 17 consecutive women of child-bearing age affected by lymphoma who underwent HSCT described a high rate of parenthood (29%). Five patients became pregnant and 1 out of 5 had two pregnancies and all women who conceived had received GnRHa co-treatment, suggesting a protective role of this therapy for fertility preservation (50).

Rational perspectives regarding the use of GnRHa

The mechanisms that are currently proposed to explain the protective role of GnRHa is that it simulates the prepubertal hormonal milieu (8, 21) and furthermore, decreases the ovarian perfusion and thus the exposure of the primordial follicles to the cytotoxic agents (21, 22). Another important advantage of GnRHa co-treatment is that it decreases the thrombocytopenia-associated menorrhagia leading to an improved survival (21, 37, 39, 51). Cytopenia achieved during transplantation includes thrombocytopenia, which can be problematic during

Table 5 Different GnRHa protocols used in the studies that assessed its potential benefit before/during high-dose chemotherapy in preserving normal gonadal function and fertility in HSCT female recipients.

Study	GnRHa	Dose	Timing
Blumenfeld, 2008, 2012	Triptorelin	A monthly depot injection of 3.75 mg	10–14 days before any gonadotoxic therapy and monthly during chemotherapy
Cheng, 2011	Leuprolide	22.5 mg in a 3-month depot i.m. injection	2 months prior to HSCT
Phelan, 2016	Leuprolide	Long-acting 11.25 mg i.m. once + short-acting 0.2 mg s.c. daily for 14 days	30 days prior to initiation of the HSCT conditioning regimen
Demeestere, 2013, 2016	Triptorelin	11.25 mg every 12 weeks in addition to norethisterone acetate at 5 mg once per day	10 days before the start of chemotherapy if possible

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menses. GnRHa provide menses suppression by inducing a hypogonadotropic, hypogonadal state that mimics prepubertal amenorrhea (52).

The GnRH-a administration should be timed as early as possible, usually within 10–14 days before starting first chemotherapy cycle (21, 25). In cases of urgency in initiating the chemotherapy, the interval may be shorter (1–7 days). Different agents have been used in the studies assessing GnRHa efficiency in preserving normal gonadal function and fertility in cancer patients and HSCT recipients (Table 5). Most studies used a monthly injection of 3.75 mg triptorelin or leuprolide depot (11.25 mg every 3 months) or 3.6 mg goserelin (7, 21, 38, 51). However, Cheng and coworkers used a very high dosage of the GnRHa, twice the commonly used dosage in previous studies (43).

The most common side effects of GnRHa are the signs and symptoms associated with hypoestrogenism including hot flashes, headaches and osteoporosis. Initially, there is an increase of FSH and LH secretion (so-called 'flare effect') that lasts for 2–3 weeks, followed by the hypogonadotropic state. GnRHa carries a known risk of hypoestrogenism-associated decreased bone mineral density (5). Therefore, its use should be limited to a short period of time, especially in patients with hematological malignancies that are exposed to high doses of glucocorticoids (44). It has been suggested that administration of the GnRHa 10–14 days before chemotherapy is sufficient to overcome the flare-up effect of the agonist and to establish the hypogonadotropic milieu (44).

GnRHa co-treatment may be beneficial in patients who receive high-dose chemotherapy before HSCT, but is not useful in conditioning regimens that include TBI. In these circumstances, ovarian shielding may be more appropriate (53, 54, 55, 56). Still, the pilot study performed by Phelan and coworkers highlighted the importance of considering temporary sex steroid blockade with GnRHa for young women undergoing MA regimens for HSCT, regardless of their prior chemotherapy or radiation exposures (7).

Conclusion

Based on the available studies, GnRHa co-treatment appears to improve ovarian function and the ability to achieve pregnancy following standard chemotherapy. There are some promising preliminary results in terms of ovarian function preservation with the concomitant use of GnRHa and conditioning chemotherapy. Still, more data are needed to define the role of GnRHa in ovarian function and fertility preservation in young women/pubertal girls undergoing HSCT.

Until further data are available, premenopausal women and pubertal girls facing chemotherapy for HSCT should be counseled about ovarian preservation option, including the use of GnRHa therapy, keeping in mind that it is inexpensive, noninvasive and has minimal side effects.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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