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Novel aspects on gonadotoxicity and fertility preservation in lymphoproliferative neoplasms

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ABSTRACT

The topic of fertility preservation in patients with a lymphoproliferative disease offers new aspects of debate, due to the introduction of novel chemotherapeutic regimens and small molecules in the clinical landscape. Cancer related infertility is mostly dependent on gonadotoxic treatments and fertile female patients are today addressed to the oocyte cryopreservation or to ovarian cortex fragment cryopreservation. These methods present advantages and disadvantages, which will be discussed in the present review, together with the options for male patients. The recent discovery of functional ovarian stem cells (OCSs) in woman ovarian cortex, opens new avenues offering a innovative procedure for fertility preservation through as model of regenerative medicine. Here, we review the gonadotoxic potential of "classical" chemotherapeutic treatments as well as of "novel" targeted therapies actually employed for lymphoproliferative neoplasms in young patients and revisit both the today available and future chances to preserve and restore fertility after the cancer healing.

1. Introduction

A counseling for fertility preservation (FP) should be offered before treatment to all patients at fertile age affected by a potentially curable lymphoproliferative neoplasm. The choice of the best preservation approach should consider several variables, both in women and men, first of all the urgency for anti-tumoral therapy (Lee et al., 2006; Loren et al., 2013; Oktay et al., 2018a).

The topic of FP in lymphoma patients presents some novel aspects of debate, given the introduction of new chemotherapeutic regimens and molecules in the clinical landscape (Traila et al., 2018). In the meanwhile, large randomized trials on lymphomas at greater incidence are available (Van der Kaaij et al., 2007; Behringer et al., 2012; Anderson et al., 2018). From the technological point of view, new highly innovative but yet experimental methodologies on FP are just entering in oncology and it is desirable that first results will be applicable within a few time (Schüring et al., 2018a).

To better face the topic of the present manuscript, we have to focus on the most common histotypes of lymphoma at fertile age. They are represented first of all by classical Hodgkin lymphoma (cHL) and Diffuse Large B-cell lymphoma (DLBCL), including Primary mediastinal Large B-cell Lymphoma (PMBL) (Swerdlow et al., 2016). Other histotypes of B-cell lymphomas could occur at fertile age, even if less frequently, for example Follicular lymphoma (FL), Mantle cell lymphoma (MCL), Burkitt lymphoma (BL) and Chronic lymphocytic leukemia / Small Lymphocytic lymphoma (CLL/SLL). Albeit rare, Peripheral T-cell lymphoma (PTCL) could affect young patients (Swerdlow et al., 2016).

Some of these histotypes present high rates of cure. According to recent evaluations, five-year overall survival (OS) of cHL now reaches more than 75% (Engert et al., 2009). DLBCL presents 5-years OS of 67% and PMBL 95% (Zelenetz et al., 2019). FL presents high rates of OS (about 70% at 10 years), but also the risk of relapse, with median 5 years progression-free survival of 60% (Zelenetz et al., 2019). All these histotypes need a poli-chemotherapeutic approach mainly with standard doses, whose percentages of gonadotoxicity will be presented thereafter. In about the 10% of cHL and the 40% of DLBCL, a salvage

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chemotherapy followed by a consolidation with autologous hematopoietic stem cell transplant (ASCT) is needed, with a higher impact on fertility. MCL and BL present rates of 5-years OS of 66% and 70%, respectively, and are generally treated with a dose intense chemotherapy since the beginning (Zelenetz et al., 2019). Differently, CLL/SLL in young patients is treated according to cytogenetic risk with chemo-immunotherapy or with targeted therapies, the lasts till progression and then for a large number of years, with reported 10 years-OS of 75% for standard risk patients (Fischer et al., 2016 Jan). PTCLs still represent a poor prognosis disease, reaching 5 years-OS of about 80% for Anaplastic large-cell lymphoma (ALCL) ALK+ (and DUSP22 positive forms), but of about 25–35% for other histotypes (PTCL-not otherwise specified, Angioimmunoblastic T-cell lymphoma) (Ellin et al., 2014). Considering the overall survivals rates, it becomes absolutely necessary to evaluate baseline fertility, in order to allow a project of parenthood.

Rates of gonadotoxicity of the available treatments for lymphoproliferative neoplasms will be discussed in the following paragraphs. They vary according to number of courses, dose intensity, type of agent or combination. Although for the regimens longer employed there are consolidate evidences (Behringer et al., 2005), for less used regimens and for new molecules data are ongoing (Traila et al., 2018). For the mentioned histotypes, we could observe negligible toxicities (i.e., for few courses of ABVD chemotherapy) to high risk of infertility, as for escalated BEACOPP for more than two courses (Van der Kaaij et al., 2007; Behringer et al., 2012). A different chapter is represented by targeted therapies employed for the treatment of CLL/SLL, which require a chronic administration (Salles et al., 2019a).

Actually, a series of less or more invasive techniques are available for the preservation of female and male fertility in oncology (Schüring et al., 2018a). The main experiences in lymphomas are reported for the oocyte and semen cryopreservation. A limited experience is available on ovarian tissue preservation and biopsy of the testis. Ovarian prophylaxis with gonadotropin-releasing hormone (GnRHa) agonist is the topic of a recent meta-analysis and will be dealt with subsequently (Chen et al., 2019; Demeestere et al., 2016). Through the years, all these experiences have lead to success in terms of pregnancy and delivery of healthy babies, also with medically assisted procreation, and for lymphoma patients we have data from many cohorts worldwide (Gini et al., 2019). Less studied are factors other than age, stage of disease and chemotherapy, which could influence the conception and its success, like some other aspects reported in the general population and in females with polycystic ovary, firstly chronicle maternal diseases (diabetes, tyreopathies) and metabolic syndrome.

In the present review, we will address new highlights in the topic of fertility in lymphoproliferative diseases, both dealing with new drugs or combinations and new preservation techniques, like the employ of ovarian stem cells (OCSs), strengthening the importance of translational and clinical research in this area. The ultimate aim of expanding the knowledge on the topic is to rise the number of patients who access to fertility preservation in different clinical situations and with different available and new methodologies.

2. Gonadotoxic effect of anti-neoplastic therapies

2.1. Gonadotoxicity of "classic" chemotherapeutic treatments and autologous stem cell transplant (ASCT): trainings from randomized clinical trials and cohort studies

It is known that the risk of infertility highly correlates with the use of alkylating agents and with the intensity of chemotherapy, and for female patients also with age. Chemotherapy could impair the primordial follicle pool and then the ovarian reserve (OR) of young women at different percentages. Amenorrhea has been used in several studies to detect gonadotoxicity and it could represent a surrogate of ovarian function. In recent years, anti-Mullerian hormone (AMH) has also been employed to study gonadotoxicity, because it reduces during chemotherapy and could recover after the end of treatment, in relationship to different treatment schedules (Anderson et al., 2018).

cHL arises in the majority of cases in the 2nd or 3rd decade of life and presents cure rates of more than 75% (Engert et al., 2009). Data about fertility in cHL have been mainly presented by the German Hodgkin Study Group (GHSG) and the European Organization for Research and Treatment of Cancer (EORTC). The standard chemotherapeutic regimen used for the treatment of cHL is ABVD (adriamycin, bleomycin, vinblastine, dacarbazine), which includes the association of alkylating and non-alkylating agents. For early stage disease, receiving a reduced number of courses (two to four), more than 90% of patients reported a regular menstrual cycle after therapy (median recovery of 1 year) and the gonadotoxic effect is low (Behringer et al., 2012). For advanced stage diseases, treated with six courses of ABVD, a complete recovery of AMH during the 3-years follow-up period was observed in all patients under 35 years, but only in 37% of older ones (Anderson et al., 2018). In a pool Cochrane meta-analysis, GnRHa appears to be effective in protecting the ovaries during chemotherapy, in terms of menstruation recovery or maintenance, treatment-related premature ovarian failure (POF) and ovulation, but data on fertility were insufficient (Demeestere et al., 2016). For male patients treated with two to four courses for early stage disease, a complete recovery of spermatogenesis occurs (Behringer et al., 2012). For patients treated with six courses within prospective trials by EORTC including 2362 male patients, a median time of 19 months for recovery of fertility in 82% of cases was observed after ABVD or EBVP (epirubicin, bleomycin, vinblastine, prednisone) (Van der Kaaij et al., 2007). The aneuploidy rate in sperm after ABVD becomes normal 1–2 years after treatment (Table 1) (Martinez et al., 2017).

Escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone), which includes high doses of alkylating agents and procarbazine, is mainly employed for the treatment of young patients with advanced stages cHL and as a salvage schedule in PET/CT (Positron Emission Tomography / Computed Tomography) -positive disease after two courses of ABVD. This schedule is associated with a high rate of amenorrhea and infertility (Behringer et al., 2005). This has been widely documented in the RATHL study, with a reduced recovery of AMH in the BEACOPP treated

Table 1
Risk of female infertility according to treatment for lymphoproliferative neoplasms.

Risk	Regimen / Agent
High (> 70%)	escalated BEACOPP (≥30 years) DA-EPOCH-R (> 40 years) ASCT
Intermediate (40 − 70%)	escalated BEACOPP (< 30 years) R-CHOP (> 35 years) DA-EPOCH-R (< 40 years)* Hyper-CVAD
Low (20 − 40%)	ABVD (> 35 years) R-CHOP (< 35 years) FCR
Very low (< 20%)	ABVD (< 35 years) R
Unknown	R-Bendamustine Brentuximab Nivolumab, pembrolizumab Lenalidomide Ibrutinib, idelalisib

escBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procabazine, prednisone); ASCT (autologous stem cell transplant); R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab); FCR (fludarabine, cyclophosphamide, rituximab); ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); R (rituximab); *–exact percentage of risk is unknown.

females and in targeted analyses within the phase 3 trials by the GHSG (Anderson et al., 2018). The recovery of a regular cycle differs depending on age (82% of women younger than 30 years versus 45% in the older age group) (Behringer et al., 2012), but data of pregnancies are lacking. For this regimen used for six to eight courses, no protection of the ovarian pool was documented with co-treatment with GnRHa or oral contraceptives (Behringer et al., 2010), while a protective role of GnRHa has been shown in the HD14 trial, in which patients had been treated with two courses of escalated BEACOPP and two ABVD (Behringer et al., 2013). Also male patients are at high risk of infertility after treatment with BEACOPP. According to reports of the GHSG, it rises more than 87% (Sieniawski et al., 2008a, b). It is to be considered that patients diagnosed with cHL have a inadequate semen quality and insufficient harvest even prior to treatment. This problem has been mainly observed in symptomatic patients and in advanced stage disease (Martinez et al., 2017; Rueffer et al., 2001).

Patients diagnosed at fertile age with DLBCL and PMBL are mainly treated with the immune-chemotherapeutic regimen R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). The risk of infertility after CHOP or CHOP-like regimens is reported as low (less than 20%), but it could increase for females treated at more than 35 years (Schüring et al., 2018b). Late ovarian impairment and early menopause have been described (Meissner et al., 2015). Ovarian protection with GnRHa have been reported in the previous cited Cochrane meta-analysis (Chen et al., 2019), but its effectiveness in fertility prevention has not been definitively established (Salama et al., 2019; Demeestere et al., 2016). Also for male patients, R-CHOP regimen seems to not impair reproduction, but in the majority of patients semen characteristics and aneuploidy rate return to normal levels only 2 years after treatment (Martinez et al., 2017).

DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, adriamycin, rituximab) is a recent dose-adjusted immune-chemotherapy for aggressive B-cell lymphomas. It showed a high response and survival rates in PMBL, which commonly affects women at childbearing age. On retrospective analysis by *Gharwan* et al, the gonadal and fertility status of 28 pre-menopausal patients receiving DA-EPOCH-R for untreated PMBL was assessed (median age 30.5 years, range 21–50) (Gharwan et al., 2016). Patients were divided into three age groups according to their ovarian reserve: a very early reproductive group (VERG, $n = 9$) age 21–25 years, an early reproductive group (ERG, $n = 9$) age 26–37 years and late reproductive group (LRG, $n = 10$) aged 38–50 years. Interestingly, in the VERG cohort, seven patients had regular periods after completing chemotherapy. Seven of nine patients in the ERG cohort, resumed menses after treatment. In the LRG cohort, all patients presented amenorrhea after treatment. All patients who conceived were from VERG and ERG cohorts (11 pregnancies overall among 6 women) and delivered healthy babies. Thus, DA-EPOCH-R induced ovarian failure in patients older than 37 years, but younger patients could recover their ovarian function.

FL may occur at fertile age in a minority of patients. This disease has been treated for many years with R-CHOP regimen. New evidences have shown a comparable efficacy of anti-CD20 monoclonal antibody rituximab or obinutuzumab associated to bendamustine for the treatment of grade 1–2 FL (Hiddemann et al., 2018). Due to recent introduction of this regimen and the need of a maintenance with the monoclonal antibody for 2 years, no data about fertility are actually available.

Young patients diagnosed with MCL are mainly treated with an alternation of R-CHOP and R-DHAP (rituximab, dexamethasone, cisplatin, high-dose cytarabine). In the majority of cases, ASCT is employed as consolidation treatment. Induction chemotherapy with CHOP or CHOP-like regimens and consolidation with ASCT is also a common approach to treat PTCL affected patients. High-dose chemotherapy and ASCT represent the salvage treatment of choice for young patients affected by cHL, DLBCL, PMBL and FL who are not responsive to front line chemotherapy or within the relapse setting. Data deriving from non-randomized trials document that ASCT presents high rates of infertility (Blumenfeld et al., 2012; Barr, 2014; Traila et al., 2018). Within a prospective non-randomized trial, Blumenfeld et al. analysed the rate of POF in lymphoma patients (cHL and non-Hodgkin's lymphomas), who received BEAC (BCNU/ carmustine, etoposide, cytarabine, cyclophosphamide) or BEAM (BCNU/ carmustine, etoposide, cytarabine, melphalan) as conditioning chemotherapy per-ASCT. Gonadotoxicity and POF reached the 82%. In patients who had received GnRHa co-treatment during conditioning chemotherapy, they decrease to 33%, but the risk of infertility depends on cumulative factors, mainly previous chemotherapies and age (Blumenfeld et al., 2012). BEAM remains actually the most commonly used conditioning regimen pre-ASCT. A large cohort study reports a menopause occurring within 5 years after BEAM in 50.9% of patients, and in higher percentages in older than 40 years (Barr, 2014). Other cohorts confirmed the same data about BEAM condition (Demeestere et al., 2016). To reduce early and late toxicities of carmustine, other replacing agents have been used (e.g. fotemustine, bendamustine) but data on fertility are lacking (Isidori et al., 2016). Alternative regimens, such as etoposide and melphalan (VP16/MEL) or busulfan, cyclophosphamide, and etoposide (BuCyE) are less employed within the daily clinical practice, and no data on fertility are available (Isidori et al., 2016). Of course, in this context, gametes preservation before treatment represent the best options for high-risk patients.

Some histotypes of high-grade B-cell lymphomas, like MCL and BL, need to be treated with dose intensive chemotherapeutic regimens containing alkylating agents. HyperCVAD (cyclophosphamide, vincristine, adriamycin, dexamethasone) presents a intermediate gonadotoxic effect. Cases of return to regular menstruation and natural conception have been described, but the median age of patients was 25 years old (Seshadri et al., 2006). This could have contributed to positive outcome. Large and prospective cohorts are lacking.

Finally, young patients diagnosed with a CLL/SLL without TP53 mutation or 17p deletion are candidate to immune-chemotherapy with fludarabine, cyclophosphamide and rituximab (FCR), which in cases of IGHV (immunoglobulin heavy chain) mutation reaches cure rate of more than 90% (Fischer et al., 2016 Jan). There are no dedicated studies on fertility in these patients, but the chemotherapeutic association seems to present a low risk of infertility.

2.2. Gonadotoxicity after "novel" targeted therapies

For the last several years, some novel targeted therapies have been implemented in clinical practice all over the world. All these innovations have improved survival rates in different types of lymphoproliferative neoplasms and for diverse cohorts of patients. The best treatment options have appeared not only for patients with a newly diagnosed lymphomas, but also for advanced stage disease and relapsed/refractory patients, after several lines of treatment (Matasar et al., 2019; LaCasce, 2019). Great progress has been made using combinations of chemo-immunotherapy and chemotherapy-free regimens with targeted molecules (Ayyappan and Maddocks, 2019). However, despite successful results in survival rates with novel approaches, there are still a lack of data about long-term toxicity. Especially, if we take into account that quite high percentage of patients are at fertile age.

2.2.1. Brentuximab vedotin

Brentuximab vedotin (BV) is a targeted antibody-drug conjugate (ADC) active against CD30-positive cancer cells with activity in CD30-positive lymphoproliferative disorders. Previously, BV has proved its activity in cHL (Moskowitz et al., 2015; Prince et al., 2017; Pro et al., 2017; Horwitz et al., 2019). Despite the large number of studies and patients treated worldwide, there are no available data about fertility outcomes. However, pre-clinical animals studies showed fetal malformations and low level of embryo viability (Scott, 2017). Taking into account the absence of clinical data for this cohort, female and male

patients should be warned to avoid conception for at least 6 months after the final dose of brentuximab (Traila et al., 2018; Wahl et al., 2002 Jul; Francisco et al., 2003).

2.2.2. Nivolumab and pembrolizumab

Nivolumab is a fully human IgG4 monoclonal antibody known as a programmed cell death 1 (PD-1) immune checkpoint inhibitor. Today, nivolumab is included in the treatment protocols of various cancer types: cHL, melanoma, lung, head and neck, renal cell carcinoma and liver cancer (Younes et al., 2016; Flint et al., 2018). Influence on fertility function in patients who received nivolumab has not been yet studied. Pembrolizumab is another active anti PD-1 humanized antibody. As for nivolumab, no clinical data are available on the possible effects on fertility. It is important to mention that patients who undergo treatment with nivolumab or pembrolizumab are already heavily pretreated. Only within clinical trails, nivolumab has been employed in first-line treatment for advanced-stage cHL, but no information about fertility has been provided (Ramchandren et al., 2019).

2.2.3. Rituximab

Rituximab is the first monoclonal antibody directed against CD20 used in lymphoma treatment. Despite more than 20 years of rituximab use, there are still few data about its influence on fertility function in lymphomas. IgG immunoglobulins are known to cross the placental barrier. Furthermore, rituximab may cause fetal B-cell depletion (Pavanello et al., 2017). Patients who receive rituximab therapy are recommended to avoid pregnancy within 12 months after the last dose (Chakravarty et al., 2011; Flint et al., 2016). Chakravarty et al. report a population of 153 inadvertent pregnant women exposed to rituximab for several indications (lymphoma, autoimmune cytopenias, other autoimmune diseases), of whom 90 resulted in live births. Twenty-two infants were born prematurely; with one neonatal death at 6 weeks; four neonatal infections were reported (fever, bronchiolitis, cytomegalovirus hepatitis, and chorioamnionitis); two congenital malformations were identified (Chakravarty et al., 2011). Borrowing data from rheumatic disorders in peri-conception paternal exposure, also for male patients it is advised to avoid conception within the first year of treatment completion (Mouyis et al., 2019).

2.2.4. Lenalidomide

Lenalidomide is classified as an immunomodulatory agent. Initially, it was approved for the treatment of multiple myeloma patients. Then, several studies confirmed its effectiveness for myelodysplastic syndromes, MCL, DLBCL, marginal zone lymphoma and FL (Flowers et al., 2018). Mostly, lenalidomide is not used as a first-line option. However, the last study by the Swiss Group for Clinical Cancer Research and the Nordic Lymphoma Group confirmed its effectiveness in combination with rituximab front line in patients with FL (Zucca et al., 2019). Taking into account that lenalidomide has a teratogenic risk, a pregnancy prevention program is routinely applied (Bwire et al., 2011).

2.2.5. Ibrutinib and idelalisib

These targeted therapies present as mechanism of action the inhibition of the Bruton's tyrosine kinase and the PI3Kδ on B-cells, respectively. They are routinely employed for the treatment of CLL/SLL, also front-line for young patients at high genetic risk. No data on the effect of ibrutinib and idelalisib on fertility are actually available (Salles et al., 2019b).

2.3. Effects of radiotherapy on fertility

Despite several strategies have been changed in last years, i.e. the introduction of PET-guided approachs, the knowledge of molecular patterns, the use of "novel" agents, radiation therapy remains one of the fundamental treatments of lymphomas. In general, its main indication is the consolidation of response for the early stage and for bulky disease after chemotherapy. It has also to be specified that, in the majority of trials, it is challenging to discriminate the direct gonadotoxic effect from the effect due to chemotherapy and data could have been missed from the analysis (Behringer et al., 2012, 2005; Gini et al., 2019; Federico et al., 2009). Moreover, many analysis on survivors focused on highly aggressive radiotherapeutic approaches performed before the advent of modern and conformational 3D ones.

Of course, the risk of gonadotoxicity determined by radiotherapy is exclusively secondary to underdiaphragmatic and pelvic irradiation. In hystorical cohorts of patients treated from 1970 to 1986, the risk of non-surgical premature menopause was higher among survivors (all cancers) with highest doses of ovarian irradiation ($\geq$1000 cGy). An increased risk had been observed for cHL compared with survivors of other cancers (Sklar et al., 2006). Impressively, the risk of premature non-surgical menopause was increased of about 20-fold in women who had received pelvic radiotherapy or classic alkylating chemotherapy, 36-fold in women who had received both, and over 50-fold in those who had received a ASCT and pelvic radiotherapy. Thus, the ovarian radiation therapy has a dose dependent risk on premature menopause. In the same study, it was also provided an analysis for cumulative risk of menopause: for women by age 40 years a cumulative risk reached 81.3% after at least 5 Gy radiation and chemotherapy; 78.6% by 35 years (Swerdlow et al., 2014). Comparable results were reported by De Bruin and coworkers among hystorical cohorts treated with abdominal or pelvic radiotherapy and old regimens of chemotherapy, as MOPP or MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone/adryamicin, bleomycin, vincristine) (De Bruin et al., 2008).

Ovarian radiosensitivity has been studied in detail. A model published by Wallace et al. predicts the age when ovarian failure will develop, depending on radiation dose and age at treatment (Wallace et al., 2005a).

The advent of Intensity modulated radiotherapy (IMRT) has changed the frequency and severity of radiation side effects. With this technique, the irradiation of the ovary for underdiaphragmatic lymphomas is reduced, but a risk above the threshold level has to be taken into account to plan an individual reproductive planning (Gini et al., 2019).

3. Fertility preservation (FP) strategies

Based on the increased life expectation and a growing attention for the effects of long-term treatments, it is no disbelief that the fertility preservation (FP) has recently become an inclusive aspect in management of these patients after their disease healing (Noone et al., 2017). In assessing the injuries of upcoming anticancer therapies on reproductive organs, international scientific societies as the American Society for Reproductive Medicine (ASRM) (Ethics Committee of American Society for Reproductive Medicine, 2013), the American Society of Clinical Oncology (ASCO) (Sklar et al., 2006), the European Society for Medical Oncology (ESMO) (Lee et al., 2006; Pentheroudakis et al., 2010) as well as the International Society for Fertility Preservation (ISFP) (ISFP Practice Committee et al., 2012), strongly recommend early counseling for all young patients, to provide safe and individualized therapeutic options with the purpose to warranty a potential renovation of the endocrine function (Roudebush and Wendy, 2008).

However, to assess the applicability of a FP procedure for young hemato-oncological women and predict the post-treatment reproductive potential, it is primarily essential to evaluate the ovarian reserve (OR) with respect to both cancer type and expected oncological treatments (Steiner et al., 2017). Several OR biomarkers, namely the circulating levels of both AMH and Follicle stimulating hormone (FSH), in association to antral follicles count (AFC) by ultrasonography during the cycle follicular phase, may generally reflect the OR consistency and are considered reliable indicator of the female reproductive state. A number of assisted reproduction technology (ART) approaches as

reproductive cryobiology and translational medicine are currently adopted to preserve and restore fertility in women after their chemotherapy and radiotherapy gonadotoxic regimens (Meirow et al., 2010). Besides well-established procedures as the oocytes and/or embryos cryopreservation, which often require an hormonal stimulation to induce a multiple follicular growth (MFG), other novel options which are at present debated in their safety or still experimental, are currently utilized or suggested to the patients.

Other FP procedures including ovarian suppression by GnRHa (Blumenfeld, 2007) and ovarian shielding during radiotherapy, are usually adopted as non-hormonal treatment, but their efficacy in the ovarian protection from anti-cancer therapies is debated (Oktay et al., 2007). In order to preserve ovarian function in reproductive age women undergoing pelvic radiation, the laparoscopic ovarian transposition (oophoropexy) is an under-adopted, yet rather simple surgical practice to relocate the ovaries away from the radiation field. Although randomized-controlled trials on the reproductive otcome about this procedure are still limited, there is a growing body of evidence on the advantages of this method, in terms of prevention of POF and FP (Moawad et al., 2017). Other methods for FP in woman include the ovarian cortex cryopreservation and the oocyte in vitro maturation (IVM) for patients urgently requiring chemotherapy (Loren et al., 2013), with no possibility of waiting periods to induce folliculogenesis.

In the precision medicine era, the discovery of stemness resources in the ovarian cortex, hypothesizes the utilization of ovarian stem cells (OSCs) in the FP field. In fact, these cells have been cultured and showed to differentiate into mature oocyte-like cells (OLCs) (Lee et al., 2006; Silvestris et al., 2019), thus opening new innovative programs to restore fertility and hormonal balance also in oncologic patients.

On the other hand, in male patients, besides the testicular shelving, which is a FP procedure for patients receiving pelvic or lymph node radiation therapy, that could result in a testicular exposure and reproductive damage, the sperm cryopreservation is considered the most widely adopted practice (Kelvin, 2017). However, others still experimental procedures as the cryopreservation of testicular tissue and spermatogonial stem cells (SSCs), are under intensive investigation for future application to prevent the anti-cancer treatments related testicular failure (Schmidt et al., 2012).

Therefore, we will next revise the numerous procedures used in both female and male patients, as reported in Table 2, with the purpose to detail advantages of each method for the best clinical option for each patient.

Besides the mentioned options, it should not be forgotten that gestational carrier and adoption are viable alternative paths.

3.1. Options for fertility preservation in females

3.1.1. Ovarian suppression with GnRHa (gonadotropin-releasing hormone agonists)

The possibility to prevent the gonadal damage produced by gonadotoxic chemotherapy by the simple administration of a noninvasive adjuvant treatment is a FP approach supported by many Authors (Blumenfeld et al., 2014). Several preclinical and clinical studies have assessed the effectiveness of a GnRHa co-treatment to protect gonads from the cyclophosphamide related gonadotoxicity, showing a superior effectiveness in females than in men (Ortin et al., 1990). Despite a number of Authors report a well preserved ovarian function in over 90% of long-term female survivors prepuberally treated for lymphoma in comparison with adult patients (Blumenfeld et al., 2015), Blumenfeld and colleagues described a lower percentage of 65.6% achieved pregnancies (Blumenfeld, 2019). Blumenfeld and coworkers, suggest also, in their recent work, few mechanisms of action by which the OR is protected by GnRHa, namely induction of prepubertal hypogonadotropic setting, stimulation on the GnRH receptors, decrease in ovarian perfusion, upregulation of a defined ovarian-protecting molecule, the sphingosine-1-phosphate, as well as a protective effect on the germinative stem cell pool (Massarotti et al., 2017). However, data appear slightly controversial in a cohort of 572 patients treated with GnRHa before and during chemotherapy, it has been reported no significant decrease in POF rate, whereas in 3100 GnRHa-treated patients with breast cancer, hematologic malignancies or autoimmune disorders investigated in 24 controlled trials a significant decrease in POF rate was recorded (Blumenfeld et al., 2014; Blumenfeld, 2019),in the presence of normal ovarian function in about 85 − 90% of patients, compared to 40–50%of the control group (Blumenfeld et al., 2014; Blumenfeld, 2019).

However, as suggested by the ASCO guidelines, there are conflicting evidences about the employ and the efficacy of GnRHa as a FP procedure, supporting that, when other established strategies as oocyte/embryo or ovarian cortex cryopreservation are not feasible as for hormone-dependent cancer and urgency to start anti-neoplastic treatment, this approach may be a valid alternative in order to reduce the impact of gonadotoxicity on the reproductive tract. Therefore, the GnRHa employment, should not be used in place of proven FP methods when applicable (Oktay et al., 2018b).

3.1.2. Oocyte cryopreservation

The oocyte cryopreservation is actually the most adopted procedure for FP in cancer patients and in patients with lymphomas or other hematologic malignancies who may schedule their anti-cancer therapies and have before treatments enough time to induce the MFG by a controlled ovarian stimulation (COS) using gonadotropins assumption, and 2–3 weeks later, after evaluating the occurrence of novel follicles by ultrasonography, a variable pool of oocytes is recruited. These mature eggs are then cryopreserved by slow freezing or vitrification, and are subsequently fertilizable in vitro by ART programs after the oncological remission (Massarotti et al., 2017). Although advantageous, one of the major limitations of this procedure, is the time required for COS namely up to three weeks which therefore makes this practice not preferable in cases of prepubertal girls,necessity of urgent chemo-treatments as occurs in several hematologic disease, or in case of hormone-sensitive cancers as for gynaecologic tumors.In order to overcome these restrictions, oocytes may be retrieved as immature and cryopreserved as mature eggs following their in vitro maturation (IVM) procedure with the final purpose of avoiding the retardation of urgent anti-cancer treatments (Lim and Chian, 2010).

In a retrospective study investigating 176 cancer female patients undergone to oocyte cryopreservation at the New York University Fertility Center, Druckenmiller and co-workers reported an implantation(IR) rate of 27% and a live birth (44%) rate per embryo transfer which was similar to non cancer women receiving the same treatment (44% IR, 33% LB) (Druckenmiller et al., 2016). Therefore, they concluded that the oocyte cryopreservation is a feasible FP option also for cancer patients to be treated with gonadotoxic therapies. However, despite these encouraging results in term of PR and LB, the available data are not still enough and further studies are needed to clarify the advantages of this procedure.

3.1.3. Embryo cryopreservation

Embryo cryopreservation is a widely adopted technique with a variably established success rates. It involves cryopreservation of in vitro-fertilized mature oocytes via slow freezing or vitrification, after 10–14 days of a COS to induce MFG and the oocyte retrieval (Gosden, 2011). Despite several ethical limitations regarding the applicability of this procedure in some countries, the embryo cryopreservation,as for the oocyte cryopreservation,it is not appropriate for prepubertal girls and hormonal-sensitive cancer. In fact, the major drawback is the female hormone stimulation which could variably stimulate malignant cells even in non-gynecological tumors as hematologic malignancies including lymphomas.

Recently, alternative COS protocols with tamoxifen, a selective estrogen receptor modulator (Meirow et al., 2014) or aromatase

Table 2
Description of the fertility preservation options in both sex (COS: Controlled ovarian stimulation, OR: ovarian reserve, OFM: ovarian function manteined, IR: implantation rate, LB: live birth, PR: pregnancy rate).

Technique	Patient	Benefits	Drawbacks	Rate
Ovarian suppression with GnRHa	-Postpuberal women	-Simple technique -No need to delay oncological treatment	-Conflicting data of effectiveness -Menopausal symptoms	-OFM: 85 – 90%
Oocyte cryopreservation	-Postpuberal women	-Well established technique	-Need for COS and cycle dependence -Need to delay oncological treatment–Oncogenic risk for hormonal-cancers -Good OR	-IR: 27% -LB: 44%
Embryo cryopreservation	-Postpuberal women	-Well established technique	-Need for COS and cycle dependence -Need to delay oncological treatment–Oncogenic risk for hormonal-cancers -Good OR -Limited to few countries	-LB: 30%
Ovarian cortex cryopreservation	-Prepuberal women	-No need to delay oncological treatment -No need for COS or cycle dependence	-Experimental technique -Pelvic surgery– Oncogenic risk after replantation -Good OR -Limited to expert infertility centers	-LB: 25%
	-Postpuberal women	-No oncogenic risk for hormonal-cancers		
Ovarian stem cells (OSCs)	-Prepuberal women	-No need to delay oncological treatment -No need for COS or cycle dependence -No need of pelvic surgery	-Theoretical application -Only animal models available -Needs to be investigated in humans	
	-Postpuberal women	-No oncogenic risk for hormonal-cancer		
Sperm cryopreservation	-Postpuberal men	-Simple well established technique -No need to delay oncological treatment	-Accurate analysis in Hodgkin	-PR: 33 – 56%
Testicular tissue cryopreservation	-Prepuberal men	-Simple technique -Experimental technique	-Only animal models available -Needs to be investigated in humans	
	-Postpuberal men	-No need to delay oncological treatment		

inhibitors as letrozole (Checa Vizcaíno et al., 2012), have been adopted to permit the accessibility of these patients to oocyte and other cryopreservation techniques, unlike women requiring immediate anticancer treatments as for acute leukemia or extensive invading lymphomas, for which this practice is not recommended for the time required for the COS. However, the efficiency of embryo cryopreservation in non-cancer women as LB rate is not so high since is around 30% (Pavone et al., 2011), and may be perhaps dependent on modalities of embryo thawing and patient's age. On the other hand, although both IR and LB live birth rates are apparently reduced, no evidence of congenital abnormalities have been reported in literature to occur by this procedure (Lawrenz et al., 2010).

3.1.4. Ovarian cortex cryopreservation

Ovarian cortex cryopreservation is currently considered an experimental 'safe' procedure for female FP which does not require the COS for its recovery and that can be completed independently from the female cycle time. This technique utilizes small bioptic specimens of the ovarian cortex.

Biopsies of ovarian tissue may be easily obtained by laparoscopic or laparotomic surgery, both in prepubertal and adult cancer patients with adequate OR, irrespective of the follicle maturation and with respect to anti-cancer treatment urgency. Within 24 h and under special conditions the ovarian fragments are cryopreserved using either slow freezing approach or the recently introduced vitrification procedure (Silber et al., 2010). After the lymphoma or other cancer's healing, thawed ovarian cortex fragments are autologously and orthotopically or heterotopically reimplanted in case of severe pelvic adhesion or vascular impairment. The ovarian function is usually restored after two to nine months, resulting in a life birth rate in 25% of patients (Stoop et al., 2014).

Despite the reported advantages of this technique,there are few underestimating issues. In fact, the recovery of inadequate oocyte pool as number and egg viability, and the possibility that the biopsy specimen may include malignant cells as described for several acute leukemias (Von Wolff et al., 2009) with the risk of malignancy reimplantation, is perhaps the major drawback, particularly in FP programs to be activated in hematologic malignancies. To this, several Authors evaluated the risk of malignant cells reintroduction during an autotransplantation of thawed ovarian cortex fragments, and demonstrated that the procedure is probably inadequate for ovarian cancers and leukemia, whereas a lower risk may recur in Hodgkin lymphoma as well as in breast and bone malignancies. However, in the same study it is described that there is a minimal risk non-Hodgkin lymphomas and gastrointestinal cancers (Dolmans et al., 2010).

Therefore, in order to evaluate the risk of reintroducing malignant cells, additional assays should be completed in these ovarian biopsies including other than histomorphologic evaluation, also molecular tests as PCR amplification of potentially deregulated genes, flow cytometry of in vitro cultured oocytes from the fragment to assess their maturative state and others (Asadi-Azarbaijani et al., 2016). Since the reimplantation of cryopreserved ovarian fragments is not suggested in leukemia patients, alternative ways to restore fertility in these patients may consider utilization of immature oocyte or the stemness technology.

3.1.5. Ovarian stem cells (OSCs)

The recent discovery of OCSs in woman ovarian cortex provides novel procedures that, although at present under intensive investigation in experimental animal models, will definitely offer in future new methods for FP in the regenerative medicine era, for treatment of several conditions ranging from the POF to the anti-cancer treatment induced ovarian failure (Johnson et al., 2004).

The demonstration of OSCs in mammals has erased the central

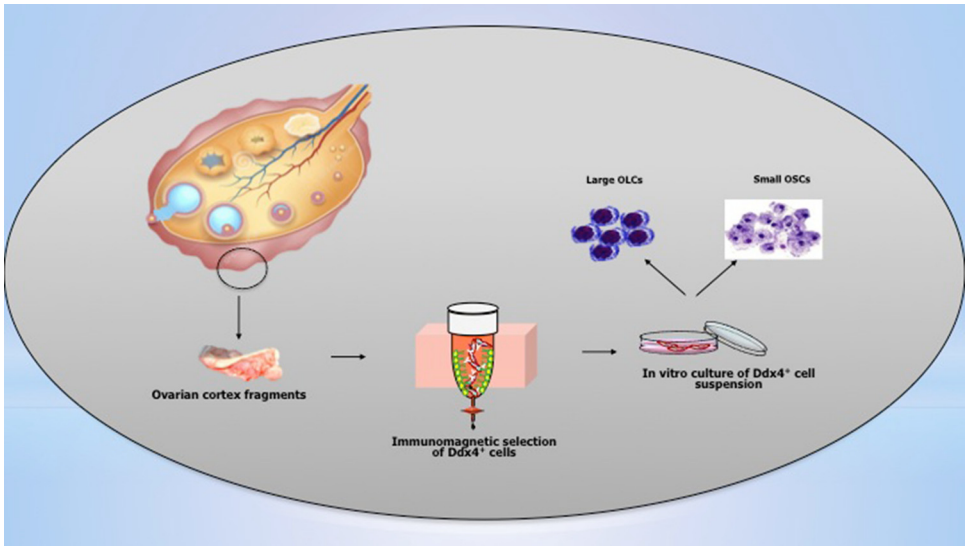

Fig. 1. The isolation and differentiation of ovarian stem cells (OSCs). The ovarian cortex fragments are dissociated by collagenase and the stem population was then isolated by immunomagnetic selection. The recruited Ddx4^{+} OSCs were cultured in vitro for 21 days and underwent differentiation into large OLCs (> 60 μm), expressing typical genes of mature oocytes (GDF9, SYCP3) and a haploid DNA content.

dogma that inherited numbers of oocytes are not subjected to renewal after birth, and from several investigators has also been proven that OSCs are detectable in women in either pre or post-menopausal age (Park and Tilly, 2015). These cells can be isolated by immunoselection using specific reagents against a transmembrane germline marker of oogonial differentiation, namely Ddx4 (DEAD box polypeptide 4) (Silvestris et al., 2018). When isolated and cultured in vitro, the OSCs undergo differentiation into large OLCs, expressing typical genes of mature oocytes (GDF9, SYCP3), and a haploid DNA content (White et al., 2012) (Fig. 1).

Therefore, the opportunity which highlights the translation of OSCs to the cancer related infertility, includes the possibility to develop in vitro a progeny of OLCs from single OSCs, thus favoring the selection of good quality eggs to be frozen and subsequently utilized in fertilization programs after the cancer or hematologic malignancy healing. Further advantage offered by regenerative medicine approach by OSCs to treat the female infertility includes the absence of COS to induce the recruitment, and the absence of the risk to reintroduce malignant cells described in the ovarian cortex cryopreservation and reimplantation. Moreover, the menstrual cycle independence and the easily recruitment of OSCs from ovarian cortex fragments by minimal surgery approaches as laparoscopy or mini-laparotomy,make this technique an encouraging approach to preserve fertility also in hemato-oncological patients.

3.2. Options for fertility preservation in men

3.2.1. Semen cryopreservation

The semen cryopreservation is a widely adopted FP procedure for men undergoing anti-cancer treatments including chemotherapies and/or pelvic radiation (Kobayashi et al., 2017). As for woman it is necessary to evaluate the OR to select patients for a FP program and identify the most suitable technique, also in men, the sperm quality needs an accurate analysis particularly in hemato-oncologic patient with cHL in whom the underlying disease can affect sperm quality (Hovav et al., 2001). Dohle and colleagues in their report estimate that the pregnancy rates after-thawing and ART for the sperm cryopreservation, is around 33–56% (Dohle, 2010). Therefore, the semen cryopreservation is a simple procedure that can be accomplished quickly and can preserve fertility, even in condition of therapeutic urgency in which the anticancer treatment needs to start immediately.

3.2.2. Testicular tissue cryopreservation

Testicular tissue cryopreservation is a still experimental FP procedure, which may allow for young pre-pubertal boys unable to produce a semen sample. In fact, although the prepubertal testis does not produce mature spermatozoa, it does contain the diploid stem germ cells from which haploid spermatozoa will ultimately derive. Therefore, at the oncological remission, the thawed fragments could be reimplanted into testes and the procedure is usually named as germ-cell transplantation (Wallace et al., 2005b). Although this procedure has not yet been utilized in humans, testicular germ cell collection, cryopreservation and transplantation has shown to be effective in mice (Frederickx et al., 2004). However, although the germ-cell transplantation is apparently effective in restoring spermatogenesis, as for ovarian cortex cryopreservation, a putative risk to reintroduce malignant cells for hematological cancers cannot be excluded (Wallace et al., 2005b), for which the in vitro maturation of spermatogonial stem cells could represent an alternative possibility to be investigated and developed in the next future for prepuberal patients. In this group of patients, indeed, a suitable approach to preserve fertility and guarantee a safe restoration of spermatogenesis still needs to be assessed (Lee et al., 2006; Wallace et al., 2005b).

4. Conclusion

Aggressive gonadotoxic anticancer regimens, including chemotherapy and other innovative treatments, are usually employed to treat patients with lymphoproliferative neoplasms, leading to temporary or permanent damage to their reproductive capabilities. Actually, the gonadotoxic effect of classic treatments and ASCT is well known, but data about "novel" targeted agents are still lacking. Thus, the topic of FP in these patients is still a widely debated issue. The increase of survival rates for several lymphoma's histotypes, makes proper the adoption of a multi-displinary councelling to frame and choose the best FP option for the single patient.

To this regard, in order to prevent or reduce the impact of these therapies on fertility, several well established procedures (ovarian suppression with GnRHa, oocyte cryopreservation, ovarian cortex cryopreservation for woman and sperm cryopreservation for men) and other ongoing experimental practices (ovarian cortex cryopreservation, OSCs for women and testicular tissue cryopreservation for men) are widely adopted for young patients before and during anticancer therapy or are under intensive investigation. The knowledge of these strategies is now essential, but it becomes also crucial to offer the widest range of choices to all eligible patients. Therefore, nowadays a FP program to both female and male lymphoma patients should be integrated as part of the oncological disease management, selected in relation to age, reproductive condition, characteristics and therapeutic urgency.

Despite the oocyte and semen cryopreservation are the most suitable procedures for FP in young hemato-oncological patients, the experimental stemness technologies appear to be a promising therapeutic alternative to the current procedures, for a future safe fertility restoration.

Translational research on this topic entails an ever increasing significance and, in future, should offer the keys to preserve fertility in more patients.

Declaration of Competing Interest

Authors declare no conflict of interest.

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