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Summary

Children, adolescent and young adult (CAYA) males with cancer are at an increased risk for infertility, if their treatment adversely impacts reproductive organ function. Future fertility is a primary concern of patients and their families. Variations in clinical practice are barriers to the timely implementation of fertility preserving interventions. The PanCareLIFE consortium in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) reviewed the current literature and developed a clinical practice guideline (CPG) for fertility preservation in male CAYA cancer patients diagnosed before age 25 years, including guidance on risk assessment and available fertility preservation methods. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used to grade the evidence and recommendations. Recognizing the need for global consensus, this CPG used existing evidence and international expertise to develop transparent, easy-to-use and rigorously-developed recommendations that can facilitate the care of CAYA males with cancer at risk of fertility impairment and enhance their quality of life.

Introduction

Advances in childhood cancer treatment have produced 5-year survival rates that exceed 80% in Europe and the United States.[1-2] This progress has focussed attention on reducing the late effects of treatment and optimizing future quality of life for the growing population of childhood, adolescent and young adult (CAYA) cancer survivors. Male CAYA cancer patients are at increased risk for hypogonadism and infertility if treatment includes gonadotoxic chemotherapy, radiotherapy to volumes exposing the testes or hypothalamic-pituitary region and/or abdominal surgery that adversely impacts reproductive organ function.[3-5] Impaired spermatogenesis and secondary sequelae of androgen deficiency can result in reduced fertility or infertility.[6,7] Newly diagnosed male cancer patients, survivors and their parents highly value biological children,[8] and for them fertility is a significant concern later in life.[9,10]
Studies indicate that CAYA cancer patients are not always adequately counselled about the adverse effects of cancer treatment on reproductive function and options for fertility preservation.[11-13] CAYAs with cancer and their healthcare providers need accurate, evidence-based clinical practice guidelines (CPGs) that provide personalized infertility risk assessment and guidance on fertility-preserving options to facilitate informed decision-making. A previous report has shown that existing CPGs for fertility preservation vary extensively and only about one-third are derived from rigorous methodology.[14] To facilitate global consensus on this topic we present a systematic review and recommendations for fertility preservation in male CAYA cancer patients diagnosed before the age of 25 years that have been proposed by the European Union-funded research project PanCareLIFE[15] in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG).[16]

Guideline panel formation

A multidisciplinary panel of 31 international experts in paediatric oncology/haematology, radiation oncology, (paediatric) endocrinology, reproductive medicine, urology, andrology, psychology, epidemiology and guideline methodology was convened (appendix p. 2-3). Members of the expert panels were selected because of their experience, publications and knowledge in the fields of paediatric and reproductive medicine. An overview of the guideline development process and the guideline development structure are presented in the appendix (p. 4-5).

Scope and definitions

The aim of this CPG is to help healthcare providers to communicate the potential risk for hypogonadism (impaired spermatogenesis, testosterone deficiency and central hypogonadism) and/or infertility and options for fertility preservation to male patients diagnosed with childhood cancer tumour types before age 25 years, and their parents, caregivers, or partners (hereafter referred to as families); and to provide

guidance about how and when to offer fertility preservation methods. This effort distinguishes between pre-pubertal and pubertal/post-pubertal patients at time of counselling. The onset of puberty was defined as Tanner Stage II (corresponding with testicular volume of ≥4cc).[17] The guideline panel defined impaired spermatogenesis and testosterone deficiency as outcomes that may lead to infertility.[5,6] Central hypogonadism as a consequence of cranial radiotherapy can result in secondary infertility. Although gonadal function is not affected, testicular function can be impaired by damage to the hypothalamic-pituitary gland. In this case, hormone therapy can restore gonadal function, thus the panel agreed that these patients should be considered as a separate group in this guideline.
The standard definitions of gonadotoxic treatment modalities and outcomes are presented in the appendix (p. 6).

Systematic literature review

The experts formulated clinical questions covering the following key issues: 1) who should be informed about potential infertility risk; 2) who should be counselled about fertility preservation; and 3) what reproductive preservation methods are appropriate to offer in counselling of pre- and post-pubertal male CAYA cancer patients (appendix p. 7-9). Formulation of clinical questions was based on the discordant areas amongst recommendations identified in existing CPGs for fertility preservation in CAYA with cancer as described in a previous publication,[14] and on controversial issues identified by the guideline panel. The search strategies and inclusion criteria are provided in the appendix (p. 10-15).

Search strategy and selection criteria

We updated the literature for the question 'who should be informed about potential infertility risk?' previously published by the IGHG.[5] For the other questions, additional systematic literature searches were performed in collaboration with Cochrane Childhood Cancer. MEDLINE (through PubMed) was searched between January 1993 and February 2020 using different combinations of the search terms, "childhood cancer", "male", "chemotherapy", "radiotherapy", "orchiectomy", "impaired spermatogenesis", "testosterone deficiency", "semen analysis", "fertility preservation". Only reports published in English were reviewed. Eligible study populations for the risk assessment working group were male CAYA cancer patients, in which 75% or more had been diagnosed with childhood cancer before the age of 25 years and at least 50% or more had been followed up for more than 2 years after cancer diagnosis. All study designs were eligible if they controlled for important confounding factors and their sample sizes were above 20 patients. We did not apply a restriction on sample size when assessing novel agents. Eligible study outcomes were impaired spermatogenesis, testosterone deficiency, ejaculation disorders, obstructive azoospermia, central hypogonadism, live births and fathering a

pregnancy. For the fertility preservation methods working group, eligible study populations included 75% or more male patients diagnosed with childhood cancer prior to age 25 years. Eligible outcomes included live births, fathering a pregnancy, quality and yield of sperm, and complications of fertility preservation method related to the patients and to the offspring.

Furthermore, due to the limited data available on fertility preservation methods, additional evidence from existing high-quality evidence-based fertility preservation guidelines was included without a restriction on cancer diagnosis below the age of 25 years (hereafter referred to as existing guidelines). We consulted experts to determine if additional evidence was missing, and we cross-checked references of relevant literature reviews and reports identified in our searches.
Selection of studies was independently performed by two reviewers (AFG/RM/EL and a panel member). Detailed information from each eligible study was extracted into evidence tables and collated in summary of findings tables. The quality of the evidence was appraised using GRADE (Grading of Recommendations Assessment, Development and Evaluation).[18]

Recommendations

The GRADE Evidence to Decision (EtD) frameworks were used to formulate recommendations in a systematic and transparent manner.[19] For each fertility preservation method, the balance between potential benefits and harms was determined. The strength of the recommendations was graded according to published evidence-based methods (appendix p. 14).[20,21] Final recommendations were based on scientific knowledge combined with other considerations including clinical judgement, costs, ethical issues and the need to maintain flexibility across healthcare systems. The recommendations were critically appraised by two independent external experts in the field (AG, ZA) and one patient/survivor representative (JdH).

Role of the funding source

The funding sources were not involved in the design or execution of the study; the drafting or editing of the manuscript; or the decision to submit for publication.

Findings

Of 2932 articles identified, 546 were subjected to a full text review and 30 were eligible, including the evidence described in the previous IGHG publication[5] (Figure 1). The conclusions of evidence and the EtD-frameworks tables are presented in the appendix (p. 19-38). The recommendations are presented in

Figure 2 and the appendix (p. 39-42). Below we present the evidence and recommendations for the three key issues described.

Who should be informed about potential infertility risk?

Evidence on desire for and satisfaction with information

Low-quality evidence showed that the not all male cancer patients and their families were satisfied with the completeness of the fertility preservation information provided.[13] Moreover, low-quality evidence showed that post-pubertal cancer patients strongly desire information about the effects of cancer treatment on fertility and their options for fertility preservation.[22] Similarly, we identified one in-depth interview study in a research setting reporting that most parents of pre-pubertal boys desired information on testicular biopsy irrespective of infertility risk before initiation of therapy (low-quality evidence).[23] Paediatric oncologists also reported that patients and their parents desire information about fertility preservation, but experience difficulties initiating discussions on this topic (very low-quality evidence).[24]

Recommendations

The panel agreed that all cancer patients and their parents have the right to be informed about their potential risk for infertility. Therefore, we strongly recommend that healthcare providers inform all patients and their families about the expected risk of infertility, which may vary in magnitude based on the specific treatment planned (very low- to low-quality evidence).

Who should be counselled about fertility preservation?

Evidence on risk groups

Alkylating agents

Based on previously published IGHG and new published data, there is high-quality evidence that alkylating agents are associated with a dose-related (higher cyclophosphamide equivalent dose (CED)) increased risk of impaired spermatogenesis in CAYA cancer survivors.[5,25,26] Low-quality evidence was found for an increased risk of testosterone deficiency in CAYA cancer survivors treated with increasing doses of alkylating agents.[5,25,27]

Regarding the risk for specific alkylating agents, the risk of impaired spermatogenesis increases with increasing doses of cyclophosphamide (high-quality evidence)[5,25,26] and with increasing doses of procarbazine and mechlorethamine (given as part of multi-agent treatment) compared to not receiving procarbazine and mechlorethamine (very low-quality evidence).[5]

Low-quality evidence was identified for a decreased likelihood of fathering a pregnancy after increasing doses of cyclophosphamide, ifosfamide (>50 g/m^2) and procarbazine in CAYA cancer survivors.[3,28]

Antimetabolites

No studies examined impaired spermatogenesis risk after antimetabolites. Treatment with antimetabolites showed no significant association with lower testosterone levels (low-quality evidence).[5] In addition, one study reported that survivors who received cytarabine were not less likely to sire a pregnancy (low-quality evidence).[3]

Platinum compounds

No studies meeting the inclusion criteria were identified that examined impaired spermatogenesis risk after platinum compounds. Treatment with platinum compounds showed no significant association with testosterone deficiency (very low-quality evidence).[5] One study showed a reduced likelihood of siring a pregnancy after cisplatin (low-quality evidence).[28]

Targeted therapies

Treatment with imatinib showed no significant association with low testosterone levels (low-quality evidence).[29] No reports were identified that investigated the effects of novel agents on the risk of impaired spermatogenesis.

Radiotherapy to testes

There is very low- to high-quality evidence for an increased risk of impaired spermatogenesis and testosterone deficiency in CAYA cancer survivors after radiotherapy to volumes exposing the testes (hereafter referred to as testicular radiotherapy).[5,25,27,30] One study showed a reduced likelihood of siring a pregnancy after > 7·5Gy radiotherapy to the testes compared to no radiotherapy (low-quality evidence).[3] The radiation threshold dose for testosterone deficiency is expected to be higher; the risk substantially increased after doses 12 Gy and higher.[5,27]

Cranial radiotherapy

An association between increasing doses of cranial radiotherapy and the risk of hypogonadotropic hypogonadism was identified (moderate-quality of evidence, respectively).[31,32] In addition, no significant effect of cranial radiotherapy and dose on the likelihood of siring a pregnancy/live birth was found (moderate-quality of evidence).[3,33]

Orchiectomy, retroperitoneal lymph node dissection or genitourinary surgery

No studies evaluating the risk of ejaculation disorders in CAYA cancer survivors after treatment with orchiectomy, retroperitoneal lymph node dissection or genitourinary surgery were identified. Similarly, no studies were found that investigated the risk of obstructive azoospermia in CAYA cancer survivors treated with retroperitoneal lymph node dissection or major surgery to the deep pelvis.

Age at cancer treatment

An association between older age at cancer treatment and risk for impaired spermatogenesis was identified in one study (low-quality evidence),[34] while two other studies could not confirm this effect.[26,35] No significant association of was found between age at treatment and testosterone deficiency. [27,36,37]

Recommendations

Male CAYA cancer patients at potential risk of infertility

The evidence is limited regarding a dose threshold for alkylating agents with the most robust data reporting that azoospermia was unlikely after a CED below 4,000 mg/m^2.[35] The panel therefore defined a high alkylating agent dose as a CED at or above 4,000 mg/m^2 and a low alkylating agent dose as CED below 4,000 mg/m^2. Patients treated with testicular radiotherapy and/or hematopoietic stem cell transplantation (HSCT) are at increased risk of infertility as well. In addition, considering expert opinions and evidence from (young) adult (testicular) cancer survivors, the panel recognizes that patients treated with cisplatin and/or orchiectomy are at potential risk of infertility.[38,39] Patients treated with cranial radiotherapy are at risk for infertility as well. Although the gonadal function is not affected, spermatogenesis can be impaired by damage to the hypothalamic-pituitary gland. Although sperm production can be stimulated by utilizing hormonal therapy when paternity is desired, the panel agreed that these patients should be counselled about fertility preservation.

The panel strongly recommends that healthcare providers discuss fertility preservation options and alternative family planning with CAYA cancer patients and their families if planned treatment will include alkylating agents (any dose) (high-quality evidence), testicular radiotherapy (moderate-quality evidence), HSCT (expert opinion), cisplatin (low-quality evidence), orchiectomy (expert opinion), and/or cranial radiotherapy (very low-quality evidence).

The panel also agreed that the choice of who should discuss fertility preservation and family planning options with the CAYA cancer patients and their families should depend more on the provider's knowledge, patient's disease state and local access to fertility specialists rather than identifying a particular discipline to assume this role. Possibilities include a paediatric oncologist, (paediatric)

endocrinologist, andrologist, fertility specialist, specialised nurse or other relevant healthcare provider. Importantly, a system should be in place that specifies the clinician(s) responsible for providing information about infertility risk, fertility preservation options, and their costs and logistics to patients and their families shortly after diagnosis. Documentation of these discussions is important. A fertility unit in the same hospital of the oncology unit is not mandatory to discuss fertility preservation, but multidisciplinary networks (onco-fertility working groups) are essential to optimize timely referral.[40]

Male CAYA cancer patients not at risk of infertility

The panel concurred that if planned treatment will not include gonadotoxic modalities, CAYA patients and their families should be advised of the benefits and harms of fertility preservation within the context of their personal low risk of infertility and taking into account the risk of cancer recurrence or disease progression (lack of response to initial therapy) that might lead to a potential future need for gonadotoxic therapy. For low risk patients, referral to a specialist to discuss fertility preservation options and family planning may be considered upon the request for additional information (moderate recommendation, no studies).

What reproductive preservation methods are appropriate to offer in counselling?

Evidence on fertility preservation methods

Sperm cryopreservation via masturbation or penile vibration

There is moderate-quality evidence that sperm quality and yield is sufficient for cryopreservation in CAYA cancer patients who can produce semen sampling via masturbation before cancer treatment.[41-45] In two of these studies, sperm motility decreased after thawing of cryopreserved sperm (moderate-quality evidence).[42,43] Although sperm cryopreservation is an established fertility preservation method, data on live births are limited to sperm obtained from older cancer and non-cancer patients. Evidence cited in existing guidelines report achievement of pregnancies (success rates ranging from 20-72%) and live births from cryopreserved sperm,[46] including pregnancies with sperm stored for up to 28 years.[47-50] Studies about birth outcomes related to cryopreserved sperm specifically in CAYA cancer patients are limited. We identified reports of two live births after 13 inseminations of cryopreserved sperm obtained via masturbation, but it was unclear from the study if the live births were from a CAYA cancer patient (very low-quality evidence).[43] No studies were found reporting pregnancies and/or live births after sperm cryopreservation via penile vibration in CAYA cancer patients. In addition, no studies were identified that evaluated complications after sperm cryopreservation via masturbation or penile vibration.

Sperm cryopreservation via electro-ejaculation or testicular sperm extraction (TESE)

Patients who produced semen samples via electro-ejaculation were reported to have diminished sperm count and motility for cryopreservation (very low-quality evidence).[41,44,51] No studies were identified describing the quality and yield of sperm after TESE. Evidence cited in existing guidelines identified case reports and small case series noting successful sperm collection after rectal electro-ejaculation under anaesthesia and TESE.[48,49] In addition, success rates after rectal electro-ejaculation have been reported to be similar to standard sperm banking via masturbation. [48,49] Three live births were reported after TESE combined with intracytoplasmic sperm injection (ICSI) in two out of nine (22%) CAYA cancer patients (very low-quality evidence).[52] No studies were found reporting pregnancies and/or live births after sperm cryopreservation via electro-ejaculation in CAYA cancer patients. In addition, two studies observed no complications after electro-ejaculation[51] or TESE[52] (very low-quality evidence).

Testicular tissue cryopreservation of cryopreserved testicular tissue or spermatogonial stem cells

In four studies where 68-100% of the patients had a malignant diagnosis, mature sperm, spermatogonia and spermatogonial germ cells were observed in testicular tissue dissection of pre-pubertal and pubertal patients (low-quality evidence).[53-56] In addition, there is low-quality evidence of complications after testicular tissue dissection, including three male patients with a wound infection, one with post-operative bleeding, one with ipsilateral epididymo-orchitis, one with ipsilateral torsed appendix testis, and one with scrotal cellulitis.[53,54,56,57] Evidence cited in existing guidelines also reported no major complications after collection of testicular tissue, but mentioned the risk of reseeding malignant cells.[50] No transplantation of spermatogonial stem cells or testes xenografting have been performed so far in CAYA cancer patients. There are no studies that describe a human birth as a result of using cryopreserved testicular tissue as a source of sperm and therefore this method is considered experimental.[47-49,58,59]

Hormone suppression

No studies were identified that investigated the effects of hormonal gonado-protection during chemotherapy among male CAYA cancer patients. Studies cited in existing guidelines reported no significant effect of hormonal gonadoprotection during chemotherapy in reducing the risk of infertility.[48,49,58]

Recommendations

<u>Male CAYA cancer patients at potential risk of infertility: high-dose alkylating agents (CED ≥4,000 mg/m^2), testicular radiotherapy or HSCT</u>

The panel emphasized that shared decision making between healthcare providers and patients and their families is essential when fertility preservation (any method) and future family planning decisions are made. It is important to inform patients and their families about the potential benefits, harms, costs and logistics associated with fertility preservation in order for them to make a well-informed decision.
Regarding sperm cryopreservation via masturbation or penile vibration, the panel considered the effectiveness of collection, cryopreservation and storage, and the non-invasiveness of the collection method. However, the subsequent need for assisted reproductive techniques (i.e. in vitro fertilization (IVF)/ intracytoplasmic sperm injection (ICSI)) with the associated costs, variable success rates after insemination of thawed cryopreserved sperm, the costs for obtaining and storing specimens and the logistics regarding the subsequent use or the discarding of specimens was also recognized. The panel acknowledged the possibility of religious/cultural or psychosocial barriers to masturbation in some patients and families and that (hospital) facilities and access to storage maybe limited. Overall, the panel's view was that the potential benefits of sperm cryopreservation outweigh the harms. For this reason, we strongly recommend offering sperm cryopreservation via masturbation or penile vibration to pubertal and post-pubertal patients whose treatment will include high-dose alkylating agents or testicular radiotherapy (very low-quality evidence, existing guidelines).
Despite the (moderate) invasiveness of sperm collection via electro-ejaculation or TESE, the need of (local/general) anaesthesia and the associated potential risks, the panel considered that the benefits likely outweigh the potential harms if having biological offspring is strongly desired. Overall, the panel concurred that potential benefits outweigh harms considering the high infertility risk, in spite of the invasiveness and risk associated with the procedures. When masturbation or penile vibration is not possible or successful, we strongly recommend offering sperm collection via electro-ejaculation or TESE to pubertal and post-pubertal patients (very low-quality evidence, existing guidelines).
Regarding the experimental technique of testicular tissue cryopreservation in pre-pubertal patients, the panel acknowledged that this procedure is invasive, that malignant cells could be re-introduced if testicular tissue is re-implanted, that no transplantation of cryopreserved testicular tissue has ever been performed in CAYA cancer patients, and thus no human live births have occurred using this method. However, the panel agreed that the benefits of future fertility in the setting of improved technology could be worth the costs (i.e. need for anaesthesia, surgical procedure and tissue storage) in high-risk patients. In addition, implementation of this procedure in a research setting is feasible, depending on the infrastructure of the hospital, clinical storage of cryopreserved tissues and availability of suitable research facilities. Moreover, it is the only fertility preservation method available for pre-pubertal boys. Overall, the panel concurred that, in the absence of suitable alternatives for fertility preservation, the potential benefits for tissue collection and cryopreservation probably outweigh potential harms. We

therefore moderately recommend offering testicular tissue cryopreservation for pre-pubertal patients in this highest risk treatment group, and also for pubertal and post-pubertal patients who cannot undergo other fertility preservation options, only as part of clinical trials or in approved protocols (very low-quality evidence, existing guidelines). It is important to centralize the testicular tissue cryopreservation procedures in centres with adequate expertise. The panel agreed that transplantation of cryopreserved testicular tissue should only be offered in the context of a research protocol, recognizing the experimental nature of the procedure in pre-pubertal patients and the insufficient evidence available about its efficacy to restore fertility and the potential risk of reintroduction of malignant cells during auto-transplantation of testicular tissue. In pubertal and post-pubertal males, auto-transplantation may not be necessary as mature sperm can be extracted from the testicular tissue at the time of collection. Despite the small costs, feasibility and ease of implementation, there is no evidence for the effectiveness of hormone suppression. Therefore, we do not recommend offering hormone suppression to pubertal and post-pubertal CAYA cancer patients (strong recommendation, existing guidelines).

Male CAYA cancer patients at potential risk of infertility: low-dose alkylating agents (CED <4,000 mg/m^2), cisplatin or orchiectomy

Despite the lower infertility risk among CAYA cancer patients in this group, the panel agreed that the potential benefits outweigh the harms of sperm cryopreservation via masturbation or penile vibration, taking into account the effectiveness of collection, storage and insemination of sperm, and the non-invasiveness of the collection method. Therefore, offering sperm cryopreservation via masturbation or penile vibration is strongly recommended for patients whose treatment will include low-dose alkylating agents, cisplatin or orchiectomy (very low-quality evidence, evidence from guidelines). It is important that patients and families are counselled about the potential risks, logistics and costs of the procedure in order to make a well-informed decision.

Considering the invasiveness of sperm cryopreservation via electro-ejaculation and TESE, the need of anaesthesia and the associated potential risks, the panel agreed that the harms outweigh the benefits for patients in this treatment group. However, as future therapy for disease progression or relapse might include gonadotoxic treatments, the panel concurred that electro-ejaculation or TESE may be beneficial before frontline therapy, as sperm collection at a later stage might not be an option for patients considered to be at high risk for cancer recurrence and who cannot undergo sperm cryopreservation via masturbation or penile vibration. In this situation, the panel agreed that the potential benefits probably outweigh the harms. We moderately recommend offering sperm collection via electro-ejaculation or TESE only to patients at high risk of recurrence and when masturbation or

penile vibration is not successful due to failure to ejaculate (very low-quality evidence, existing guidelines).
Regarding testicular tissue cryopreservation, the panel concluded that due to the uncertainty of the future benefits and the lower infertility risk in this treatment group, the overall balance of potential harms and benefits is uncertain. Therefore, no recommendation can be formulated (insufficient evidence).

Male CAYA cancer patients at potential risk of infertility: cranial radiotherapy

High-dose cranial radiotherapy may impair spermatogenesis by interrupting the hypothalamic-pituitary-testicular hormonal axis (hypogonadotrophic or central hypogonadism). In this case, when paternity is desired, sperm production can be stimulated by utilizing pulsatile GnRH or pituitary hormonal therapy (gonadotropin therapy (follicle stimulating hormone (FSH) and human chorionic gonadotropin (hCG)). Considering the non-invasiveness of sperm collection via masturbation or penile vibration post-pubertal patients at risk for central hypogonadism may benefit from upfront cryopreservation of semen to avoid the need for exogenous gonadotropin therapy at a later stage. However, cryopreserved sperm can only be used for assisted reproduction, whereas spontaneous pregnancy can be pursued following induction of spermatogenesis with gonadotrophins. The panel agreed that potential benefits outweigh the harms and therefore we strongly recommend offering sperm cryopreservation via masturbation or penile vibration to post-pubertal patients whose treatment will include high-dose cranial radiotherapy (existing guidelines).
Regarding electro-ejaculation, TESE and testicular tissue cryopreservation, the panel agreed that the potential harms outweigh the benefits, taking into account that potential for sperm production is not affected in patients with hypogonadotropic hypogonadism and the invasiveness of the procedures. However, for patients who are at high risk of recurrence and may need gonadotoxic treatment in the future, the panel agreed that electro-ejaculation or TESE may be beneficial upfront as sperm collection at a later stage might not be an option. In this situation, the potential benefits probably outweigh the harms. Therefore, we moderately recommend offering sperm cryopreservation via electro-ejaculation or TESE only to patients at high risk of recurrence who cannot undergo sperm cryopreservation via masturbation or penile vibration (very low-quality evidence, existing guidelines).
Because of the uncertainty of the future benefits and the fact that the testes are not directly injured, we do not recommend offering testicular tissue cryopreservation to pre-, pubertal and post-pubertal patients in this treatment group (very low-quality evidence, existing guidelines).

Male CAYA cancer patients not at risk of infertility: other therapies

Although there is no evidence for adverse effects of treatments other than alkylating agents, testicular radiotherapy, cisplatin, orchiectomy and cranial radiotherapy, the panel concluded that the benefits of sperm cryopreservation via masturbation or penile vibration probably outweigh potential harms for any patient who wishes to do so. Therefore, we moderately recommend offering sperm cryopreservation via masturbation or penile vibration to any patient based on their wishes and shared decision-making with their healthcare provider (very low-quality evidence, existing guidelines).

Regarding sperm cryopreservation via electro-ejaculation or TESE, the panel agreed that the benefits of upfront sperm collection probably outweigh harms only in patients who are at high risk of recurrence and may need gonadotoxic treatment in the future. We moderately recommend offering sperm cryopreservation via electro-ejaculation or TESE only to patients at high risk of recurrence and who cannot undergo sperm cryopreservation via masturbation or penile vibration (very low-quality evidence, existing guidelines).

Due to their perceived low risk of infertility, the invasiveness of the procedure and the uncertainty of the future benefits, the panel agreed that the potential harms of testicular tissue cryopreservation outweigh benefits. Therefore, we do not recommend offering testicular tissue cryopreservation to pre-, pubertal and post-pubertal patients in this treatment group (very low-quality evidence, existing guidelines).

Discussion

We present a systematic review of the evidence and recommendations for optimizing fertility preservation counselling and utilization in male patients diagnosed with cancer before age 25 years. This CPG harmonizes efforts across Europe, Canada, Australia, New Zealand and the US. The global dissemination of this guideline aims to assist healthcare providers in effectively communicating infertility risk and facilitating informed decision-making to male CAYA cancer patients and their families regarding fertility preservation options. Additionally, we identified major gaps in knowledge and future directions for research (Table 1). This CPG is one of the three CPGs that we have developed, together with one focusing on fertility preservation for female cancer patients, and another focusing on guidance for communicating with patients and their families about fertility preservation and its associated ethical issues.

Male CAYA cancer patients who will be treated with alkylating agents, testicular radiation, HSCT, cisplatin, cranial radiotherapy and/or unilateral orchiectomy are at potential risk for infertility and should therefore be counselled about fertility preservation options. Patients who will be treated with bilateral orchiectomy will by definition become infertile and are therefore qualified for any of the fertility preservation options.

Although anthracyclines have been speculated to increase the risk of infertility in the adult cancer population, we identified no evidence that these agents are an independent risk factor for permanent gonadotoxicity in CAYA cancer patients. van Beek et al.[34] showed no significant effect of EBVD/ABVD regimen on sperm concentration and Tromp et al.[60] reported no significant association with testosterone levels. In addition, Green et al.[3] observed that daunomycin was not significantly associated with the reduced likelihood of siring a pregnancy. Moreover, guideline panel members reported no clinical experience to support that anthracyclines increase the risk of permanent gonadotoxicity in young cancer patients. Consequently, we based our recommendations on available evidence in the published literature and clinical experience with our target population.

Regarding fertility preservation procedures, the current CPG includes offering sperm cryopreservation not only to post-pubertal males but to pubertal males as well. Even among young pubertal patients and those with small testicular volumes, collection of a semen specimen that is acceptable for cryopreservation is feasible prior to gonadotoxic treatment.[41,61,62] This is especially important as previous reports have shown that sperm cryopreservation in adolescent males with cancer is underutilized.[63,64] In line with previous guidelines,[47,49,50,59] we moderately recommend offering testicular tissue harvesting for cryopreservation and storage as a fertility preservation within the context of an approved research protocol for high risk patients. While this fertility preservation technique remains experimental in pre-pubertal patients, the procedure has the potential to be coupled with other interventions that require general anesthesia[65] and its future use remains promising.[57,66,67] A caveat, however, is the potential risk of reintroduction of malignant cells during auto-transplantation of testicular tissue, especially for survivors of leukaemia, non-Hodgkin lymphoma and metastasized solid tumours.[68]

The strength of the present CPG lies in the wide geographical representation of the working group members, the international collaboration and the multidisciplinary expertise that is needed to derive consensus and facilitate applicability of recommendations across diverse institutions providing care for CAYA cancer patients. Application of rigorous GRADE methodology[18] in combination with previously published CPG of the IGHG[5] facilitated a transparent and systematic approach to guideline development. We also involved two patient representatives to ensure that the patient views were considered in the process of guideline development. As this is a rapidly changing field, both in technologies and in patient's acceptance, comprehensive periodic updates of the CPG are planned by the IGHG. Acknowledging that the recommendations in this CPG will be subjected to specific country legislation, the panel carefully formulated recommendations to facilitate implementation in diverse settings. This CPG aims to make fertility preservation accessible to all CAYA males with cancer.

The CPG is limited by the lack of high-quality research data identified in the review. The panel reviewed additional evidence from high-quality existing CPGs that included cancer and non-cancer study populations older than 25 years at diagnosis and presented this information separately to ensure transparency in the guideline development process.

Conclusions

As part of the international European-funded project PanCareLIFE and in collaboration with IGHG, we have developed a transparent and rigorous CPG to optimize fertility preservation for male CAYA cancer patients that carefully balances harms and benefits of fertility preservation methods for different treatment risk groups. Because evidence related to reproductive technologies is rapidly evolving, the recommendations reflect the current state of reproductive sciences. Implementation of this CPG aims to support patients' desire for biological offspring. Healthcare professionals are encouraged to tailor these recommendations to their patients' needs. With this CPG we ultimately expect to increase future international collaborative research that addresses knowledge deficits relevant to male onco-fertility and to enhance patients' and their families' quality of life.

Contributors

AF-G, RLM, EAHL, MMH, JL, WJET, LCMK, LBK and MDvdW contributed to the conception and design of the study. All authors contributed to the search strategy, data extractions, interpretation of the data. All authors and collaborators contributed to the formulation of the recommendations. AF-G, RLM, MMH, JL, WJET, LCMK, LBK and MDvdW drafted the manuscript; and DMG, EAHL, JL, RY, JPG, RTM, JB, RS, AA, LSC, AdV, KJ, AL, AM, LN, MDS, HT, RH, MMvdH-E, HMvS, AMMvP, UD, JdH, EvD-dB, WHW, CB, TD, AG, DG, CG, SEH, JI, PK, JFK, JK, JL, BAL, SJCMMN, WN, NWP, MP, BP, GPQ, DRR, EMT, MvdB, CV critically revised the manuscript. All authors and collaborators approved the final version.

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Declarations of interest

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