INVITED REVIEW ARTICLE

Preservation of fertility of adult male cancer patients treated with chemotherapy

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Abstract

Chemotherapy-induced gonadal dysfunction resulting in transient or persistent infertility depends on the type of drugs and cumulative dose, and it is an important long-term complication, especially for adolescent and young adult (AYA) cancer patients. Due to its importance, a clinical practice guideline for fertility preservation in childhood and AYA cancer patients was published by the Japan Society of Clinical Oncology (JSCO) in 2017. Although the precise mechanisms remain unclear, several studies reported that the cancer itself, not the cancer treatment, adversely affected semen quality. It is reported that that poor pretreatment semen quality is commonly seen in various cancer types including testicular cancer, leukemia, brain tumor, and sarcoma. Fortunately, however, even men with poor sperm quality can be candidates for sperm cryopreservation due to recent advances in assisted reproductive technology (ART) and sperm banking techniques. Therefore, the JSCO guideline and others recommend that sperm cryopreservation should be considered as early as possible when patients are planning to undergo treatment that may render them infertile. The previous studies showed that testicular cancer and hematological tumors are the two leading types of cancer among patients who requested sperm cryopreservation. This is followed by bone and soft-tissue tumors and central nervous system tumors and others. Although the efficacy of postchemotherapy testicular sperm extraction (TESE)/intracytoplasmic sperm injection (ICSI) was reported recently, it is quite important to inform patients of the potential risk of treatment-induced infertility and the possibility of fertility preservation by sperm cryopreservation before chemotherapy.

Keywords Infertility · Fertility preservation · Sperm cryopreservation · Adolescent and young adult

Introduction

Recently, gonadal dysfunctions and alterations in reproductive health have been recognized as the most common long-term morbidities in cancer survivors. The clinical manifestations of gonadal dysfunction vary widely by patient age and gender, type of cancer, and treatment modality. A male patient can suffer from menopausal symptoms, termed late-onset hypogonadism. In addition, chemotherapy-induced gonadal dysfunction resulted in transient or persistent infertility depending on the type of drugs and cumulative dose. Treatment-induced infertility is an important long-term complication for adolescent and young adult (AYA) cancer patients, usually defined as patients 15–39 years of age at the initial diagnosis [1–5]. The National Comprehensive Cancer Network (NCCN) guidelines suggest that fertility preservation should be an essential part in the management of cancer in AYA patients [1]. Because of its importance, clinical practice guidelines for fertility preservation in childhood and AYA cancer patients have been published by the Japan Society of Clinical Oncology (JSCO) in 2017 [5]. Although pelvis surgery or radiation to the gonads can also damage reproductive functions, we will briefly discuss and review fertility preservation in adult men treated with chemotherapy in this article.

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Principle of fertility preservation and risk assessment

Figure 1 shows an algorithm for fertility preservation of male patients before the start of cancer treatment (modified from JSCO guidelines) [5]. The JSCO, NCCN, and American Society of Clinical Oncology (ASCO) guidelines recommend discussing the risks of infertility associated with cancer and its treatment prior to initiating treatment [1–3, 5]. If ejaculated sperm is available, as shown in Fig. 1, freezing sperm obtained through masturbation is the most common technique for fertility preservation in men.

Several studies reported that the cancer itself, not cancer treatment, adversely affects semen quality. In 2004, William et al. reported that pretreatment sperm counts of patients with testicular cancer, the most common AYA cancer, were significantly lower than those in other malignancies. The proportion of oligospermic patients was as high as 52% in testicular cancer, compared to 12–30% in men with other cancers [6]. More recently, Auger et al. reported that poor pretreatment semen quality is more commonly seen in various cancer types using a database that consisted of 4480 young cancer patients [7]. They found that the percentage of normozoospermic men was only 37% of leukemia patients, 41% of brain tumor patients, 51% of testicular cancer patients, and around 60% of lymphoma and sarcoma patients [7].

The mechanism of unfavorable pretreatment semen quality of cancer patients is not fully understood. In a large study of Hodgkin's lymphoma, 10% of patients showed poor semen quality (concentration $< 5 \times 10^6$/mL), and it was associated with the presence of fever or night sweats [8]. For testicular cancer patients, Suzuki et al. reported that smaller tumor diameter and greater noncancerous testicular tissue width were positive predictors of spermatogenesis in testicular cancer patients [9], but it is difficult to conclude that testicular cancer is a cause of infertility, because several cohort studies showed a higher risk for developing testicular cancer in infertile men.

Cytotoxic drugs induce temporary or persistent spermatogenic dysfunction. Among the germ cells, the differentiating spermatogonia are most sensitive to cytotoxic drugs. Therefore, in general, azoospermia develops several months after the initiation of treatment, the interval needed for spermatogonia to become sperm [10]. The risk of impairment of spermatogenesis by chemotherapy largely depends on types of drugs and cumulative dose. Although many drugs are gonadotoxic, as shown in Table 1, alkylating drugs are considered to carry a high risk for infertility. The risk is associated with the cumulative dose or drug combination [2–4]. Cyclophosphamide > 7.5 g/m^2 and use of multiple alkylating drugs carry a high risk, while cisplatin ≥ 400 mg/m^2 and carboplatin ≥ 2 g/m^2 are considered to carry an intermediate risk for oligospermia or azoospermia [3]. In addition to cytotoxic drugs, combined use of radiation such as total-body irradiation with stem-cell transplantation and radiation to testes or pelvis are definite risk factors for infertility. While there are a few human data available for new molecular targeted drugs, Lorenzi et al. reviewed preclinical and clinical data and suggested consideration of cryopreservation for patients beginning treatment with sunitinib, everolimus, or crizotinib [11].

Because of recent advances in assisted reproductive technology (ART) and sperm banking techniques, even men with poor sperm quality are candidates for sperm cryopreservation. Figure 2 shows the tumor types of patients who requested sperm cryopreservation [12–15]. Studies conducted by Yumura et al. and Daudin et al. are nationwide surveys of Japan and France, respectively [12, 13]. Two other studies are long-term experiences of single-treatment

Fig. 1 Algorithm of fertility preservation for male patients before the start of cancer treatment. Modified from the Japan Society of Clinical Oncology (JSCO) guideline
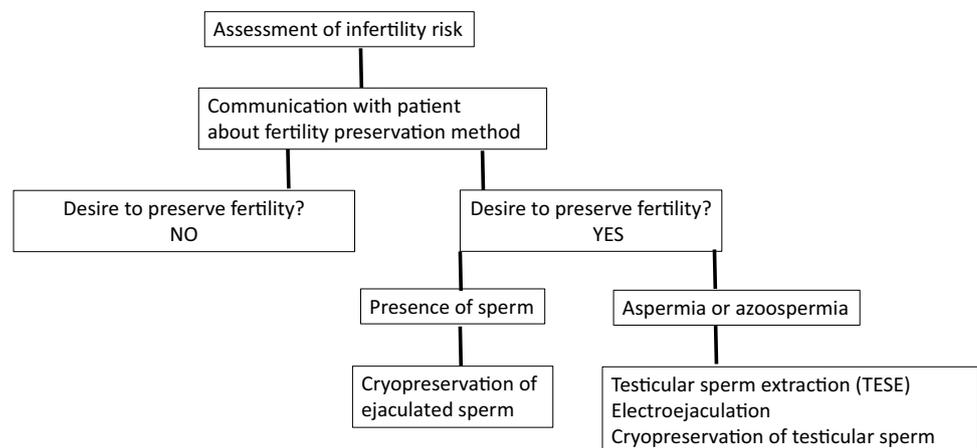
modified from Japan Society of Clinical Oncology (JSCO) guideline

Table 1 Estimated risk for male gonadal dysfunction

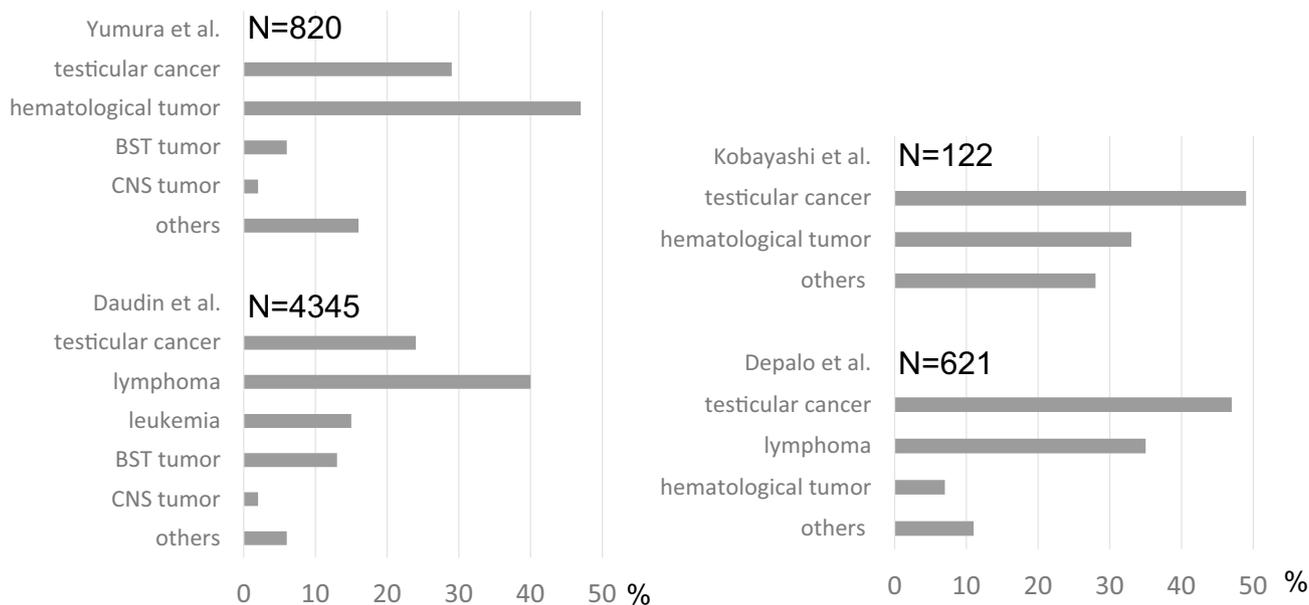|	Drugs	Regimens
High risk	Cyclophosphamide	MOPP
	Ifosfamide	
	Busulfun	
	Dacarbazine	
	Chlorambucil	
	Procarbazine	
	Melphalan	
Intermediate risk	Chlormethine	BEP
	Cisplatin	ABVD
	Carboplatin	
	Doxorubicin	
Low risk		
	Vincristine	
	Vinblastine	
	Methotrexate	
	Dactinomycin	

MOPP nitrogen-mustard, vincristine, procarbazine, prednisone, *BEP* bleomycin, etoposide, cisplatin, *ABVD* doxorubicin, bleomycin, vinblastine, dacarbazine

centers [14, 15]. In all studies, patients with testicular cancer and hematological tumors were most likely to request sperm cryopreservation. This is followed by bone and soft-tissue tumors and central nervous system tumors and others. Among hematological tumors, the proportion of lymphoma tended to be higher than others.

Fertility preservation recommendation for testicular cancer patients

The most common standard primary chemotherapy for testicular cancer is 3–4 cycles of bleomycin, etoposide, and cisplatin (BEP), and the cumulative doses of cisplatin in the treatment are 300–400 mg/m^2. Table 2 summarizes sperm counts of testicular cancer patients after chemotherapy [16–20]. Stephenson et al. and Lamp et al. showed that the proportions of oligospermic and azoospermic men were 23–25% and 20–30%, respectively, more than 1 year after chemotherapy [17, 18]. Good pretreatment sperm counts are associated with recovery of spermatogenesis after chemotherapy. When limited to patients with pretreatment sperm counts less than 9×10^6/ml, Lamp et al. reported that the proportion of oligospermic and azoospermic men was 30–41 and 34–50% after chemotherapy [18]. The risk of azoospermia also depends on the cisplatin dose; Petersen et al. reported that 47% of patients treated with high-dose cisplatin (cisplatin 200 mg/m^2 per course) had azoospermia [16].

To elucidate actual paternity after testicular cancer treatment, Brydøy et al. conducted a large-scale study including 1433 men [21]. They were treated with unilateral orchiectomy, radiotherapy, retroperitoneal lymph-node dissection (RPLND), and chemotherapy. When all treatment types were combined, the cumulative paternity rate at 12 years after treatment was 71% without the use of cryopreserved semen. The median actuarial time from diagnosis to the birth of the first child was 6.6 years. However, the paternity rate depends on the types and intensities of treatment. Most metastatic

Fig. 2 Cancer type of patients who requested semen cryopreservation. *BST* bone and soft tissue, *CNS* central nervous system

Table 2 Sperm count of testicular cancer patients after chemotherapy

Authors	Regimens	N	Interval from chemotherapy	Normospermia	Oligospermia	Azoospermia
Peterson et al. (1994)	BEP	33	79 months	–	–	19%
	High-dose BEP	21	59 months	–	–	47%
Stephenson et al. (1995)	BEP	30	24–78 months	57%	23%	20%
Lamp et al. (1997)	BEP, BECarbo, and others	170	Over 1 year	43%	25%	32%
				(15–24%*)	(30–41%*)	(34–55%*)
Pectasides et al. (2004)	BECarbo	44	2.9 years	59%	30%	11%
Gandini et al. (2006)	BEP**	32	6 months	–	–	34%
		42	9 months	–	–	12%
		46	1 year	–	–	6%
		33	2 years	–	–	3%

BEP bleomycin, etoposide, cisplatin, *BECarbo* bleomycin, etoposide, carboplatin

*Patients with pretreatment sperm count $< 9 \times 10^6$ ml

**Approximately 30% of patients were treated with 2 courses of BEP

nonseminoma patients were treated with chemotherapy followed by postchemotherapy RPLND. Retrograde ejaculation is one of the most important complications of RPLND, and can result in male infertility. When limited to patients maintaining normal ejaculation, the fraction of posttreatment fathers was 76% after low-dose chemotherapy (total cisplatin dose < 850 mg, nearly equivalent to four or less cycles of BEP). The paternity rate decreased to 52% after high-dose chemotherapy (total cisplatin dose > 850 mg) [21]. The median time from diagnosis to birth of the first child ranged from 6.9 years in low-dose chemotherapy to 19 years after high-dose chemotherapy. In addition to the intensity of chemotherapy, the ejaculation function has an impact on paternity. Brydøy et al. showed that the paternity rate was only 10% in men with retrograde ejaculation, compared to 83% in men with normal ejaculation [21].

As discussed above, semen findings after primary chemotherapy for testicular cancer are improved when observed over a long period in some patients. However, it is also true that intensive chemotherapy is needed for advanced disease or relapsed cases. Kojima et al. reported that 46 and 76% of patients having intermediate- and poor-risk advanced testicular cancer needed the second-line or more chemotherapy [22]. Most of those patients received cumulative doses of cisplatin over 500 mg/m^2; therefore, they did not escape the higher risk of infertility. It is also important to note that ejaculatory dysfunction greatly reduces the rate of pregnancy. At present, to some extent, it is possible to predict the strength of the treatment required before the start of therapy. On the other hand, it is difficult to reliably evaluate the risk of recurrence or the possibility of RPLND before treatment.

Therefore, the JSCO guidelines recommend pretreatment discussions about the risks of infertility and advantages of semen cryopreservation for all testicular cancer patients planning to undergo systemic chemotherapy [5]. If ejaculated sperm is available, treatment delay for semen cryopreservation is acceptable in most advanced testicular cancers. However, there are cases in which accelerated chemotherapy is necessary. Chemotherapy, sometimes, should be started as soon as possible for patients having symptomatic brain metastases or patients having bleeding from metastases and an extremely high hCG level (choriocarcinoma syndrome). For those cases, after sufficient explanation and consent, fertility preservation can be abandoned and chemotherapy should proceed [5].

Fertility preservation recommendation for hematological, brain, and other tumors

Although there are various types of hematological tumors, the major diseases are leukemia and the related diseases, lymphoma, and multiple myeloma. Leukemia usually develops in patients aged 60 years and older, but approximately 15% of leukemia patients in Japan are 40 years old or younger. Accordingly, it is estimated that about 1900 new AYA patients develop leukemia annually in Japan [5]. Similarly, about 1400 lymphoma AYA patients per year are diagnosed in Japan. In contrast, multiple myeloma is rarely seen in the AYA generation. With hematological tumors, the risk of infertility largely depends on type and intensity of treatment, and there is a possibility that more intense treatment will be needed due to disease progression. Therefore, the JSCO guidelines recommend pretreatment semen cryopreservation for leukemia and lymphoma patients in the AYA generation [5]. However, in clinical practice, this is difficult in acute leukemia and aggressive to highly aggressive lymphoma due to rapid progression. Accordingly, the

JSCO guideline also recommends reconsideration of semen cryopreservation before the start of subsequent more intense treatment when pretreatment semen cryopreservation could not be performed [5]. However, in this case, because the safety of semen after initiation of chemotherapy has not been established, sufficient explanation and consent is mandatory.

It has been well recognized that the previously used combination of nitrogen-mustard, vincristine, procarbazine, and prednisone (MOPP) for Hodgkin's lymphoma may carry a risk of permanent infertility [23], but the risk of the current standard regimen, ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) is considered to be low [3] to moderate [4]. In general, the risk of persistent oligo- or azoospermina is low in the standard chemotherapy for leukemia and non-Hodgkin's lymphoma without using alkylating drugs. In contrast, a procarbazine-containing regimen and preparative regimens for hematopoietic stem-cell transplantation (HSCT) are associated with a higher risk for persistent azoospermia. Borgmann-Staudt et al. reported that 69% of 190 patients treated with HSCT were considered to be infertile based on sperm or hormonal analysis with a median follow-up of 6 years [24]. Rovo et al. reported that 69% of 224 patients had complete azoospermia at 63 months (median) after HSCT [25]. The authors found that age over 25 years, total-body irradiation, and ongoing chronic graft-versus-host disease were significant adverse factors for sperm recovery.

According to Japanese registration data, 1108 AYA patients were diagnosed with malignant bone tumors between 2006 and 2013 [5]. Osteosarcoma and Ewing sarcoma are the most common tumors, and account for about 75% of young patients with malignant bone tumors. In the same period, 1491 AYA patients were registered with malignant soft-tissue tumors. The major histological types were liposarcoma and synovial sarcoma followed by rhabdomyosarcoma, extra-osseous Ewing sarcoma, and malignant peripheral nerve sheath tumor. Those five tumor types account for about 67% of young patients with malignant soft-tissue tumors. In chemotherapy for malignant soft-tissue tumors, osteosarcoma, and Ewing sarcoma, high doses of cyclophosphamide or ifosfamide are frequently used. In addition, cisplatin at a cumulative dose ≥ 400 mg/m^2 is used in combination chemotherapy for osteosarcoma. The JSCO guidelines recommend pretreatment semen cryopreservation for those patients [5].

There are a variety of histological types in brain tumors. In AYA brain tumors, pituitary adenoma, glioma, and meningioma are major histologic types [5]. Among them, temozolomide, an oral alkylating drug, is used for glioma. A temozolomide-containing regimen, especially in combination with whole brain radiation (WBR), is considered to be a high risk for infertility [3]. Central nervous system germ cell tumor (CNSGCT) is rare, but it, sometimes, occurs in pediatric and AYA patients. The regimens for CNSGCT are similar to testicular cancer regimens, and are used with WBR. Thus, patients have a risk for infertility.

Usage of cryopreserved sperm

The outcomes of intracytoplasmic sperm injection (ICSI) and in vitro fertilization (IVF) using cryopreserved sperm are known to be better than intrauterine insemination [26, 27]. A systemic review on usage and effectiveness of cryopreserved sperm including 30 studies with 11,798 patients has been reported. In this review, the usage rate of cryopreserved sperm was limited to 8% [28]. In overall, 237 of 488 patients (49%) achieved paternity. The usage rate was low, but the proportion of patients who discarded their cryopreserved sperm was also limited to 16%. In addition, there was a positive correlation between the rate of sperm usage and duration of follow-up. Based on these observations, the authors suggest that the observed usage rate is a significant underestimation of the real ultimate usage rate [28].

Hamano et al. also reviewed nine studies, and of them, five studies included 2974 male patients with various types of cancer [29]. The other four studies included 887 testicular cancer patients. In patients with various types of cancers, usage rates of sperm were 3.4–10.3%. The rates of pregnancy were 36–50%. For testicular cancer patients, the usage rates were 6.9–18.1% and the success rates for paternity were 31–82%. The authors suggested that the time and cost of receiving fertility care might be a barrier to sperm usage [29].

Soda et al. analyzed the experiences of Japanese patients in a private hospital. Among 88 patients, including 39 with hematological tumor and 33 with testicular tumor and others, five patients (5.6%) used cryopreserved sperm [30]. The paternity rate of the five patients was 60%. Suzuki et al. analyzed 163 patients consisting of 76 hematological tumors, 72 testicular cancers, and others [31]. Only six patients (3.7%) used cryopreserved sperm with an average preservation period of 6.0 years. The cryopreserved sperm was abandoned in 115 cases (71%), mainly due to recovery of spermatogenesis. The abandonment rate of testicular cancer patients was 78%, which tended to be high compared to hematological tumor patients (65%). This may be due to the relatively high recovery rate of testicular cancer patients compared to those with hematological tumors, 56% and 35%, respectively. In contrast, the mortality rate was high in hematological tumor compared to testicular cancer, 32% and 0%, respectively [31].

Table 3 Outcomes of testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI)

Authors (date)	N	Tumor types	Retrieval rate (%)	Pregnancy rate (%)	Live birth rate (%)
Meseguer et al. (2003)	12	HT: 5, TC: 6, others: 1	42	25	25
Hisao et al. (2011)*	73	HT: 50, TC: 16, others: 7	43	50	42
Shiraishi et al. (2014)*	26	HT: 14, TC: 8, others: 4	42	27	19
Shin et al. (2016)*	66	HT: 32, TC:21, others: 13	47	35	27

HT hematological tumor, *TC* testicular cancer

*Micro-TESE

Outcomes of testicular sperm extraction (TESE) and ICSI for patients with postchemotherapy azoospermia

The recent success of TESE combined with ICSI for nonobstructive azoospermia indicates that the technologies offer a new treatment option for patients who have not undergone sperm cryopreservation. Table 3 shows the outcomes of TESE and ICSI for patients with postchemotherapy azoospermia [32–35]. The retrieval rates of sperm were similar among studies, 42–47%. The pregnancy rates and live birth rates were 25–50% and 19–42%, respectively. Although the authors still recommended sperm cryopreservation before chemotherapy, they concluded that TESE can be offered to patients who have not undergone sperm cryopreservation [32–35].

Conclusions

Recent developments of reproductive technology such as in IVF and ICSI made have sperm cryopreservation a more important and efficacious procedure for preserving the fertility potential of men treated with chemotherapy. The guidelines recommend that sperm cryopreservation should be considered as early as possible when patients are planning to receive treatment that may render them infertile [1–5]. Although the efficacy of postchemotherapy TESE-ICSI was reported recently, it is quite important to inform patients of the potential risk of treatment-induced infertility and the possibility of fertility preservation by sperm cryopreservation before chemotherapy [1–5].

Compliance with ethical standards

Conflict of interest No author has any conflict of interest.

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