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Committee for Medicinal Products for Human Use (CHMP)

SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug

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*Corr. 1 - Title changed from 'Response from SWP to CMDh questions regarding Genotoxicity and Contraception' to 'SWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug'.

Corr. 2 - update of section 3.3 to clarify to which type of products the recommendations apply.

Corr. 3 - update of section 4.3 to align with 3.3.

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1. Background

Genetic alterations in somatic and germ cells may play a part in serious health effects, which in principle may occur even with low exposures to certain medicinal products. Mutations in germ cells can lead to spontaneous abortions, infertility or heritable damage to the offspring and possibly to the subsequent generations.

To minimise the risk of drug-induced heritable DNA damage and to ensure that genomic integrity of gametes at the time of conception is maintained, patients are generally advised to use highly effective contraception during treatment and for an adequate period of time following the end of treatment with genotoxic drugs. Therefore, clear guidance should be provided by regulators and pharmaceutical companies to healthcare professionals and patients in order to determine the appropriate duration of contraception.

Based on a request coming from CMDh, the Safety working party (SWP) was consulted to give advice on the duration of contraception in male and female patients after cessation of treatment with a genotoxic drug in the context both of clinical trial applications as well as marketing authorisation applications. This SWP document has the objective to support a harmonised EU position and facilitate MAHs to introduce consistent recommendations within the relevant sections of the SmPC.

2. Questions to SWP

- What should be the recommended duration of contraception following the end of treatment with a genotoxic drug for male patients?
- What should be the recommended duration of contraception following the end of treatment with a genotoxic drug for female patients?
- Would these recommendations apply only to genotoxic anticancer drugs, or to any genotoxic active substance regardless of its therapeutic indication?

3. Summary of SWP responses

3.1. What should be the recommended duration of contraception following the end of treatment with a genotoxic drug for male patients?

The recommended duration of contraception in male patients should be until the end of relevant systemic exposure to the genotoxic compound incl. potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 90 days.

Implications for Clinical trial applications:

For male patients in clinical trials the recommendation for use of effective contraceptive measures after cessation of treatment with a genotoxic compound should be the following:

"Use of a condom plus an additional contraceptive method that together result in a failure rate of <1% per year to avoid conception during treatment and until the end of relevant systemic exposure in the exposed male or for 5 terminal half-lives plus 90 day (life span of spermatozoa of 60–75 days for sperm production + 10–14 days for transport to epididymis)." [3]

Implications for SmPC Section 4.6:

SmPC section 4.6 should also reflect the recommendations for duration of contraception for men as stated above.

3.2. What should be the recommended duration of contraception following the end of treatment with a genotoxic drug for female patients?

It takes approximately 6 months for an oocyte to mature from the primordial to the Graafian stage. Animal studies have demonstrated that oocytes exposed to a genotoxic compound at the earliest stage of maturation led to an increase in foetal malformation in pregnancies, whilst exposure of oocytes at the preovulatory stage entailed the highest abortion rate.

Implications for Clinical trial applications

The recommended duration of contraception in female subjects participating in clinical trials should be until the end of relevant systemic exposure incl. potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 6 months. In the more theoretical case of treatment with a pure aneugenic pharmaceutical recommended duration of contraception should be until the end of relevant systemic exposure (i.e. five half-lives after the last dose) plus 1 month.

Implications for SmPC Section 4.6

SmPC section 4.6 should also reflect the recommendations for duration of contraception for women of childbearing potential as stated above and on contraceptive measures when appropriate.

3.3. Would these recommendations apply only to genotoxic anticancer drugs, or to any genotoxic active substance regardless of its therapeutic indication?

Genotoxicity / genetic damage at the level of the germ cells and/or conceptus may deserve particular attention due to its potential irreversible nature. This is independent of the therapeutic indication. Therefore, the recommendations should apply to any genotoxic active substance regardless of its therapeutic indication. However, these recommendations should not apply to active substances whose mechanism of genotoxicity is known to have a threshold which is not expected to be attained in patients.

3.4. Further considerations

In addition to the recommended duration of contraception, the following aspects should be considered for harmonisation:

Sperm and oocyte DNA damage and its recovery may also depend on the disease, the co-medication, the dose and time period of treatment. Therefore, recommendations should be given in the SmPC to seek advice regarding cryopreservation of sperm prior to treatment and/or to use individual genetic counselling for male or female patients intending to have a child after treatment with a genotoxic compound. Similarly, these aspects should be considered in clinical trials with genotoxic compounds.

4. Scientific background and conclusions

4.1. What should be the recommended duration of contraception following the end of treatment with a genotoxic drug for male patients?

Genotoxic substances may have an impact on male fertility and can induce adverse effects on the offspring. These adverse outcomes include spontaneous abortion, birth defects and childhood cancer. The mechanism by which genotoxic drugs may affect progeny outcome is via a detrimental effect on sperm DNA.

Spermatogenesis is initiated in the male testis with the beginning of puberty. This comprises the entire development of the spermatogonia up to sperm cells. It takes place in the seminiferous tubules in the testicles and is classically divided into three stages: spermatogonial proliferation, meiosis, and spermatogenesis (see Figure 1).

The main function of the mature sperm cell is to transfer the undamaged haploid genome to the oocyte. This is ensured by protection of the DNA through sperm-specific packaging during the spermatogenetic process.

Genotoxic agents may induce both single gene and chromosomal mutations in germ cells, both of which can cause genetic disease in offspring [20, 24].

Animal studies [16] and a further study in mice [12] have shown that spermatozoa damaged by paternal exposure to genotoxic cancer therapeutic agents can lead to adverse effects in the offspring, including heritable translocations, mutations and malformations such as hydrocephaly and micrognathia in the F1 progeny.

The susceptibility of the germ cell to DNA insult is stage specific during spermatogenesis in the testis and maturation in the epididymis (see Figure 1).

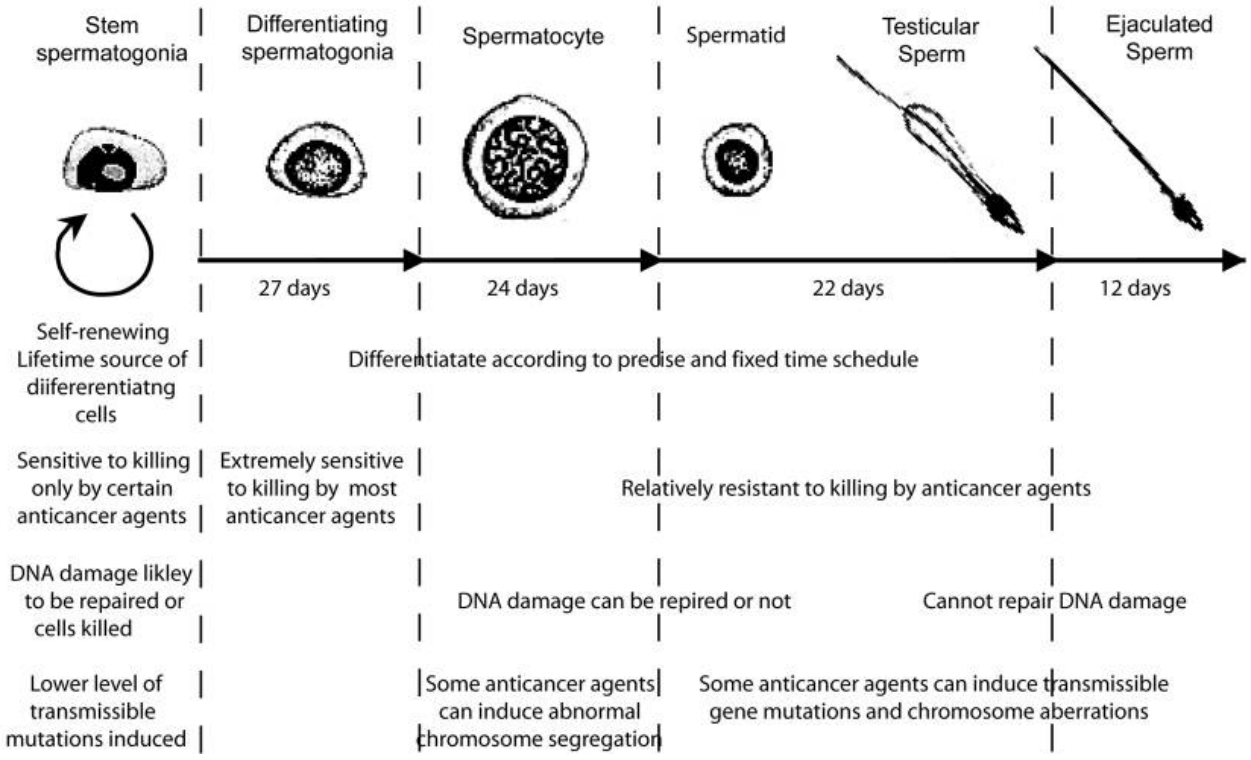


Figure 1. Sequence of spermatogenic cells showing the cell morphology, kinetics, relative sensitivity to killing by anticancer agents, ability to accumulate and repair DNA damage, and sensitivity to induction of transmissible mutations (From Meistrich et al., 2009 [20]).

The damaged sperm cell may have three options: (a) repair the damage, (b) activate the apoptotic process, causing cell death, or (c) tolerate the damage, resulting in mutations which could be transmitted to future generations [21].

Owing to down-regulation of DNA repair mechanisms that occurs during late spermatogenesis, spermatogenic cells further along the differentiation pathway typically cannot repair incurred DNA damage, nor are they usually capable of undergoing complete apoptosis. As a result, the ejaculated

spermatozoa may harbour extensive genomic damage that could theoretically be transmitted to a resulting embryo upon fertilisation [7]. However, repair of DNA damage may also be possible in the oocyte to some extent.

Mutations induced exclusively in the later stages of spermatogenesis will yield a risk period for the production of genetically compromised sperm that is limited to the time it takes for the entire spermatogenic cycle to complete [7, 20). This time-period is about 3 months.

Spermatogonial stem cells have the capacity to repair induced mutations by inherent DNA repair mechanism or by complete removal of the damaged cell via apoptosis. However, as these spermatogonial cells represent the progenitors from which all future germ lines are derived, any sustained mutations in these cells that escape repair or elimination will continue to be transmitted, resulting in the possible production of mutation-carrying sperms for the duration of a man's lifetime.

Animal studies indicate that the differentiating germ cells are more sensitive to induction and transmission of mutations than are stem spermatogonia [4, 9, 20, 24].

Human data on the effects of genotoxic agents on spermatogenesis, on the time period for recovery and outcomes of pregnancies after paternal exposure to genotoxic agents are limited. Most data are available from cancer treatments with genotoxic compounds [1, 6, 7, 20, 21].

Some literature reports (reviewed by Paoli et al. [21]) of cancer treatment-induced sperm DNA changes indicated increased sperm chromatin damage for up to 2 years after end of treatment. The damage was more marked in advanced cancer stages and was also influenced by treatment type and dose. However, cancer treatment is in the majority a combination treatment of several cytotoxic and genotoxic compounds, often in combination with radiotherapy. Therefore, more pronounced effects are likely. Furthermore, studies in lymphoma patients and testicular cancer patients have also shown that cancer patients *per se* had altered sperm DNA before treatment with anticancer agents [6, 21] or an increased risk of congenital malformations in offspring [1].

The incidence of any adverse effects in the offspring of fathers treated with anticancer agents has also been reviewed by Paoli et al. [21]. There are contradictory reports of the incidence of any effects in the offspring of fathers treated with antineoplastic therapies. Most authors did not find any increased risk of congenital or genetic abnormalities, perinatal death, low birth weight or preterm birth in the children of male cancer survivors treated with chemotherapy or radiotherapy. However, others reported an increased risk of congenital abnormalities, at their peak in children born within 2 years of their father’s cancer diagnosis [21].

A recent study in children of fathers with testicular germ-cell cancer have not shown evidence of more frequent abnormalities in offspring after treatment with radio- or chemotherapy [1]. However, all these studies have some limitations and the exact interval between the end of cancer treatment and safe conception is still not known precisely.

Nevertheless, it can be assumed that mutational risk will be highest when a pregnancy occurs during or within several months after the male is exposed to the genotoxic agent. After this time, the incidence of mutations declines to a lower level.

Therefore, the time period for use of contraception measures for male patients after treatment with genotoxic agents should last until the end of relevant systemic exposure (generally defined as five half-lives after the last dose) plus at least 90 days (i.e. 60–75 days for sperm production plus 10–14 days for the transport to the epididymis). This recommendation will significantly reduce the risk for transmission of damaged DNA to the F1 generation.

Implications for Clinical trial applications:

For male patients in clinical trials the recommendation for use of effective contraceptive measures after cessation of treatment with a genotoxic compound should follow the current recommendations of the HMA/CTFG [14] and the FDA [8]:

"Use of a condom plus an additional contraceptive method that together result in a failure rate of <1% per year to avoid conception during treatment and until the end of relevant systemic exposure in the exposed male or for 5 terminal half-lives plus 90 day (life span of spermatozoa of 60–75 days for sperm production + 10–14 days for transport to epididymis)." [3]

Implications for SmPC Section 4.6:

SmPC section 4.6 should also reflect the recommendations for duration of contraception for men as stated above.

4.2. What should be the recommended duration of contraception following the end of treatment with a genotoxic drug for female patients?

Folliculogenesis begins with the recruitment of a primordial follicle into the pool of growing follicles and ends with either ovulation or death by atresia. Each primordial follicle comprises a non-growing, meiotically arrested oocyte, surrounded by a single layer of squamous granulosa cells. Primordial follicles are the storage unit of the female germline and following their activation to enter folliculogenesis, they give rise to fully grown, mature, developmentally competent oocytes [22, 23].

In humans, Gougeon [10, 11] estimated that the maturation phase from primordial to primary follicle takes > 120 days. Once in the growing pool, the follicle requires 65 days to reach the early antral phase (follicle of 2–5 mm diameter), at which point it becomes dependent on gonadotrophins for further growth. In rodents, the time span between initiation of follicle growth and formation of the antral cavity is a few weeks (see Figure 2).

The ovaries of adult mammals contain vast quantities of follicles in nearly every stage of growth. There are large numbers of small follicles that are growing very slowly and fewer medium-sized and large follicles accelerating in their rate of growth as they approach the end of their developmental program. This constant stream of growing follicles is essential for fertility. The enormous excess of growing follicles provides the basis for the mechanism that regulates within narrow limits the number of ova shed during each oestrous or menstrual cycles and the length of time between cycles [13].

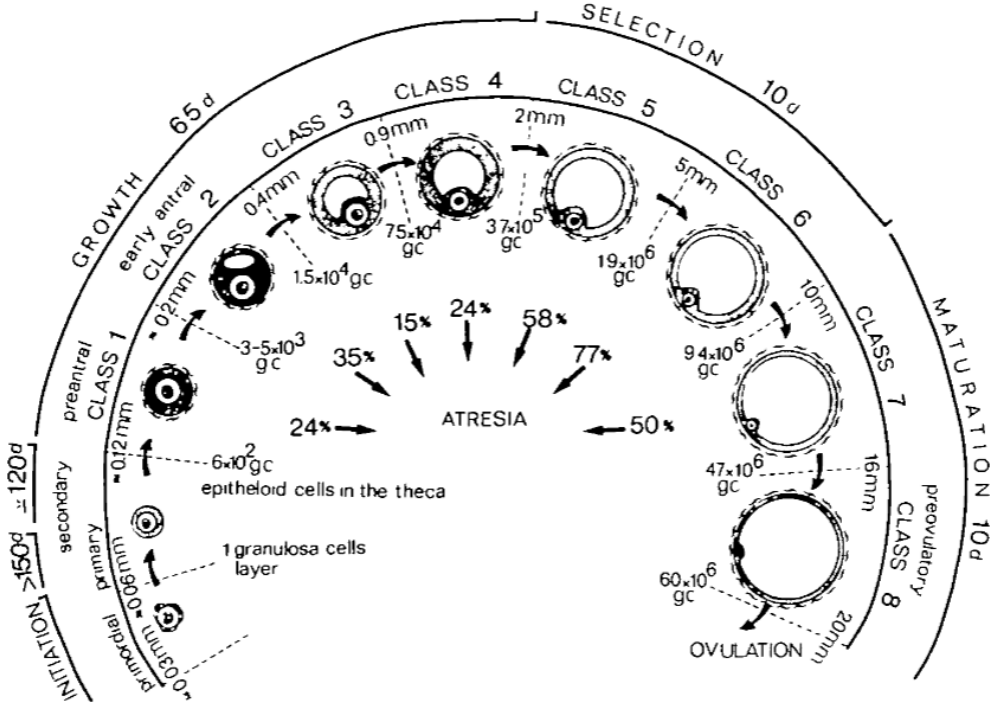


Figure 2: The timetable of normal folliculogenesis in women (From A. Gougeon, 1986 [10])

Folliculogenesis can be divided into two phases [22]:

1. The first phase, termed the preantral or gonadotropin-independent phase, is characterised by the growth and differentiation of the oocyte. The enormous growth occurs as a consequence of the reactivation of the oocyte genome.

2. The second, termed the antral or gonadotropin-dependent phase, is characterised by the tremendous increase of the size of the follicle itself. During the growth phase, the oocyte is highly transcriptionally active because it must generate sufficient proteins and mRNA transcripts to support its own growth as well as future critical processes of oocyte maturation, fertilisation and early embryo development. Some oocyte transcripts are immediately translated, and the resulting proteins contribute to ongoing oocyte growth and differentiation, while others required for future developmental processes are stored for later translation. When the oocyte completes its growth during preantral folliculogenesis, it will spontaneously resume meiosis if removed from the follicle environment. However, fully-grown oocytes rarely resume meiosis during folliculogenesis.

Antral follicles have been detected throughout the human menstrual cycle. The pattern of emergence of these follicles, however, is a matter of long-standing debate with some investigators suggesting continuous development, while others proposing ‘cohorts’ or ‘waves’ of antral follicles that develop in a cyclic manner during the menstrual cycle [2].

In mammals, 99.9% of the follicles (oocytes) die by atresia. A fundamental property of atresia is the activation of apoptosis in the oocyte and granulosa cells. This follicle atresia is controlled by a balance between pro-survival factors that promote cell proliferation, follicle growth and differentiation and pro-apoptotic factors that promote cell death [22].

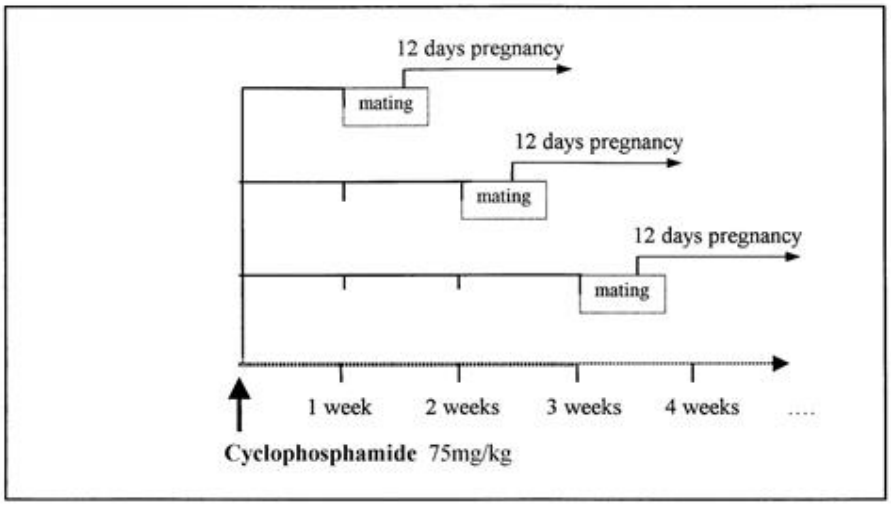
Toxicity of chemotherapy and radiation on female reproduction

Chemotherapy and radiation can induce ovarian damage, leading to diminished fertility potential and lower post treatment birth rates in female cancer survivors. The mechanisms of gonadotoxicity of anticancer drugs including alkylating agents, antitumor antibiotics, platinum-based drugs, antimetabolites and taxanes has been explored in various experimental models, such as analysis of histological female ovary sections after chemotherapy, animal models treated with injections, xenograft models, or cell cultures in the presence of active metabolites of chemical agents, and are not yet fully understood. Several hypotheses have been proposed and could coexist. On the one hand, chemotherapeutic agents could exert direct toxicity on primordial follicles, inducing DNA damage and subsequent apoptosis. On the other hand, it has been suggested that these drugs could trigger an indirect depletion of primordial follicles by over-recruitment [5, 19].

Differential effects have been observed depending on the type of follicle, i.e. primordial, dormant follicles and growing larger ovarian follicles. Chemotherapy targets actively dividing cells, and therefore, destroys mature ovarian follicles during treatment specifically by inducing apoptosis in granulosa cells. The effects that chemotherapy has on primordial dormant follicles are variable and the question remains as to whether the same effect is observed in growing larger ovarian follicles. Patients exposed to chemotherapy initially stop menses as a result of destruction of growing follicles and resume cycling after a period of recovery. Even low doses of chemotherapy can wipe out the population of maturing follicles, but partial ovarian reserve remains intact, allowing for the eventual resumption of menses. Although some publications report normal pregnancies years after cancer treatment, exposure to anticancer drug therapies may harm the quality of maturing eggs and therefore, there is a concern regarding pregnancy and health of future offspring conceived with oocytes exposed to chemotherapy in a nondormant state [19].

The risk of mutagenesis has been demonstrated to be related to the stage of oocyte development during exposure and the drug regimen used [18]. As such alkylating agents have been demonstrated to induce increased abortions and foetal malformations with the highest rates occurring when oocytes were exposed during early maturation.

Meirow and co-workers [17] exposed female inbred Balb/c mice to cyclophosphamide, a widely used chemotherapeutic and immune-suppressive alkylating agent with potent ovarian toxic effects, attributed to its ability to cause DNA cross-links and target metabolically active cells within the ovary, such as granulosa cells. A dose of 75 mg/kg intraperitoneally was selected as it reduced the ovarian primordial follicle reservoir by 50% without any effect on mating or pregnancy rate. Mating was either 1, 2, 3 or 4 weeks and 6, 9, or 12 weeks post-cyclophosphamide treatment, each mating group representing a different stage of follicular growth at the time of exposure to the chemotherapy. Conceptions in females mated 1 week after injection will have resulted from oocytes exposed to cyclophosphamide at late pre-antral stages of follicular development, conceptions in mice mated after a 2-week interval were from follicles exposed at growing stages and conceptions which followed a 3 or more week interval were from oocytes exposed as primordial follicles (see Figure 3).



	Time post treatment						
	1 week	2 weeks	3 weeks	4 weeks	6 weeks	9 weeks	12 weeks
Antral							
Large growing follicles	+						
Small growing follicles	+/-	+/-					
Primary follicles		+	+/-				
Primordial follicles			+	+	+	+	+

Figure 3: Diagrammatic representation of methods: groups of mice were mated at weekly intervals following exposure to cyclophosphamide (75 mg/kg). Oocytes, which contributed to the pregnancies, would have been at the stages indicated at the time of exposure (from Meirow et al., 2001 [17]).

Results indicated that conceptions attributable to follicles exposed to cyclophosphamide at a mature stage had a significantly lower number of implantation sites and a high resorption rate versus in controls. The proportion of corpora lutea in this group which resulted in viable foetuses was extremely low (see Figure 4).

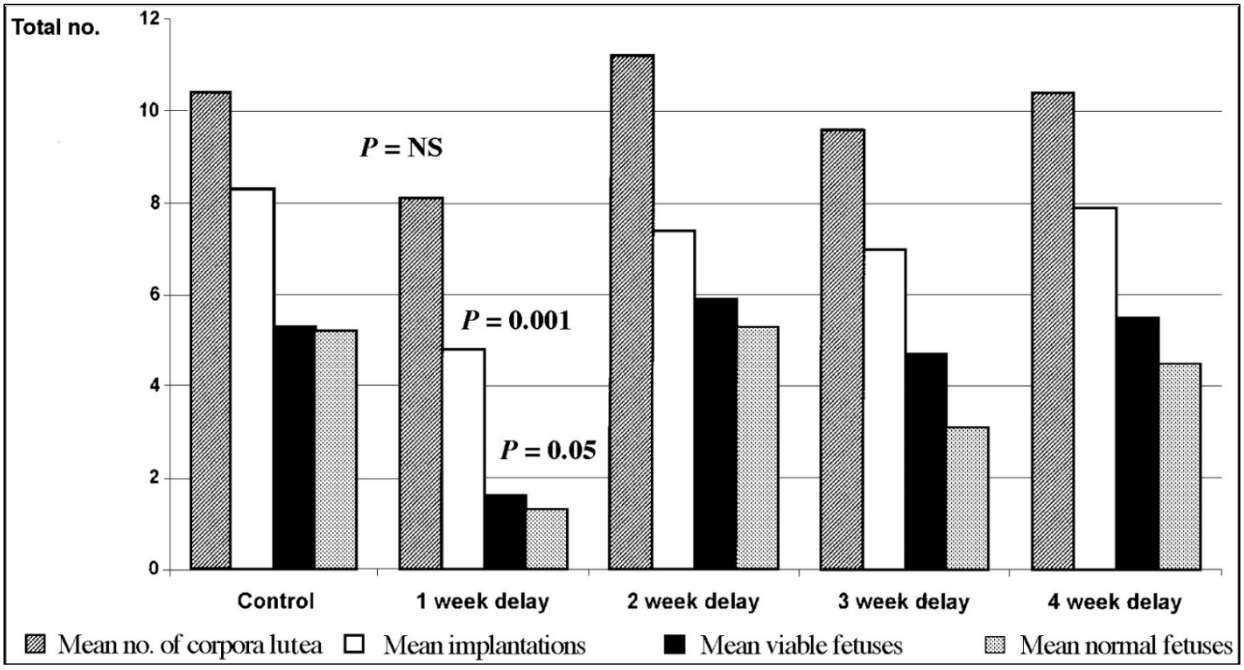


Figure 4: Comparison of the mean numbers (for each female) of corpora lutea, implantations (viable fetuses and resorption sites), viable fetuses and normal (not malformed) fetuses seen in the pregnant females 1, 2, 3 and 4 weeks after treatment with cyclophosphamide, as well as controls (females unsuccessfully mated were not included). P value indicates the significance of the results compared with controls. NS = not significant (from Meirow et al., 2001 [17]).

Malformation rate was more than 10 times higher in all treated groups ($P < 0.05$) and a particularly high incidence of 33% ($P = 0.0014$) was observed in conceptions attributable to oocytes exposed to cyclophosphamide at the earliest stages of follicle growth. With an extended interval between exposure and mating the malformation rate gradually decreased towards normal values in the 12th week group (see Figure 5).

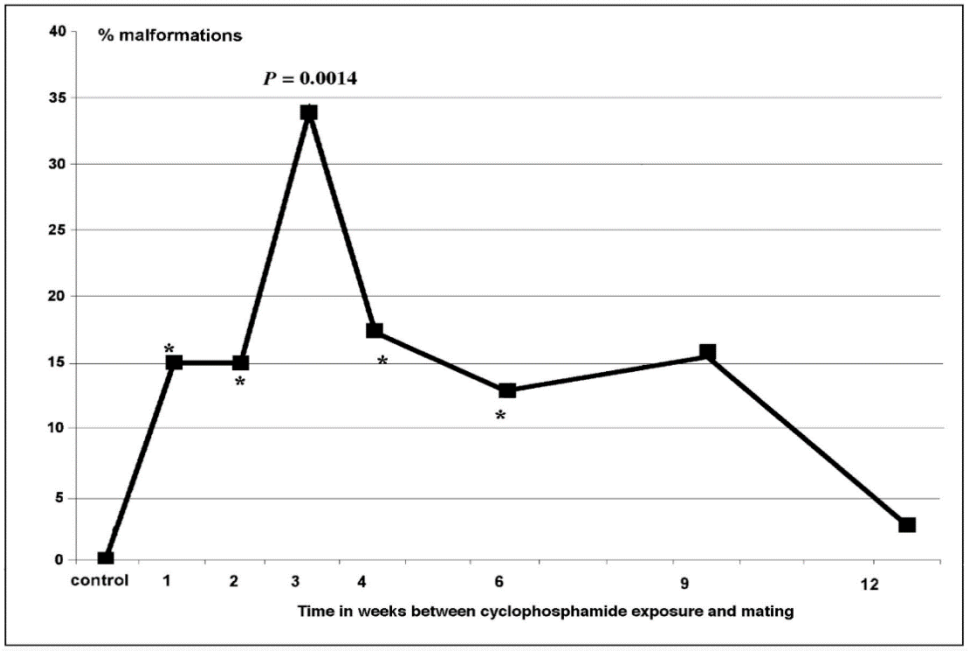


Figure 5: Incidence of malformations in the fetuses of mice mated at different time intervals (1–12 weeks) following injection with cyclophosphamide (75 mg/kg). * indicates P < 0.05 (from Meirow et al., 2001 [17]).

As such Meirow and coworkers [17] demonstrated that the effect of cyclophosphamide on female gametes and subsequently on future reproduction is time dependent and is influenced by the stage of follicle development at the time of exposure. Oocytes exposed to chemotherapy as late pre-antral follicles (group mated 1 week following treatment) seem particularly vulnerable to cyclophosphamide-induced lethal damage with failed fertilisation, or preimplantation/implantation failure and early resorption.

Oocytes exposed to cyclophosphamide during growing stages suffer from increased sublethal damage as a result of the teratogenic effects of cyclophosphamide. As the rate of malformations peaked in the group treated 3 weeks prior to mating (oocytes exposed as follicles just beginning the maturation process) this would indicate that oocytes, which began the maturation process during chemotherapy treatment, were most susceptible to non-lethal damage. Reduced malformation rates were observed from 4 weeks onwards and by 12 weeks post-cyclophosphamide treatment, this rate dropped to 3%, suggesting that DNA repair occurred in surviving primordial follicles and was sufficient to give rise to healthy offspring. Another possible option for the reduction in malformation rate is that damaged oocytes were gradually lost during the following weeks [2, 17, 19].

This rise in foetal malformations peaking in week 3 and then decreasing again has also been observed by Kirk and Lyon [15], when exposing female mice to varying absorbed doses of X-rays and mating them a different intervals after irradiation (1, 2, 3, and 4 weeks). Similarly, the incidence of abnormalities and lethality increased with the time interval between exposure and mating, peaking in animals exposed to X-rays 2–3 weeks before mating, followed by a significant decrease when the interval was between 3–4 weeks.

As such, the duration of contraception following the end of treatment with a genotoxic non-aneugenic drug for female patients amounts to 6 months in order to cover growth, selection and maturation stages of folliculogenesis and thus to ensure that the majority of the potentially damaged oocytes would be eliminated by atresia.

The recommended duration of contraception following the end of treatment with a purely aneugenic drug for female patients is of 1 month as exclusive aneugens will only affect oocytes reentering meiosis.

An additional contraception period should be considered to account for elimination of the drug from the systemic exposure. Therefore, the 6 months (or 1 month) period should be added to the time needed to end relevant systemic exposure (i.e. five half-lives after the last dose).

Implications for Clinical trial applications

The recommended duration of contraception in female subjects participating in clinical trials should be until the end of relevant systemic exposure incl. potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 6 months. In the more theoretical case of treatment with a pure aneugenic pharmaceutical recommended duration of contraception should be until the end of relevant systemic exposure (i.e. five half-lives after the last dose) plus 1 month.

Implications for SmPC Section 4.6

SmPC section 4.6 should also reflect the recommendations for duration of contraception for women of childbearing potential as stated above and on contraceptive measure when appropriate.

4.3. Would these recommendations apply only to genotoxic anticancer drugs, or to any genotoxic active substance regardless of its therapeutic indication?

Genotoxicity / genetic damage at the level of the germ cells and/or conceptus may deserve particular attention due to its potential irreversible nature. This is independent of the therapeutic indication. Therefore, the recommendations should apply to any genotoxic active substance regardless of its therapeutic indication. However, these recommendations should not apply to active substances whose mechanism of genotoxicity is known to have a threshold which is not expected to be attained in patients.

List of References

1. Al-Jebari Y, Glimelius I, Berglund Nord C, Cohn-Cedermark G, Ståhl O, Tandstad T, Jensen A, Sagstuen H Haugnes, Daugaard G, Rylander L, Giwercman A. Cancer therapy and risk of congenital malformations in children fathered by men treated for testicular germ-cell cancer: A nationwide register study. PLoS Med 16(6): e1002816, 2019. https://doi.org/10.1371/journal.pmed.1002816

2. Baerwald AR, Adams GP, Pierson RA. Ovarian antral folliculogenesis during the human menstrual cycle: a review. Hum Reprod Update 18(1):73-91, 2012.

3. Banholzer ML, Wandel C, Barrow P, Mannino M, Schmitt G, Guérard M, Müller L, Greig G, Amemiya K, Peck R, Singer T and Doessegger L. Clinical trial considerations on male contraception and collection of pregnancy information from female partner: update. Clin Trans Med 5:23, 2016. https://doi.org/10.1186/s40169-016-0103-8.

4. Barnett LB, Lewis SE. Chlornaphazine and chlorambucil induce dominant lethal mutations in male mice. Mutation Research. 543(2):145-54, 2003.

5. Bedoschi G, Navarro PA, and Oktay K. Chemotherapy-induced damage to ovary: mechanism and clinical impact. Future Oncol. 12(20): 2333-2344, 2016.

6. Bujan L, Walschaerts M, Brugnon F, Daudin M, Berthaut I, Auger J, Saias J, Szerman E, Moinard N, Rives N, and Hennebicq SA. Impact of lymphoma treatments on spermatogenesis and sperm deoxyribonucleic acid: a multicenter prospective study from the CECOS network. Fertility and Sterility, 2014. http://dx.doi.org/10.1016/j.fertnstert.2014.06.008

7. Choy JT, Brannigan RE. The determination of reproductive safety in men during and after cancer treatment. Fertility and Sterility Vol. 100, No. 5, November 2013 http://dx.doi.org/10.1016/j.fertnstert.2013.07.197

8. FDA. Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations. 13, 2019.

9. Generoso WM, Witt KL, Cain KT, Hughes L, Cacheiro NLA, Lockhart AMC, Shelby MD. Dominant lethal and heritable translocation tests with chlorambucil and melphalan in male mice. Mutation Research 345, 167-180, 1995.

10. Gougeon A. Dynamics of follicular growth in the human: a model from preliminary results. Hum Reprod. 1(2):81-7, 1986.

11. Gougeon A. Regulation of ovarian follicular development in primates: facts and hypothesis. Endocr. Rev. 17:121-155, 1996.

12. Hales BF, Barton TS, Robaire B. Impact of Paternal Exposure to Chemotherapy on Offspring in the Rat. Journal of the National Cancer Institute Monographs, No. 34, 28-31, 2005.

13. Hirshfield AN. Overview of ovarian follicular development: considerations for the toxicologist. Environmental and molecular mutagenesis 29:10-15, 1997.

14. HMA/CTFG. Recommendations related to contraception and pregnancy testing in clinical trials, https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf (2014).

15. Kirk M, Lyon MF. Induction of congenital anomalies in offspring of female mice exposed to varying doses of X-rays. Mutational Research. 106(1):73-83, 1982.

16. Lewis SEM, Aitken RJ. DNA damage to spermatozoa has impacts on fertilization and pregnancy. Cell Tissue Res 322: 33–41, 2005.

17. Meirow D, Epstein M, Lewis H, Nugent D & Gosden RG. Administration of cyclophosphamide at different stages of follicular maturation in mice: effects on reproductive performance and fetal malformations. Human reproduction. 16(4): 632-637, 2001.

18. Meirow D, Schiff E. Appraisal of chemotherapy effects on reproductive outcome according to animal studies and clinical data. J. Nat. cancer Inst Monographs. 34: 21-25, 2005.

19. Meirow D, Biederman H, Anderson RA, and Wallace WH. Toxicity of chemotherapy and radiation on female reproduction. Clinical obstretics and gynecology 53(4): 727-739, 2010.

20. Meistrich ML. Male Gonadal Toxicity. Pediatr Blood Cancer. 53:261–266, 2009.

21. Paoli D, Pallotti F, Lenzi A and Lombardo F. Fatherhood and Sperm DNA Damage in Testicular Cancer Patients. Front. Endocrinol. 9:506, 2018 https://doi.org/10.3389/fendo.2018.00506

22. Williams CJ, Erickson GF. Morphology and Physiology of the Ovary. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP, editors. SourceEndotext. South Dartmouth (MA): MDText.com, Inc.; 2012.

23. Winship AL, Stringer JM, Liew SH and Hutt KJ. The importance of DNA repair for maintaining oocyte quality in response to anti-cancer treatments, environmental toxins and maternal ageing. Human reproduction update 24(2): 119-134, 2018.

24. Witt KL, Bishop JB. Mutagenicity of anticancer drugs in mammalian germ cells. Mutation Research 355, 209-234, 1996.