Editorial

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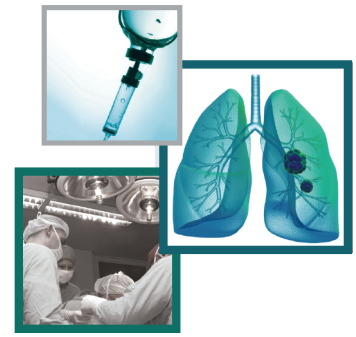
Lung Cancer Management



We need to educate young lung cancer patients about menopause risk

Fahad Faruqi[1], Elizabeth Cathcart-Rake[1] & Kathryn J Ruddy*,[1]

[1]Mayo Clinic, Department of Medical Oncology, 200 First Street, SW, Rochester, MN 55901, USA

*Author for correspondence: ruddy.kathryn@mayo.edu

"Those who have not yet completed their desired childbearing at the time of a lung cancer diagnosis should be referred to reproductive endocrinology prior to systemic therapy initiation to consider fertility preservation"

First draft submitted: 4 December 2018; Accepted for publication: 17 December 2018; Published online: 12 February 2019

Keywords: fertility • lung cancer • menopause

Background

Approximately 220,000 Americans are diagnosed with lung cancer each year, leading to 150,000 deaths annually [1]. While the incidence of lung cancer has been decreasing in men, among women the rate has plateaued after increasing for years [1]. A recent study revealed that the incidence of lung cancer in young women has surpassed that of young men between 30 and 54 years of age [2]. These recent trends underscore the importance of understanding the effect of lung cancer treatments on fertility and menopause in young women.

Chemotherapy-associated infertility and premature menopause are known to be frequent concerns among young women diagnosed with other cancers, sometimes impacting cancer-directed therapy decisions and quality of life [3,4]. Amenorrhea (particularly when it is long lasting) is a surrogate for gonadotoxicity in women. Anticancer drugs may diminish fertility and lead to menopause via ovarian atrophy, stromal fibrosis and vascular toxicity [5]. Various types of chemotherapy have been shown to destroy rapidly growing mature ovarian follicles and to induce apoptosis in primordial ovarian follicles [5]. Chemotherapy-induced infertility is most burdensome for younger patients (who have more frequently not completed their desired child-bearing). Female patients treated for cancer during childhood go on to have half as many live births as their sisters who did not get chemotherapy [6]. Alkylating agents such as cyclophosphamide are known to be more gonadotoxic than many other classes of chemotherapeutics and higher doses of cyclophosphamide are most problematic [7]. An analysis of patients with breast cancer enrolled in the International Breast Cancer Study Group Trials V and VI revealed that time to menopause after receiving cyclophosphamide, methotrexate and 5-fluorouracil is dose-dependent; in women younger than 35 who received one or no cycles of cyclophosphamide, methotrexate and 5-fluorouracil, 37% were menopausal in 5 years, significantly less than the 65% of women under 35 who received six or seven cycles [8]. Risk of ovarian toxicity increases with age; amenorrhea occurs at least temporarily in more than 80% of premenopausal women treated with the more modern combination of anthracycline, taxane and cyclophosphamide for early stage breast cancer, but nearly half of women less than 40 eventually resume menses while less than 5% of those over age 50 do [9]. Similarly, in lymphoma patients, treatment regimens that contain high doses of alkylating agents are associated with the highest risk of menopause and risks are age dependent [10].

While the gonadotoxic effects of many standard treatment regimens for breast cancer and lymphoma are well studied, the risk of menopause and infertility in premenopausal women with lung cancer remains uncertain. In small cell lung cancer, cisplatin plus etoposide is the standard first-line chemotherapy treatment for both limited and extensive stage disease. Platinum-based chemotherapy regimens are frequently first-line choices for non-small-cell lung cancer in both the nonmetastatic and metastatic setting [11]. A patient with metastatic disease often instead receives tyrosine kinase inhibitors (TKIs) as first-line treatment if the tumor has a targetable mutation. Immunotherapy plus chemotherapy is recommended for tumors with low PDL-1 expression, whereas immunotherapy alone is used in patients with high PDL-1 expression [11]. The gonadotoxicity of these drugs is understudied; while cisplatin is

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known to cause significant atresia of ovarian follicles and apoptosis in granulosa cells in rats [12], rates of amenorrhea during and after cisplatin are less clear in humans. It is known that nearly all men who receive cisplatin-based chemotherapy for testicular cancer experience at least temporary azoospermia but 50% recover by 2 years and 80% by 5 years [13]. This is similar to the rate and duration of azoospermia during and after cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) for non-Hodgkin lymphoma [14].

Our recent longitudinal study analyzed the risk of menopause in 182 premenopausal women treated for lung cancer between 1999 and 2016. 85 received platinum-based chemotherapy, while 97 did not. Overall, 55% of women who received chemotherapy reported becoming menopausal within 2 years of treatment compared with only 31% of women who received no treatment or targeted therapy [15]. Interestingly, the rate of menopause among women receiving doxorubicin–cyclophosphamide (AC) for breast cancer historically is similar to the rate we identified in these young women who received chemotherapy for lung cancer. While the heterogeneity of populations in the aforementioned studies makes it difficult to draw direct comparisons, these results do suggest that the risk of gonadotoxicity with common platinum-based regimens for lung cancer may mimic that of standard doses of cyclophosphamide given for breast cancer (usually 2400 mg/m^2).

Our study included too few patients treated with immunotherapy and TKIs alone to assess this. Preclinical studies have revealed that epidermal growth factor receptor expression is a required component of ovarian maturation [16]. Consequently, epidermal growth factor receptor-targeting TKIs could plausibly disrupt normal ovarian function, though larger clinical studies are needed to address these questions.

Treatment of menopausal symptoms

Diminished ovarian function often leads to the onset of amenorrhea and moderate-to-severe menopausal symptoms after chemotherapy such as hot flashes, sleep disturbance, fatigue and mood changes [17].

For mild vasomotor symptoms, behavior modification such as lowering the room temperature, cooling fans and weight loss have demonstrated efficacy for reducing hot flashes and night sweats [17]. Women who have moderate to severe vasomotor symptoms are often treated with medications. Selective serotonin reuptake inhibitors have been shown in multiple randomized controlled trials to reduce hot flashes by as much as 40% without a significant increase in adverse events compared with placebo. Gabapentin and pregabalin have also been studied in menopausal women and have demonstrated efficacy in reducing hot flashes. However, they are generally used as second-line drugs in women who do not achieve adequate symptom control with a selective serotonin reuptake inhibitor. Oxybutynin, clonidine and stellate ganglion blockage are other therapies that are potentially promising to reduce severe vasomotor symptoms [17].

In addition to vasomotor symptoms, women who experience premature menopause often have genitourinary symptoms of menopause (GSM) such as vaginal dryness and discomfort with sexual activity. While GSM symptoms significantly impair quality of life, women are unlikely to discuss such symptoms with their healthcare provider [17] and oncologists may be less likely to ask patients with lung cancer about GSM than patients who are receiving endocrine therapies for breast or gynecologic cancers. A number of therapies may improve GSM symptoms, including nonpharmacologic methods, such as vaginal lubricants, topical lidocaine and hyaluronic acid gel or pharmacologic preparations such as vaginal DHEA and estrogen [17]. Because lung cancers do not seem to be hormonally driven (despite evidence of some hormone receptor expression), and because hormone replacement therapy (HRT) does not increase lung cancer incidence, HRT may also be considered (though safety and efficacy of HRT have not been well studied in lung cancer survivors specifically) [18].

Options for fertility preservation

Because of the risk of early menopause, premenopausal women should be counseled about fertility preservation options prior to initiating lung cancer therapy.

Embryo cryopreservation is the most well-established method of maintaining fertility. However, embryo cryopreservation is only a viable option for women who have a male partner or wish to use a sperm donor. For others, the cryopreservation of mature and immature oocytes may be available [19]. Vitrification, which allows for rapid freezing of oocytes, has led to greater success rates with oocyte cryopreservation than were previously possible [19]. Ovarian tissue cryopreservation remains investigational, though several small studies have reported successful live births with this technique [19].

As the aforementioned options may delay therapy for 2–6 weeks, ovarian function suppression may also be an attractive alternative. There is some controversy about the value of suppressing ovarian function during chemotherapy

with gonadotropin-releasing hormone agonists to reduce the vulnerability of maturing ovarian follicles to cytotoxic chemotherapy. While these agents appear to increase the rate of ovulation and menses after chemotherapy for breast cancer, no study has shown a definitive increase in the number of live births with the use of ovarian suppression during chemotherapy [19]. Consequently, the American Society of Clinical Oncology (ASCO) guidelines do not include gonadotropin-releasing hormone agonists as recommended fertility preservation technique for patients with cancer [20].

Recommendations

While we await larger studies of the impact of specific lung cancer therapies on ovarian function, it is important for clinicians to counsel young women that systemic therapy for lung cancer may increase their risk of infertility and premature menopause. Those who have not yet completed their desired childbearing at the time of a lung cancer diagnosis should be referred to reproductive endocrinology prior to systemic therapy initiation to consider fertility preservation (e.g., oocyte and/or embryo cryopreservation). In addition, clinicians should ask about and offer therapies for the genitourinary and vasomotor symptoms of ovarian dysfunction during and after lung cancer treatment.

Financial & competing interests disclosure

Funded by the TracyStarr Breast Cancer Research Fund. K Ruddy previously owned shares of Pfizer and Merck, which were sold in February 2018.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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