Letter to the Editor

The cost implications of the use of pegylated liposomal doxorubicin when choosing an anthracycline for the treatment of platinum-resistant ovarian cancer: A low-value intervention?

We read with interest the manuscript by Kushnir et al. regarding the financial impact of selective cardiac surveillance strategy in women undergoing treatment with pegylated liposomal doxorubicin (PLD) for gynecologic cancer (70% of whom had ovarian, peritoneal or tubal cancer, and 90% of which were recurrent) (Kushnir et al., 2015). The investigators found that elimination of routine cardiac surveillance (as was done in 157 of the 184 women thought to be at low risk for cardiac toxicity from PLD) resulted in a cost savings of $182,552 in these patients. Considering current estimates that over a third of all healthcare spending is wasteful, the identification of "low-value" interventions (those with limited benefit or those with lower cost alternatives) are potential opportunities for cost savings without sacrificing quality outcomes (Colla, 2014). The authors are commended for their identification of the low-value of routine cardiac monitoring in women with gynecologic cancer receiving PLD without risk factors predicting an adverse cardiac outcome. However, consistent with the widespread use of PLD in the treatment of gynecologic cancers, the authors passed over an even greater opportunity to propose a much greater reduction in the use of low-value care — that of their choice of anthracycline (the use of PLD compared with native doxorubicin).

If one considers the cost of brand name PLD at $873 for a 20 mg vial (or the generic cost of $888 for a 20 mg vial — no cost savings at all!) at the FDA-approved dose of 50 mg/m² every 28 days, the cost is $4363 per cycle for a patient with a body surface area (BSA) of 2 m². This is in contrast to the use of doxorubicin (where a 200 mg vial costs $50), which at a dose of 60 mg/m² every 21 days, would cost $30 per cycle for a patient with a BSA of 2 m². In the 187 patients treated in the study by Kushnir et al., if every patient were treated with 6 cycles of doxorubicin rather than PLD (and every patient underwent routine cardiac surveillance at baseline and after 3 cycles of therapy), the cost for the entire population would be:

\[
((6 \text{ cycles} \times $30/\text{cycle}) + $821/\text{baseline echocardiogram} + $821/\text{mid-course echocardiogram}) \times 184 \text{ patients} = ($180 + $821 + $821) \times 184 = $335,248.
\]

In comparison, in the study by Kushnir et al., the cost for the population treated with PLD would be:

\[
((6 \text{ cycles} \times $4363/\text{cycle}) \times 184 \text{ patients}) + ($821/\text{baseline echocardiogram} + $821/\text{mid-course echocardiogram}) \times 27 \text{ patients} = ($26,178 \times 184 \text{ patients}) + ($368 \times 27 \text{ patients}) = $4,816,752 + $9,936 = $4,826,688.
\]

Thus, the cost savings incurred by using native doxorubicin rather than PLD in these 184 patients with gynecologic cancer would be:

\[
$4,826,688 - $335,248 = $4,491,440.
\]

So, if almost $4.5 million can be saved in a population of fewer than 200 women getting treated for their gynecologic cancers just with the substitution of one chemotherapy (doxorubicin) for another (PLD), one would certainly conclude there must be valid scientific barriers to the use of doxorubicin. On the other hand, if the efficacy and toxicity of these anthracyclines were assumed to be identical, then there would be no rationale to use PLD, since it would be considered a "low value" intervention.

Does this data exist? Unfortunately, there has never been (and certainly never will be) an ovarian cancer study comparing the responses with doxorubicin and PLD. Without these data, one is forced to take a look back into the volumes of history (a history that was at its most robust more than 40 years ago!) regarding the use of doxorubicin in ovarian cancer.

The demonstration of the efficacy of doxorubicin in the treatment of gynecologic cancers dates back to 1973, where Barlow et al. (1973) reported the use of this agent with or without bleomycin in various gynecologic malignancies. This paper (the lead article in that issue of Cancer) reported a 25% response rate in women with ovarian cancer treated with doxorubicin alone. In a larger study in 1974 by O'Bryan et al. (again, the lead article in that issue of Cancer) (O'Bryan et al., 1973), a more modest 11% response rate to doxorubicin. In a comparison with melphalan (the standard chemotherapy in 1975), de Palo et al. (1975) reported a 42% response rate (similar to that of melphalan), causing doxorubicin to be considered a standard management option in this disease. In 1977, the same group reported a 25% response rate with doxorubicin (with no difference in response when melphalan was added to the regimen) (de Palo et al., 1977). In the recurrent setting, doxorubicin was also shown to have clinical benefit, with 32% of patients treated, showing disease that was either stable or responsive to treatment (Bolis et al., 1978).

In these data from the pre-platinum and pre-taxane era, doxorubicin was shown to have a response rate similar to many of the chemotherapy agents considered to be the standards of care for the treatment of platinum-resistant, recurrent disease (including PLD, whose objective response rate was 12% in a contemporary, randomized clinical trial in women with recurrent ovarian cancer) (Mutch et al., 2007).

Currently, in response to a petition by community oncologists, the National Comprehensive Cancer Network (NCCN) has reinstate doxorubicin as a "potentially active agent", in the same category as other chemotherapy agents that are not uncommonly used to treat recurrent ovarian cancer (including albumin-bound paclitaxel, premetrexed, vinorelbine, cyclophosphamide, capecitabine, altretamine, and hormonal therapies such as aromatase inhibitors, megestrol and tamoxifen) (Anon, 2015). Despite similar response rates compared to doxorubicin, however, PLD remains listed as a preferred single agent.

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Regarding the toxicity of doxorubicin (versus PLD), the most commonly cited argument for the use of PLD is its lower incidence of cardiotoxicity compared to doxorubicin. This is likely to be true at higher cumulative exposures (above 400 mg/m²); however at the limited exposures most patients with platinum-resistant recurrent ovarian cancer are destined to receive (due to the low response rates of anthracyclines in general), the cardiotoxicity is likely to be similar. In a prospective study comparing doxorubicin (60 mg/m² every 3 weeks) and PLD (50 mg/m² every 4 weeks) in the first-line treatment of metastatic breast cancer, multigated blood-pool imaging (MUGA) scans were performed to measure LVEF before onset of treatment, after 300 mg/m² cumulative anthracycline exposure, and after every additional 100 mg/m² of PLD and every 120 mg/m² of doxorubicin. The incidence of symptomatic heart failure was 0% in the PLD group and 4.4% in the doxorubicin group (O'Brien et al., 2004). Interestingly, in this and other studies in women with breast cancer (Harris et al., 2002; Batist et al., 2001), PLD was not shown to be any more effective than doxorubicin, and thus the FDA has not approved PLD in this disease. As expected, non-cardiac toxicity in these studies demonstrates a higher rate of hand foot syndrome and stomatitis with PLD, and a higher rate of alopecia and neutropenia with doxorubicin. However, the overall toxicity profiles of these drugs are relatively similar (Table 1).

Table 1

Table Non-cardiac adverse events with pegylated liposomal doxorubicin 50 mg/m² every 4 weeks versus doxorubicin 60 mg/m² every 3 weeks in metastatic breast cancer (O’Brien et al., 2004).

|              | Pegylated liposomal Doxorubicin | Doxorubicin |
|--------------|---------------------------------|-------------|
|              | All grades                      | Grade 3/4   | All grades | Grade 3/4 |
| Hand foot syndrome | 48%                              | 17%         | 2%         | 0%        |
| Rash         | 10%                              | 2%          | 2%         | 0%        |
| Nausea       | 37%                              | 3%          | 51%        | 5%        |
| Vomiting     | 19%                              | < 1%        | 31%        | 4%        |
| Fatigue      | 12%                              | < 1%        | 16%        | 2%        |
| Anorexia     | 11%                              | 1%          | 10%        | < 1%      |
| Stomatitis   | 22%                              | 5%          | 15%        | 2%        |
| Alopecia     | 20%                              | 0%          | 66%        | 0%        |
| Anemia       | 5%                               | 1%          | 7%         | 2%        |
| Neutropenia  | 4%                               | 2%          | 10%        | 8%        |
| Thrombocytopenia | 1%                              | 0%          | 1%         | < 1%      |

So, given the comparable (and limited) efficacy combined with a similar toxicity profile (including cardiac toxicity) in women receiving an anthracycline for recurrent, platinum-resistant ovarian cancer, the cost differences between PLD ($4363/cycle) and doxorubicin ($30/cycle) cannot be ignored. The Kushnir study touts what amounts to a minor cost savings opportunity of less than $200,000. What about the larger question of using PLD instead of doxorubicin, and missing a cost savings opportunity of nearly $4.5 million? As providers for patients with gynecologic cancers, we have to ask ourselves what has been accomplished by substituting PLD for native doxorubicin. Do we know something about anthracyclines that have escaped detection (and been ignored) by the rest of the oncology community? Next time (and always) before prescribing chemotherapy for a patient with recurrent, platinum resistant ovarian cancer, we should pause and question the value of the intervention we are considering. Is PLD really a high-value intervention in this setting, especially at more than 100 times the cost of doxorubicin?

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