



Lecture at Cancer Lifeline, Part 1 Relapsed Small Cell Lung Cancer

**Howard (Jack) West, MD
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Hello, my name is Dr. Jack West, and I'm a medical oncologist specializing in lung cancer at the Swedish Cancer Institute in Seattle, WA. I also serve as the President & CEO of GRACE, the Global Resource for Advancing Cancer Education. The following video presentation is an excerpt from a lecture I delivered in June of 2009 at Cancer Lifeline, a Seattle-based non-profit organization for cancer patients and caregivers.

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The first point I'd make is that we're really moving toward a time when we are going to be personalizing and individualizing lung cancer management more than we have previously. In years past, the breakdown has really just been between small cell lung cancer and non-small cell lung cancer. Non-small cell is the clear majority accounting for now about 85% even close to 90% of lung cancer that we see. Small cell declining every 5-10 years when we look at the numbers for reasons that we don't entirely understand, but it probably has to do with smoking patterns changing overall, fewer people smoking for years and years and years.

Small cell lung cancer arises in the center of the chest and filtered cigarettes allow for smaller particles to get out into the further parts of the chest. So what we see is more adenocarcinomas from out in the periphery of the chest from the smaller particles and fewer squamous cell carcinomas and small cell lung cancers.

So, this distinction between small cell and non-small cell is based on a pathologist looking at the biopsy tissue from a tumor under a microscope. It's just looking at it. And that is something that is pretty reliable, not airtight, but generally good. The breakdown of these subtypes of non-small cell lung cancer has not been perfect because cancer cells often become chaotic and don't look the way they started. And as they become more poorly differentiated or mutated from their normal starting point, it gets difficult to see the difference between what was an adenocarcinoma over a small cell or some other type.

So, there is not clear correlations of one pathologist's version of an adenocarcinoma versus a squamous, etc. We didn't used to care about that because everything called non-small cell lung cancer was treated the same way. The reason I'm focusing on this question now is that it's starting to matter the subtypes of lung cancer because we are coming up with algorithms where some treatments seem to work better or not as well or have more side effect issues if you have one subtype versus another. And I'll talk more about that.

So, I'm going to start by talking about small cell lung cancer. That has been a difficult nut to crack. Small cell lung cancer is generally treated with a combination of platinum and etoposide, or cisplatin is the older drug. Carboplatin is sometimes used. These drugs have been used for small cell lung cancer for 15 years or so. We have been trying to find something that will work better and it has been very difficult to find that.

One of the developments in small cell lung cancer has been a focus on how to better treat patients who have it come back, which unfortunately is all too common with small cell. There is a drug approved by the FDA called topotecan or Hycamtin® is its trade name. It's modestly helpful, but not as much as we would like. We really haven't had a lot of tools that have any proven benefit otherwise.

This agent amrubicin is in trials; it's actually approved in Japan where they have more experience with it. And what we see in this study which is actually from Japan is that they give this drug for three days to patients who have relapsed small cell lung cancer. In the breakdown of relapsed small cell, we talk about sensitive or refractory disease and that has to do with the time that it took after you stopped your last chemo before the cancer started to progress. It's either two or three months depending on the study and the exact definition, but if the progression is within 60-90 days it's usually called refractory; and if it's longer we call it sensitive. And refractory disease has been very, very hard to treat. Small cell often responds very nicely early on. But when it comes back, we have a very difficult time with it.

So this work coming out of Japan was exciting because it showed a response rate of 50% or so and that held up whether you had the relapsed form, the resistant form refractory or sensitive. And the response, the survival rate median is approaching a year which means that half of the patients do better and half do not do as well. But these numbers are really better than we have seen with the agents we've had up to now. So, that is interesting work out of Japan.

What we are also starting to appreciate is they are differences in different populations—Asia and Japan specifically versus North American or European populations. The cancer is different. How these drugs work in people can be different. So it's worth seeing how these agents actually work in North American populations. And this study is one of those that directly compared amrubicin to our current standard of topotecan, or Hycamtin®, the FDA-approved second-line treatment. And when they're tested head-to-head, this is not a large study — 76 patients — but we can see that more patients on amrubicin are actually getting more of the treatment. The response rate is fully ten times higher, 4% response rate versus 34% with amrubicin and an extra month going by before we see progression to needing something else or considering moving to supportive care.

We see that the side effect profile is not remarkably different, certainly not clearly worse with amrubicin. This is a chemotherapy drug that primarily drops blood counts as the leading side effect. And it really compares similarly to more favorably than our current standard. So, encouraging to see but not a very large study.

This is a Japanese experience, really the same design of comparing amrubicin to topotecan, also known as Hycamtin®. This is 60 patients, or 59. And again we see a response rate difference that's pretty significant—38% versus 13% and in the sensitive population it's more than doubled. We saw no responses to topotecan in the resistant population. I would like to say it's 50%, but it's not, it's 17%, but that's a lot better than zero; and again more than a month

improvement in progression-free survival. And toxicity differences, again nothing really to concern us very much.

So these are not the definitive studies yet. They are only modest-sized. But they certainly give us some legitimate reason to be hopeful that we can break this impasse that we've been at for very long of not having enough effective agents. It would be very welcome to have a new one available.

This is a summary of some of the studies that have been done with amrubicin in the second-line setting. And we are seeing response rates that are all the way up in the 50% range in some, and in others at least in the high teens to 30%-40%. So, it definitely has activity and it's being tested in some larger studies that really should clarify whether it is going to earn a place as a standard treatment for small cell lung cancer in the next few years. And it's being tested both in first-line and second-line.

I'd mentioned that the platinum-etoposide combination has been our go-to combination for a very long time. We'd love to move beyond it if we could find something better. Perhaps this is the combination—cisplatin and amrubicin. It's also being tested in the second-line setting. Cisplatin directly compared with amrubicin in a trial large enough to really say something conclusive. And there is certainly a lot of interest among the physicians and in the small-cell community to move beyond what we have.