

## Abstract

This 5-part Lung Cancer Supplement includes an overview of what is new in lung cancer from the most recent ESMO meeting (October 2011), authored by Gwyn Bebb, MA, BMBCh, PhD, FRCPC. A summary by Peter Ellis, MBBS, MMed, PhD, FRACP, FRCPC, on the current challenges posed by metastatic NSCLC reflects the many strides that have been made in improving treatment options. Christopher W. Lee, MD, FRCPC, and Nimira Alimohamed, MD, with Gwyn Bebb, MA, BMBCh, PhD, FRCPC, address mesothelioma and small cell lung cancer respectively, malignancies where progress seems disappointingly slower. Julia Devonish, PhD, Nicole Culos-Reed, PhD, and Gwyn Bebb, MA, BMBCh, PhD, FRCPC, review the emerging role of physical activity in lung cancer, an intervention that is validated in other cancers, but has yet to make useful inroads in lung cancer management. The fact that this topic is now entering consciousness is testament in itself that expectations in lung cancer management are growing. We need to tout our successes in lung cancer treatment and let our marathon-running lung cancer survivors start to take the limelight.

## Keywords

lung cancer, pulmonary cancer, small-cell lung cancer, non-small cell lung cancer, mesothelioma, physical activity, exercise, chemotherapy, radiotherapy.

### **16<sup>th</sup> ECCO/36<sup>th</sup> ESMO EUROPEAN CANCER CONGRESS, STOCKHOLM**

Update on research and management implications in NSCLC and SCLC

**Gwyn Bebb, MA, BMBCh, PhD, FRCPC**

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## 16<sup>th</sup> ECCO/36<sup>th</sup> ESMO EUROPEAN CANCER CONGRESS, STOCKHOLM

### Update on research and management implications in NSCLC and SCLC

Gwyn Bebb, MA, BMBCh, PhD, FRCPC

As summer faded and autumn announced its presence, Stockholmers, not unlike their Canadian counterparts, were enjoying the last pleasures of balmy weather while anticipating an early start to what is forecast to be a long, cold winter. A brief glimpse at the geography of the Swedish capital reveals an unlikely location for a city, not to mention the seat of government. It consists of a system of islands, scattered in a mixture of sea and fresh water, all connected by a series of bridges to somehow create a cohesive, urban theme. From a lung cancer perspective, the 16<sup>th</sup> European CanCER Organization (ECCO)/36<sup>th</sup> European Society for Molecular Oncology (ESMO) European Cancer Congress, hosted by Stockholm for the second time in 4 years, will not go down in the annals as a meeting that rocked clinical practice in lung cancer to its core. Indeed, at times, the lung cancer program appeared to resemble Stockholm's own geography, an archipelago of seemingly unrelated trials, topics and presentations. Nevertheless, with some help from Swedish icons, it is possible to string some of these threads together to form cohesive commentary from the lung cancer presentations related to locally advanced Stage III non-small cell lung cancer (NSCLC), metastatic NSCLC, small cell lung cancer (SCLC), key trial data from AVAPER1, ECOG 5508, FLEX and BMS-099, as well as important findings regarding IHC and H scores.



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#### **LOCALLY ADVANCED STAGE III NSCLC: RADIATION MAY BE KEY TO BETTER OUTCOME**

Combination radical chemoradiation remains the mainstay of treatment for patients with locally advanced Stage III NSCLC, a paradigm based on research initiated in the 1990s. Long-term survival remains stubbornly steady at about 15-20%.

Changing this outcome has been challenging: newer agents are proving difficult to incorporate into this recipe, while the role of surgery as the third component of a trimodality approach remains controversial. In addition, increasing the dose of radiation seems unlikely to be the key to further improvements since, as pointed out by Senan et al,<sup>1</sup> even in countries such as the Netherlands, only about one-third of patients are candidates for radical treatment. Clearly, a concerted effort to make radical treatment more feasible to a larger proportion of patients is required.

So what can be done? A number of presentations at the 16<sup>th</sup> ECCO/36<sup>th</sup> ESMO European Cancer Congress by Senan,<sup>1</sup> Price<sup>2</sup> and Pastorani<sup>3</sup> contributed to the impression that the key may lie in improving radiation approaches. Clearly, increasing what is already considered "a radical dose" is not generally feasible, but making minor adjustments to several other approaches may pay dividends. While we cannot improve one thing by 100%, it may be possible to improve 100 things by 1%. Better imaging allows for improved staging and better subclassification of what is a very heterogeneous group of patients. Radiating only positron emission tomography (PET)-positive disease may lead to improved targeting of active disease and a reduction in the volume of lung treated. Better tumour targeting using newer techniques such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) may also play a substantial role. True, we may have heard this before, but a few tweaks here and there can, just as in a cover version of an ABBA song, make the sound a lot more palatable. In practical clinical terms, this will require (i) a more integrated multi-disciplinary approach, (ii) the willingness to apply more expensive technology to the cause of lung

cancer, and (iii) a willingness to design more Phase III trials for this heterogeneous category of NSCLC patients. Although the first two seem doable, the last, as alluded to by Dr. E Felip, the discussant, does not seem forthcoming at present.

## **METASTATIC NSCLC: MAINTENANCE TREATMENT UNDER DEBATE**

There was more to digest in the world of metastatic NSCLC, which is still confronted by 2 main topics of interest: maintenance chemotherapy and the identification of predictive markers of response. The relentlessness of Swedish tennis star Bjorn Borg is echoed by attempts to demonstrate that treatment beyond the classic 4-6 cycles of first-line platin-based chemotherapy yields useful clinical benefits. This area of research is clouded by, among other things, matters of definition: Does “maintenance” constitute merely the continuation of one of the agents used in the initial therapeutic regimen — such as in the continuation of bevacizumab — to progression, or does it also include what may be termed “early second-line” treatment with a different agent, such as pemetrexed initiated immediately after completion of 4-6 cycles of platin-based treatment? An acknowledgement of the need for clarity here was reflected by Des Guetz<sup>4</sup> in his presentation of the results of a meta-analysis of maintenance treatment in NSCLC. His findings pointed to a benefit of using maintenance treatment, but the magnitude of benefit seemed to depend on its specific nature. A hazard ratio (HR) of 0.93 was quoted for “continuation treatment,” 0.85 for “switch treatment” and 0.83 for “biologic treatment.” These benefits come at the expense of toxicity. However, given the inconsistency of trial design in this field to date, it was concluded that the jury is still out on this issue.

### **AVAPERL AND ECOG 5508 TRIALS — MAINTENANCE TREATMENT HERE TO STAY?**

More light on the maintenance issue was provided by the presentation of the AVAPERL trial (AVAPERL: A Study of Avastin (Bevacizumab) With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous Non-Small Cell Lung Cancer) by Barlesi.<sup>5</sup> In this trial, patients with metastatic NSCLC were assessed for response after completing first-line chemotherapy.

Those who had progressed were excluded from the rest of the trial and those with either stable disease or partial responses and who had not experienced significant toxicity were then randomized to maintenance pemetrexed versus maintenance pemetrexed and bevacizumab. A total of 376 patients were enrolled. At the end of definitive first-line chemotherapy, the disease control rate was 62%, meaning that 253 patients were randomized to the maintenance arms. Analysis showed a significantly longer progression-free survival (PFS) (starting from the beginning of treatment) in the maintenance pemetrexed and bevacizumab combination arm, at 10.2 vs. 6.6 months (HR 0.50,  $p < 0.001$ ).

There were a number of criticisms laid against this trial as outlined by the discussant R. Dziadziuszka: there was no non-maintenance arm for comparison. In addition, the design of the trial whereby those who progressed on chemotherapy were excluded made for a very select group of patients. Consequently, it is difficult to ascertain how much of the benefit was attributable to the nature of the enrolled patients. As was pointed out by the discussant, it is also difficult to know which of the agents is really responsible for the benefit seen. Additional, more meaningful information will come from the ECOG 5508 trial (a randomized Phase III study of maintenance therapy with bevacizumab, pemetrexed or a combination of bevacizumab and pemetrexed, following carboplatin, paclitaxel and bevacizumab for advanced NSCLC) currently ongoing in the US. We were left with the impression that this Borg-like relentlessness is paying off and that maintenance treatment will soon be here to stay, but that the concept does need one of those classic Borg winning passes from the baseline to secure its place in the lung cancer management paradigm.

Another Swedish icon, IKEA, has taught us that great things can be achieved in small spaces. It could be said that “IKEAfication” is the way we would like to go in NSCLC. Although we have recognized several histologic subtypes of NSCLC since pre-ABBA days, the management implications of that analysis was until recently non-existent. Over the last several years the need to distinguish squamous from non-squamous cancers has been highlighted by the need to avoid treating those tumours with anti-angiogenic agents and to reserve pemetrexed for the treatment of non squamous disease. However,

the most significant trend is that of the further subdivision of the broad swathe of NSCLC into several molecularly-defined subgroups. A vision exists for NSCLC to be divided into a range of smaller subgroups, each maybe making up no more than 5-7% of the total, whereby a more individualized approach to treatment can be made. Currently, this is most notable in the EGFR-activating mutation positive and the EML4 ALK translocation positive subgroup of NSCLC, where molecular classification is already directing treatment decisions.

## FLEX TRIAL: POST HOC ANALYSIS

Recent experience has tempered some of this enthusiasm because of an inexplicable inability to put K-RAS into context in NSCLC in the way it has been placed in colorectal cancer. A very interesting and potentially management-changing series of presentations was made by O'Byrne,<sup>6</sup> Lynch<sup>7</sup> and Rüschoff<sup>8</sup> regarding the post hoc analysis of the FLEX (First-Line Erbitux in Lung cancer) trial.

In this trial, Stage IV NSCLC patients were randomized to receive chemotherapy with or without the anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) cetuximab. Of note, a biopsy assessable for EGFR expression was a required for enrolment. O'Byrne explained how previous analysis using classic immunohistochemistry (IHC), with a 1+, 2+, 3+ scoring system, suggested that IHC-based assessment of EGFR was not a factor in determining the utility of cetuximab in this setting. However, a more quantitative IHC method, H analysis, whereby samples are given a score out of 300 based on both intensity of staining and the proportion of the sample that stains (H score = 1 x [% 1+ cells] + 2 x [% 2+ cells] + 3 x [% 3+ cells]), seemed to change this picture. Statistical analysis suggested that patients whose tumours scored 200 or more on this scale benefited from the addition of cetuximab, increasing the median overall survival from 8.9 to 11.2 months. While more pronounced in adenocarcinomas, this benefit was seen across all histologies.

## BMS-099 TRIAL: IHC SCORES AND RESPONSE RATES

In light of the preliminary analysis presented at International Association for the Study of Lung Cancer (IASLC) earlier in Amsterdam, a similar analysis was carried out on the BMS-099 trial. In this trial,

cetuximab was added to carboplatin and paclitaxel in the same setting. Unlike the FLEX trial, tissue availability was not a prerequisite for enrolment and only 22% of patients had tissue available for IHC analysis, compared with 96% in FLEX. Despite this, a high IHC H score (>200) predicted for a better response rate to the cetuximab-containing regimen and showed a trend toward better survival. This was interpreted by Lynch<sup>7</sup> as lending significant support to the finding in the FLEX trial and adds further weight to the utility of this quantitative IHC approach.

## VALIDATION OF H SCORING

The final part in this series of presentations outlined how H scoring had been validated during its introduction into the trial and how interobserver variation was evaluated, then minimized. Rüschoff<sup>8</sup> explained that 14 "blinded" pathologists had independently scored 30 NSCLC samples stained for EGFR using the same antibody. The importance of this approach was illustrated by showing 2 examples of IHC EGFR staining that would both have been assessed as 3+ on the classic scoring system, but which on H scoring differed dramatically, scoring 30 (10% of cells staining 3+) vs 270 (90% of cells scoring 3+). Pretraining concordance rate was 76% with a  $\kappa$  of 0.5 but a posttraining concordance rate of 90% and  $\kappa$  of 0.8 was achieved. As usual, the concordance rate was lowest in the mid-scoring range, between 150 and 200.

As summarized by the discussant Hirsch, it is difficult to be certain what the implications of these results will be, but there are grounds for thinking that they will soon affect clinical practice. First, these findings demonstrate that a methodologic approach to IHC can yield a more meaningful, less subjective scoring system. While not quite as quantitative a system as HistoRX AQUA,<sup>®</sup> the H system does account for both intensity and extent of expression within a given sample while still not requiring "fancy" equipment. Second, from a mechanistic angle, it makes sense that the efficacy of a therapeutic mAb is related to the density of the target in the tissue of interest. Whether the mAb is thought to exert its effect through modulation of the target in the cancer cell or by inducing an immune response against those cells, the target needs to be there for binding to occur. It would seem therefore that more quantitative assessment

of the presence of specific targets will become a watchword in this era of personalized medicine. Third, it helps put the role of K-RAS into context and suggests that at least in NSCLC, as long as there is enough EGFR expression, K-RAS status may not be important in determining the usefulness of anti-EGFR mAbs. Last, although it is a post hoc analysis, samples in the FLEX study were collected prospectively in 100% of the patients and so the quality of the data is high. There is no doubt that Sanofi-aventis will now file for an indication for use in NSCLC based on these data — probably the biggest clue that day-to-day oncology practice will be affected. The IKEAfication of NSCLC must continue.

### PROGRESS IN LUNG CANCER EXCEPTIONAL IN NSCLC, NOT SCLC

From a lung cancer perspective, a striking feature of the 16<sup>th</sup> ECCO/36<sup>th</sup> ESMO European Cancer Congress was continued silence in the field of SCLC, an area of study that continues to be a graveyard for investigative treatments. Discouragingly, management of this disease remains remarkably similar to its management in the heyday of ABBA and when Borg last won Wimbledon. As reviewed later in this supplement, recurrent SCLC remains incurable and is an area of particular research and therapeutic need. SCLC represents one of the few areas of oncology where management is yet to be influenced by an improved understanding of its molecular basis.

However, in surveying the field of NSCLC in 2011, it is impossible not to marvel at the progress that has been made in 20 years: from no systemic treatment to the availability of third- and fourth-line options; from no molecular guidance to the acceptance of 2 predictive markers into current management paradigms; and from a culture of “no hope” to one of increasing possibilities and even an expectation that significant progress is just around the corner. One discussant from the 16<sup>th</sup> ECCO/36<sup>th</sup> ESMO European Cancer Congress commented that the fact that other tumour sites are trying to emulate the success of the adoption of multidisciplinary management in NSCLC is testament to how far things have come.

Equally noteworthy is that this remarkable progress has not come about as a result of one Nobel prize-worthy “eureka moment,” but rather as a consequence of a series of difficult small steps.

Each small step represents years of dedication by researchers, extensive and sometimes protracted clinical trials, the meticulous translation of new evidence into oncology practice and the time and energy of many thousands of patients who are rather anonymously represented on all those survival curves. While Alfred may be disappointed that there is no award to be given on his behalf in the field of lung cancer, he would be at least happy to think that the previous nihilism associated with lung cancer has been exploded: boom goes the dynamite.

### REFERENCES

1. Senan S. Intensity modulated radiotherapy: fixed beam and arc delivery techniques for locally advanced disease. 6th ECCO/36th ESMO European Cancer Congress. Abstract 256.
2. Price A, Kerr GR, Erridge SC et al. Integrating systemic and radiation therapy in advanced disease JAD 6th ECCO/36th ESMO European Cancer Congress. Abstract 257.
3. Pastorino U. Does surgery improve outcome? 6th ECCO/36th ESMO European Cancer Congress. Abstract 258.
4. Des Guetz G, Uzzan B, Chouahina K et al. Is there a benefit to maintenance therapy after first line chemotherapy in advanced non-small cell lung cancer - a systematic review with meta-analysis. 6th ECCO/36th European Cancer Congress. Abstract 9005.
5. Barlesi F, de Castro J, Dvornichenko V et al. AVAPERL: Final efficacy outcomes after first-line bev-cisplatin for patients with advanced non-squamous non-small cell lung cancer randomized to continuous maintenance with bevacizumab (bev) or bev + premetrexed after first-line bev-cisplatin- premetrexed treatment. 6th ECCO/36th ESMO European Cancer Congress. Abstract 34LBA.
6. O'Byrne K, Paz-Ares L, Pereira JR et al. Epidermal growth factor receptor expression as a predictive biomarker of survival in patients with advanced non-small cell lung cancer receiving first-line therapy with cetuximab combined with chemotherapy in the FLEX trial. 6th ECCO/36th ESMO European Cancer Congress. Abstract 9000.
7. Lynch T, Bhagavatheeswaran P, Mukhopadhyay P. A retrospective subgroup analysis of EGFR immunohistochemistry expression by histo-score correlated to outcomes from the BMS099 1st line phase III NSCLC trial of cetuximab plus carboplatin/taxane. 6th ECCO/36th ESMO European Cancer Congress. Abstract 9001.
8. Rüschoff J, Kerr KM, Buttner R et al. Round robin test to evaluate the reproducibility of a therapeutically relevant immunohistochemical score for the categorization of non-small cell lung cancer (NSCLC) into tumours with high and low epidermal growth factor receptor (EGFR) expression. 6th ECCO/36th ESMO European Cancer Congress. Abstract 9002.

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## SYSTEMIC THERAPY FOR NON-SMALL CELL LUNG CANCER IN 2011

### Multiple options linked to improved survival and quality of life

Peter M. Ellis, MBBS, MMed, PhD, FRACP, FRCPC

The last 2 decades have seen a movement from relative nihilism about the role of systemic therapy for non-small cell lung cancer (NSCLC) to support based on high-quality evidence for the use of chemotherapy in the adjuvant setting<sup>1,2</sup>, as well as first<sup>3-5</sup> and subsequent lines of therapy for advanced disease.<sup>6-9</sup> Data have emerged to promote the use of maintenance therapy following first-line chemotherapy.<sup>10-11</sup> Targeted agents have been incorporated into treatment algorithms for advanced NSCLC,<sup>12-14</sup> and an understanding of the molecular phenotypes of NSCLC is being used to guide treatment selection.<sup>15-17</sup> This article provides an overview of the current status of therapy for NSCLC.

#### ADJUVANT CHEMOTHERAPY

Prior to 2004, routine use of postoperative adjuvant systemic therapy was not recommended. Many trials published since then<sup>1,2,18</sup> demonstrate about a 10% improvement in overall survival (OS) for completely resected stage II and III NSCLC patients receiving adjuvant cisplatin-vinorelbine chemotherapy.<sup>19</sup> Retrospective subgroup analyses of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) BR.10 and Cancer and Leukemia Group B (CALGB) 9633 trials also support improved survival from adjuvant chemotherapy for patients with larger, Stage IB tumours ( $\geq 4$  cm).<sup>20,21</sup> Adjuvant chemotherapy is now the standard of care for patients with resected Stage IB  $\geq 4$ cm, II and IIIA NSCLC.

#### FIRST-LINE CHEMOTHERAPY

We have known for some time that chemotherapy results in modest survival improvements for patients with advanced NSCLC.<sup>22</sup> Gemcitabine, vinorelbine, paclitaxel or docetaxel combined with a platinum agent are all similarly effective and result in gains in median survival of 3 to 4 months.<sup>3,5</sup> Typically, chemotherapy would not be continued

beyond 4 to 6 cycles. Recent data have shown the importance of histologic subtypes in the selection of chemotherapeutic drugs.<sup>4,23</sup> For patients with non-squamous histology, regimens containing pemetrexed may offer small OS improvements compared to other regimens. However, recent evolution of the NSCLC treatment paradigm means that no one first-line treatment option is clearly superior.

#### MAINTENANCE THERAPY

Recent data have challenged the theory on duration of therapy. Several trials have shown improved survival for patients switching to pemetrexed or erlotinib immediately following 4 cycles of first-line chemotherapy.<sup>10,24</sup> Questions exist about the design of these trials and whether the benefit is limited to subgroups of patients with stable disease following first-line therapy. Nevertheless, maintenance therapy is now a consideration for patients completing first-line chemotherapy.

#### TREATMENT BEYOND PROGRESSION

Data from a number of randomized trials indicate that second- and third-line treatments improve survival of NSCLC patients.<sup>6-9</sup> Trials initially demonstrated that docetaxel increased median survival by 2 to 3 months.<sup>8</sup> These gains were associated with quality of life improvements.<sup>25</sup> Subsequently, pemetrexed was shown to be noninferior to docetaxel.<sup>7</sup> A retrospective analysis also showed non-squamous histology was predictive of improved survival for patients treated with pemetrexed.<sup>23</sup> More recently, molecular-targeted agents have also shown benefit for this patient group. Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, improves survival and quality of life as second- or third-line therapy in patients not eligible for further chemotherapy.<sup>9,26</sup>

Questions continue about the appropriate



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sequence of therapy following progression on first-line therapy. Two trials, INTEREST (IRESSA NSCLC Trial Evaluating Response and Survival against Taxotere),<sup>27</sup> which compared second-line docetaxel vs gefitinib, and TITAN (Tarceva in Treatment of Advanced NSCLC,<sup>28</sup> evaluating pemetrexed vs erlotinib, showed similar progression-free survival (PFS) and OS for second-line chemotherapy or second-line EGFR therapy. These data suggest that the sequence of second- and third-line therapy is probably less important than maximizing the number of patients who receive both lines.

## INTEGRATING TARGETED THERAPIES INTO SYSTEMIC TREATMENT

Many molecular targets have been identified that appear important in NSCLC cell growth and proliferation. To date, the most promising approach has been the inhibition of angiogenesis. Bevacizumab, a monoclonal antibody against circulating vascular endothelial growth factor (VEGF), is the only agent approved for NSCLC. The Eastern Cooperative Oncology Group (ECOG) 4599 trial evaluated the addition of bevacizumab to carboplatin-paclitaxel chemotherapy.<sup>13</sup> Results showed increased objective response rates (ORR) and PFS, translating to a 2-month OS improvement. A second trial, AVAIL (Avastin in Lung), studied bevacizumab in combination with cisplatin and gemcitabine,<sup>12,29</sup> but was not able to demonstrate any improvement in OS. Nevertheless, bevacizumab is incorporated in first-line treatment algorithms for advanced NSCLC. Toxicity concerns limit this to good-performance status patients with non-squamous histology, no brain metastases, no history of hemoptysis and no history of venous thromboembolic or bleeding disorders.

Several trials have assessed the addition of cetuximab, a monoclonal antibody against EGFR, in combination with chemotherapy.<sup>14,30</sup> FLEX (First-Line Erbitux in Lung Cancer) showed a small OS improvement, with increased toxicity.<sup>14</sup> Cetuximab does not have regulatory approval for NSCLC and has had limited impact on treatment. To date, approaches targeting the insulin-like growth factor receptor (IGFR) have not improved survival.<sup>31</sup>

## MOLECULAR-GUIDED THERAPY

The discovery of activating mutations of the EGFR gene has changed the paradigm that all NSCLC

patients should be treated in the same manner.<sup>32,33</sup> The presence of an exon 19 deletion or an L858R point mutation of exon 21 is predictive of a high likelihood of response to EGFR tyrosine kinase inhibitors. Multiple randomized trials have now demonstrated large improvements in PFS for EGFR mutation-positive patients receiving first-line gefitinib or erlotinib in comparison to platinum-based doublets.<sup>15,16,34</sup> Additionally, EGFR wild-type patients appear to suffer harm from first-line EGFR therapy.<sup>15</sup> Testing for the presence of an EGFR mutation should be routinely performed in patients with advanced NSCLC.

More recently, a new molecular subset of NSCLC has been defined based on a translocation of the echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) genes.<sup>35</sup> The presence of such translocations appears to predict benefit from crizotinib, an ALK inhibitor.<sup>17</sup> Comparative trials against first- and second-line chemotherapy options are ongoing, as is research to further characterize the molecular phenotypes of lung adenocarcinomas.

## BALANCING BENEFITS AND RISKS

Multiple options now exist for the systemic treatment of NSCLC. Benefits are modest but linked to both improved survival and quality of life. The challenge for clinicians treating patients with NSCLC remains to balance the expected benefits against toxicities and patient preference.

## REFERENCES

1. Winton T, Livingston R, Johnson D et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005;352:2589-97.
2. Douillard JY, Rosell R, De Lena M et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006;7:719-27. Erratum in *Lancet Oncol* 2006;7:797.
3. Fossella F, Pereira JR, von Pawel J et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group.[see comment]. *J Clin Oncol* 2003;21:3016-24.
4. Scagliotti GV, Parikh P, von Pawel J et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543-51.
5. Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92-8.

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6. Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354-62.
7. Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589-97.
8. Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000;18:2095-103.
9. Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123-32.
10. Cappuzzo F, Ciuleanu T, Stelmakh L et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521-9.
11. Douillard JY, Shepherd FA, Hirsh V et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. *J Clin Oncol* 2010;28:744-52.
12. Reck M, von Pawel J, Zatloukal P et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. *J Clin Oncol* 2009;27:1227-34.
13. Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542-50.
14. Pirker R, Pereira JR, Szczesna A et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial.[see comment]. *Lancet* 2009;373:1525-31.
15. Mok TS, Wu YL, Thongprasert S et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. [see comment]. *N Engl J Med* 2009;361:947-57.
16. Rosell R, Gervais R, Vergnenegre A et al. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomized trial. ASCO Meeting Abstracts 2011;29:7503.
17. Kwak EL, Bang YJ, Camidge DR et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363:1693-703.
18. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351-60.
19. Douillard JY, Tribodet H, Aubert D et al. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the lung adjuvant cisplatin evaluation. *J Thorac Oncol* 2010;5:220-8.
20. Butts CA, Ding K, Seymour L et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. *J Clin Oncol* 2010;28:29-34.
21. Strauss GM, Herndon JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008;26:5043-51.
22. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995;311:899-909.
23. Peterson P, Park K, Fossella F et al. Is pemetrexed more effective in adenocarcinoma and large cell lung cancer than in squamous cell carcinoma? A retrospective analysis of a phase III trial of pemetrexed vs docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2007;2:P2-328.
24. Ciuleanu T, Brodowicz T, Zielinski C et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;374:1432-40.
25. Dancey J, Shepherd FA, Gralla RJ, Kim YS. Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial. *Lung Cancer* 2004;43:183-94.
26. Bezzak A, Tu D, Seymour L et al. Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol* 2006;24:3831-7.
27. Kim ES, Hirsh V, Mok T et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008;372:1809-18.
28. Ciuleanu T-E, Stelmakh L, Cicenias S et al. Efficacy of second-line erlotinib versus chemotherapy relative to biomarker status in the phase III global TITAN study in advanced non-small cell cancer (NSCLC). *J Thorac Surg* 2011;6(6 Suppl 2):S316.
29. Manegold C, Von Pawel J, Zatloukal P et al. BO17704 (AVAIL): A phase III randomized study of first-line bevacizumab combined with cisplatin/gemcitabine (GC) in patients with advanced or recurrent non-squamous, non-small cell lung cancer (NSCLC). *Ann Oncol* 2008;19:LBA1.
30. Butts CA, Bodkin D, Middleman EL, et al. Randomized phase II study of gemcitabine plus cisplatin or carboplatin, with or without cetuximab, as first-line therapy for patients with advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2007;25:5777-84.
31. Jassem J, Langer CJ, Karp DD et al. Randomized, open label, phase III trial of figitumumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin in patients with non-small cell lung cancer (NSCLC). ASCO Meeting Abstracts 2010;28:7500.
32. Lynch TJ, Bell DW, Sordella R et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129-39.
33. Paez JG, Janne PA, Lee JC et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497-500.
34. Maemondo M, Inoue A, Kobayashi K et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380-8.
35. Shaw AT, Yeap BY, Mino-Kenudson M et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009;27:4247-53.

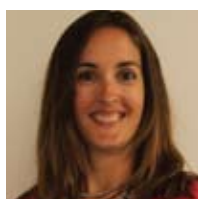
## PHYSICAL ACTIVITY IN LUNG CANCER

# Emerging data link physical activity with long-term benefits

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Interventions aimed at improving physical activity (PA) levels in cancer patients have been established as safe and generally well tolerated both during and after cancer treatments, providing numerous benefits, and perhaps extending survival.<sup>1,2</sup> PA guidelines for exercise testing and prescription in adult survivors of breast, prostate, colon, hematologic and gynecologic cancers have been published.<sup>3</sup>

Although lung cancer (LC) is the second most common malignancy, guidelines do not include this patient population. Emerging data suggest PA benefits both as an exercise-based physiologic assessment during evaluation for resection and as a complementary approach to reproduce benefits observed in other cancer and chronic lung disease populations.<sup>1,4,5</sup> PA interventions must be tailored to 3 distinct clinical settings: 1) resectable disease, 2) unresectable locally advanced disease and 3) metastatic disease.

### RESECTABLE DISEASE

The majority of LC PA research has focused on the surgical population. Approximately two-thirds of patients report activity levels insufficient to meet guideline recommendations.<sup>6</sup> Importantly, those meeting guidelines report better quality of life (QoL) than less active counterparts.<sup>7</sup>

Cardiopulmonary exercise testing (CPET) has become an integrated component of the preoperative risk assessment, as it replicates stressful conditions similar to those experienced during surgical procedures.<sup>8</sup> Evidence of its safety and feasibility in LC has been documented.<sup>9</sup> Exercise testing that assesses maximal oxygen consumption ( $\text{VO}_2\text{max}$ ) is preferred as it is a strong independent predictor of both survival and surgical complications as well as a key factor in determining candidacy in patients whose predicted postoperative forced expiratory volume in 1 second ( $\text{FEV}_1$ ) or diffusing capacity of lung for carbon monoxide ( $\text{D}_{\text{LCO}}$ ) are  $<40\%$ .<sup>4,8,10</sup> Patients with a preoperative  $\text{VO}_2\text{max}$  of  $\geq 15\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ,  $10\text{-}15\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , and  $<10\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  are at low,

increased, and very high risk of surgical complications respectively.<sup>8,11,12</sup>

A compelling reason for PA intervention in LC is the possibility of increasing the number of candidates for curative intent treatments. Through improvements in  $\text{VO}_2\text{max}$  via exercise training, potential surgical candidates may alter their risk category, potentially deeming themselves eligible. Feasibility was demonstrated in 8 patients who, despite favourable clinical stage, were denied surgery based on poor pulmonary functioning.<sup>13</sup> Following 4 weeks of individualized aerobic and resistance training, each patient significantly improved exercise capacity and subsequently received surgery with no mortality and 25% morbidity. Another investigation provided aerobic training at 60-100% of baseline  $\text{VO}_2\text{max}$  until surgical resection.<sup>14</sup> Intention-to-treat analyses found a  $2.4\text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  improvement in  $\text{VO}_2\text{max}$  prior to surgery. Per protocol analyses revealed greater improvement in those attending  $\geq 80\%$  of the prescribed sessions ( $3.3\text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ). Despite small patient series and no level I evidence, some European bodies recommend early pre- and post-operative programs to surgical candidates.<sup>12,15</sup> Improvements in peri- and post-operative recovery have also been noted with this approach.<sup>14</sup>

### LOCALLY ADVANCED AND METASTATIC DISEASE

Advanced LC poses additional challenges. CPET feasibility in inoperable disease found 28% lower  $\text{VO}_2\text{max}$  in patients than in sedentary age- and sex-matched controls.<sup>9</sup> In unresectable or medically inoperable disease, sequential chemotherapy and radiation provides modest improvements in survival in Stage II and III disease, while concurrent radical chemoradiotherapy offers long-term control at the cost of increased toxicity (i.e. Grade 3-4 esophagitis).<sup>16</sup> The systemic effects of chemotherapy on physical functioning, compounded by radiation-induced fatigue and fibrosis likely contribute to the observed

exercise intolerance.<sup>9,16</sup> Significantly more physical symptoms, psychological problems and QoL declines in comparison to other populations of cancer survivors are reported.<sup>17</sup>

Only one intervention in this clinical subset (i.e. Stage IIIB or IV) exists within the literature.<sup>18</sup> The program involved aerobic, resistance and flexibility exercise. No significant differences in QoL, fatigue, mood, muscular strength or functional capacity were observed from pre- to post-intervention, with the exception of improved LC symptoms. While this lone study does provide preliminary evidence of the feasibility of such interventions, it also suggests that maintaining the status quo for longer may be the main benefit. Within the general cancer literature, evidence suggests PA benefits in both metastatic disease and palliation, but extrapolating these conclusions to LC may not be an easy proposition.<sup>19,20</sup>

## FUTURE DIRECTIONS

Guidelines for exercise testing and prescription in cancer have been recently published, with general adult PA guidelines serving as a framework.<sup>3</sup> Given the likelihood that a LC patient will be of an advanced age at presentation, guidelines for older adults may be a more appropriate framework.<sup>21</sup> To further the LC PA evidence, researchers should employ these recommendations around the specificity, frequency, intensity and type of aerobic, resistance and flexibility exercise.

Clearly, there is a dearth of evidence to guide how PA can be incorporated into LC management. While the naysayers will tend to point to the dismal outlook associated with LC as a reason for not pursuing this line of research, there are compelling reasons to drive new research forward. The last decade has seen the acceptance of second- and third-line treatments which have extended LC survival even in the metastatic setting. The incorporation of targeted treatment for molecularly defined patients extends progression-free survival while creating minimal toxicity. It is also important to recognize that 15% of LC patients are never-smokers and are therefore not prone to the classic exercise limitation often associated with LC. There is a need for statistically powered randomized controlled trials within the 3 broad patient categories to examine and validate efficacious intervention, with adequate followup to assess long-term effects, so that the benefits of PA demonstrated in other cancers can potentially be extended to the LC patient.

## REFERENCES

1. Speck RM, Courneya KS, Masse L et al. An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. *J Cancer Survivors* 2010; 4(2), 87-100.
2. Holmes M, Chen WDF, Kroenke C et al. Physical activity and survival after breast cancer diagnosis. *JAMA* 2005; 293:2479-86.
3. Schmitz KH, Courneya KS, Matthews C et al. American College of Sports Medicine. American College of Sports Medicine Roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010.42(7):1409-26.
4. Spiro SG, Gould MK, Colice GL. American College of Chest Physicians Initial evaluation of the patient with lung cancer: Symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines. 2nd Edition. *Chest* 2007. 132(3 Suppl),149S-160S.
5. Shannon VR. Role of pulmonary rehabilitation in the management of patients with lung cancer. *Curr Opin Pulmon Med* 2010.16(4):334-9.
6. Coups EJ, Park BJ, Feinstein MB et al. Physical activity among lung cancer survivors: Changes across the cancer trajectory and associations with quality of life. *Cancer Epidemiol Biomarkers Prev* 2009.29(2):664-72.
7. Coups EJ, Park BJ, Feinstein MB et al. Correlates of physical activity among lung cancer survivors. *Psycho-Oncology* 2009b.18:395-404.
8. Colice GL, Shagazand, Keenan R et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidence-based clinical practice guidelines. 2nd Edition. *Chest* 2007. 132 (3 Suppl):161S-177S.
9. Jones LW, Eves ND, Mackey JR et al. Safety and feasibility of cardiopulmonary exercise testing in patients with advanced cancer. *Lung Cancer* 2007.55(2):225-32.
10. Jones LW, Watson D, Herndon, J. E. 2nd et al. Peak oxygen consumption and long-term all-cause mortality in non-small cell lung cancer. *Cancer* 2010.116 (20):4825-32.
11. Benzo R, Kelley GA, Recchi L et al. Complications of lung resection and exercise capacity: A meta-analysis. *Respir Med* 2007.101(8):1790-7.
12. Brunelli A, Charloux A, Bolliger CT et al. On behalf of the European Respiratory Society and European Society of Thoracic Surgeons joint task force of fitness for radical therapy. *ERJ* 2009. 34:17-41.
13. Cesario A, Ferri L, Galatta D et al. Pre-operative pulmonary rehabilitation and surgery for lung cancer. *Lung Cancer* (2007a).57(1):118-9.
14. Jones LW, Peddle CJ, Eves ND et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer* 2007.110(3):590-8.
15. Nici L. Preoperative and postoperative pulmonary rehabilitation in lung cancer patients. *Thorac Surg Clin* 2008.18:39-43.
16. DeVita VT, Lawrence TS, Rosenberg SA. *Cancer: Principles and Practice of Oncology*. 8th Edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2008.
17. Schag CA, Ganz PA, Wing DS et al. Quality of life in adult survivors of lung, colon, and prostate cancer. *Qual Life Res* 2004.3(2):127-41.
18. Temel JS, Greer JA, Goldberg S et al. A structured exercise program for patients with advanced non-small cell lung cancer. *J Thorac Oncol* 2009. 4(5):595-601.
19. Beato R, Pagdin-Friesen W, Roberston C et al. Effects of exercise intervention on persons with metastatic cancer: A systematic review. *Physiother Can* 2009.61(3): 141-53.
20. Lowe S. Physical activity and palliative cancer care. *Recent Results Cancer Res* 2011.186: 349-65.
21. American College of Sports Medicine, Chodzko-Zajko WJ, Procto DN, Fatarone Singh MA et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc* 2009. 41(7):1510-30. rights reserved.

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## MESOTHELIOMA UPDATE

# Aggressive management under debate

Christopher W. Lee, MD, FRCPC

The incidence of mesothelioma in Canada has been steadily increasing since the 1970s. The number of new cases diagnosed in 2007 was 514, up from 276 in 1992.<sup>1</sup> From 1960 to 1968, there only 99 cases of mesothelioma in Canada.<sup>2</sup>

The main goal of treatment for malignant pleural mesothelioma (MPM) is disease control. Aggressive management involving radical surgery, chemotherapy and radiotherapy is feasible in suitable candidates,<sup>3</sup> but long-term survivorship may be a function of patient selection.<sup>4</sup>

### AGGRESSIVE MANAGEMENT: ROLE OF RADICAL SURGERY

The results of the Mesothelioma and Radical Surgery (MARS) trial have raised questions about the role of extrapleural pneumonectomy (EPP).<sup>5</sup> Intended to address the feasibility of performing a randomized trial of radical surgery, a total of 50 subjects were assigned to either EPP or no EPP. Based on an intention-to-treat analysis, the no-EPP group had a better outcome, with a median survival of 19.5 vs 14.4 months, a difference primarily due to perioperative complications, leading the MARS trialists to caution against EPP. Proponents of EPP have criticized this conclusion given the small size of the trial and because survival was not the primary endpoint.

The next study planned by the MARS trialists eschews EPP in favour of pleurectomy.<sup>6</sup> A large retrospective review of surgery at major American centres demonstrated no major differences in outcomes between EPP and pleurectomy.<sup>7</sup> However, with the goal of surgery to achieve maximal cytoreduction, the latest strategy of the MARS trialists has also been criticized,<sup>8</sup> and the definition of what qualifies as a pleurectomy for MPM is under debate.

The MARS trial highlights another important management issue. Enrollment occurred at 12 centres in the United Kingdom over a 3-year period. Screening logs were not mandatory, and only 261 patients were accounted for in this manner. Of all those diagnosed with MPM, 112 were registered for the trial, and

over half were not randomized due to a variety of factors, such as disease progression and the decision by patients to withdraw. Regardless of the exact denominator, the 50 patients randomized to EPP or no EPP undoubtedly represent a small fraction of the patients diagnosed with MPM.

In Ontario, there are at least 2 major thoracic surgery centres that routinely perform radical surgery for MPM. A recent review of practice in the province indicates that approximately 10% of patients are managed aggressively<sup>9</sup> (probably representing the upper limit of the MPM population in whom radical surgery might be performed). In many other communities, there is a lack of expertise and/or interest in performing radical surgery for MPM.

### MANAGEMENT WITH CHEMOTHERAPY

Chemotherapy is associated with a modest survival benefit in fit patients with MPM.<sup>10</sup> The combination of cisplatin + pemetrexed is standard, although reimbursement issues may affect access to pemetrexed. Retrospective reviews suggest comparable survival outcomes using gemcitabine or raltitrexed in place of pemetrexed.<sup>9,11</sup> Similarly, carboplatin can substitute for cisplatin. Vinorelbine and pemetrexed have demonstrated activity as single agents, and may be alternatives for individuals with platinum-analog contraindications.

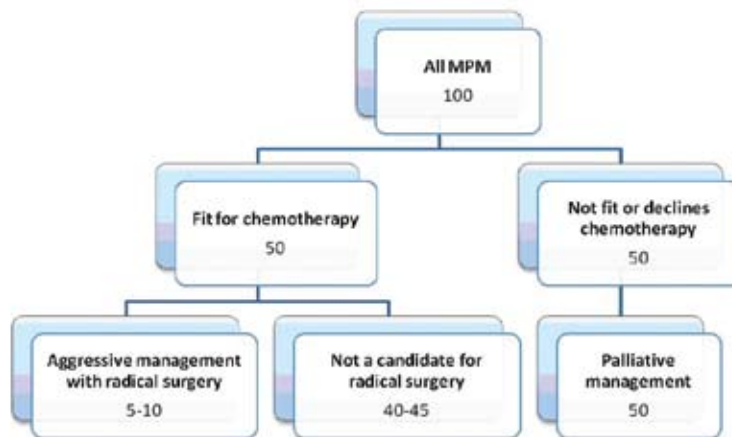
In individuals with a long progression-free interval, retreatment may be considered.<sup>12</sup> However, there is little data to support second-line systemic therapy. A trial of single-agent pemetrexed as salvage therapy following a platinum-based doublet failed to demonstrate any benefit.<sup>13</sup> Recently, a large placebo-controlled trial of the histone deacetylase inhibitor, vorinostat, in the second-line setting has also reported negative results.<sup>14</sup>

There remains hope that novel targeted agents will prove useful in treating MPM despite the finding that epidermal growth factor tyrosine kinase inhibitors, specifically gefitinib and erlotinib, and angiogenesis inhibitors, such as bevacizumab and sunitinib, have demonstrated little activity.<sup>10</sup>



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**FIGURE 1. MPM, with proportion (%) of patients suitable for each treatment category**



## PALLIATIVE TREATMENT

While 10% of patients are candidates for aggressive management, only about 50% are suitable for chemotherapy. For the rest, the focus is entirely on palliative measures (see Figure 1). Radiotherapy is used primarily for control of chest pain.<sup>15</sup>

Essential elements of active symptom management include:<sup>16</sup> regular specialist followup; structured assessments for physical, psychologic and social issues; rapid access to other specialty services, such as pain management and social work; and parallel nursing support. With the benefit of early integration of palliative care into management of advanced non-small cell lung cancer, it is likely that there would be a comparable advantage in MPM.

## REFERENCES

1. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2011. Toronto, ON, 2011.
2. McDonald AD, Magner D, Eyssen G. Primary malignant mesothelial tumors in Canada, 1960-1968. A pathologic review by the Mesothelioma Panel of the Canadian Tumor Reference Centre. *Cancer* 1973. 31:869-76.
3. de Perrot M, Feld R, Cho BC et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Clin Oncol* 2009. 27:1413-18
4. Hasani A, Alvarez JM, Wyatt JM et al. Outcome for patients with malignant pleural mesothelioma referred for Trimodality therapy in Western Australia. *J Thorac Oncol* 2009.4:1010-16.
5. Treasure T, Lang-Lazdunski L, Waller D et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol* 2011.12:763-72.
6. Treasure T. Surgery for mesothelioma: MARS landing and future missions. *Eur J Cardiothorac Surg* 2010. 37:509-10.
7. Flores RM, Pass HI, Seshan VE et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg* 2008.135:620-6, e621-3.
8. Rusch VW. The Mars trial: resolution of the surgical controversies in mesothelioma? *J Thorac Oncol* 2009. 4:1189-91.
9. Hasani A, Sun B, Liu G et al. Systemic therapy usage and outcomes for patients diagnosed with malignant pleural mesothelioma (MPM) between 2005 and 2010 in Ontario, Canada. *J Clin Oncol* 2011;29 suppl:abstr 7085.
10. Tsao AS, Wistuba I, Roth JA et al. Malignant pleural mesothelioma. *J Clin Oncol* 2009. 27:2081-90.
11. Lee CW, Murray N, Anderson H et al. Outcomes with first-line platinum-based combination chemotherapy for malignant pleural mesothelioma: a review of practice in British Columbia. *Lung Cancer* 2009;64: 308-13.
12. Ceresoli GL, Zucali PA, De Vincenzo F et al. Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma. *Lung Cancer* 201. 72:73-7.
13. Jassem J, Ramlau R, Santoro A et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol* 2008; 26:1698-1704.
14. Krug L. VANTAGE 014: Vorinostat in patients with advanced malignant pleural mesothelioma (MPM) previously treated with pemetrexed and either cisplatin or carboplatin therapy: a phase III, randomized, double-blind, placebo-controlled trial. ESMO 36. Stockholm, Sweden, 2011
15. Ung YC, Yu E, Falkson C et al. The role of radiation therapy in malignant pleural mesothelioma: a systematic review. *Radiother Oncol* 2006; 80:13-8.
16. BTS statement on malignant mesothelioma in the UK, 2007. *Thorax* 2007; 62 Suppl 2:ii1-ii19.

### Disclosure:

Dr. Lee has served on ad boards for Lilly oncology.

# SMALL CELL LUNG CANCER AND PROGRESS OVER 20 YEARS

## Effort: B Achievement: F

Nimira Alimohamed MD; Gwyn Bebb, MA, BMBCh, PhD, FRCPC

Small cell lung cancer (SCLC) is characterized by a rapid doubling time, early development of metastatic disease and sensitivity to chemotherapy and radiation. Despite additions to treatment regimens over the past 20 years, including prophylactic cranial radiation, improvements in survival with this disease have been modest: the vast majority of patients with SCLC will die within 2 years.

### INCIDENCE AND ETIOLOGY

The incidence of SCLC is declining, representing 13% of all lung cancers in 2002, compared with 17% in 1986.<sup>1</sup> Despite this, SCLC continues to account for approximately 4% of all cancer mortality.<sup>2</sup>

### STAGING

The 2-stage Veterans Administration Lung Group staging system continues to be used in clinical practice. Limited-stage SCLC (LSCLC) refers to a volume of disease that can be encompassed within a tolerable radiation field, an area that may include hilar, mediastinal and supraclavicular adenopathy, while extensive-stage disease (ESCLC) is everything else. A recent study showed that survival of patients with LSCLC with an effusion is intermediate between those with limited-stage disease without effusion and those with extensive-stage disease, suggesting that the tumour, node, metastasis (TNM) staging systems can identify patients with distinct prognoses.<sup>3</sup> In practice, most patients with a cytology proven malignant effusion are considered to have extensive-stage disease. The American Joint Committee on Cancer - L'Union Internationale Contre le Cancer (AJCC/UICC) TNM classification, 7<sup>th</sup> edition, is now the recommended staging system for SCLC, although the adoption into clinical practice is slow. At the time of diagnosis 60-70% of patients have extensive-stage disease.

### THE ROLE FOR SURGERY

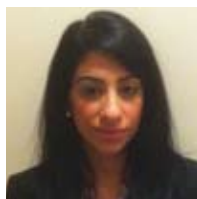
There is no role for surgery alone as the primary treatment for LSCLC. As part of multimodality therapy, initial surgery may improve survival in a limited set

of patients with Stage IA disease who have had appropriate preoperative nodal evaluation, although data is retrospective.<sup>4</sup> Due to the presumed high likelihood of disseminated micro-metastases, most centres recommend adjuvant treatment with cisplatin and etoposide. Surgery after induction chemoradiotherapy may improve local control and survival in a carefully selected subset of patients with Stage I-IIIa disease if complete resection is achieved, as demonstrated by recent Phase II data.<sup>5</sup>

### EVOLUTION OF CHEMOTHERAPY

In LSCLC, the relatively inexpensive combination of cisplatin + etoposide chemotherapy (EP) along with thoracic radiation remains the standard of care, as these modalities can be combined at full doses with tolerable toxicity profiles. EP regimens are superior to cyclophosphamide combination chemotherapy.<sup>6</sup> Attempts to increase dose intensity or add other agents caused more hematologic and nonhematologic toxicities with lower survival rates when compared to full-dose EP and radiation.<sup>7</sup> Paclitaxel + EP in a Phase II trial seemed to have comparable survival numbers, but significant esophagitis and mortality due to toxicity resulted.<sup>8</sup>

For ESCLC, combination chemotherapy with a platin and etoposide remains the standard of care in the first-line setting. Cisplatin-containing regimens are superior to cyclophosphamide-based therapies.<sup>9</sup> Carboplatin can be used if cisplatin is contraindicated, although response rates are lower compared with EP.<sup>10</sup> Adding other agents such as paclitaxel or ifosfamide to EP has not impacted survival enough to outweigh the added toxicities.<sup>11</sup> Irinotecan when combined with cisplatin initially had promising results in a Japanese study, with median survivals of 12.8 months vs 9.4 months. However, a Phase III North American study, of irinotecan and cisplatin with a different dosing regimen failed to show any benefit over standard EP.<sup>12</sup> Epirubicin combined with cisplatin compared to EP has similar outcomes but less hematologic toxicity and presents another viable alternative for treatment of ESCLC in the first-line setting.<sup>13</sup> Four drug regimens



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have shown modest improvements in response rates and overall survival (OS), however the added toxicities have also limited their clinical application.<sup>14</sup>

For ESCLC, 4 to 6 cycles of induction treatment is optimal. A meta-analysis revealed small but statistically significant improvements in progression-free survival (PFS) and OS with maintenance chemotherapy.<sup>15</sup> However, randomized trials have failed to prove superiority.

## RADIATION THERAPY

Radiation therapy, when combined with chemotherapy, has improved intrathoracic tumour control rates and OS in patients with LSCLC.<sup>16,17</sup> Modest survival improvements occur with early concurrent therapy, and if treatment is completed within 30 days of chemotherapy initiation.<sup>11</sup> Total dose and fractionation schedules remain an area of active research. One study demonstrated a 10% improvement in OS when 45 Gy of radiation therapy was delivered twice-daily over 3 weeks compared to 45 Gy daily over 5 weeks. Although rates of esophagitis were higher in the twice-daily treatment group, overall tolerability was comparable.<sup>18</sup>

## PROPHYLACTIC CRANIAL IRRADIATION

At the time of diagnosis of ESCLC, 14-24% of patients will have brain metastases.<sup>11</sup> A meta-analysis of 7 randomized trials, with a predominantly LSCLC population with complete response to initial therapy, demonstrated a 50% reduction in the development of brain metastasis and a 5.4% improvement in 3-year OS with prophylactic cranial irradiation (PCI).<sup>19</sup> A randomized Phase III trial evaluated the role of PCI in ESCLC after chemotherapy and demonstrated a reduction in the incidence of symptomatic brain metastases and improvement in survival.<sup>20</sup> PCI has thus been established as the standard of care for all patients with SCLC who respond to initial therapy.

## SECOND-LINE THERAPY

Relapses are common despite high response rates to initial chemotherapy and recurrent disease is considered incurable. Chemosensitivity is inversely related to the rapidity of recurrence: SCLC that progresses through initial therapy or within 3 months of completion is considered "refractory." Disease recurring >3 months after completion of first-line therapy is considered sensitive, and disease that

occurs >6 months after initial treatment is often treated with the same regimen with a useful response.

Response rates of 8-28% are seen with CAV treatment after first-line EP.<sup>21</sup> Single-agent topotecan, intravenous and oral, improves survival, quality of life and symptom control when compared to best supportive care in relapsed SCLC.<sup>22</sup> Oral topotecan has emerged as one viable option in the second-line treatment of SCLC. Amrubicin has also shown activity in relapsed SCLC and, when compared in a Japanese Phase II study to oral topotecan, demonstrated higher response rates and PFS.<sup>23</sup> In a North American Phase II trial, the response rate was lower although still promising.<sup>24</sup> Many other drugs have been investigated in the second line, including irinotecan, gemcitabine, paclitaxel, docetaxel and vinorelbine, but none demonstrates significant improvements in efficacy.

## CURRENT OUTCOMES

Survival of patients with LSCLC and ESCLC has modestly increased over the past 3 decades. Two-year survival of patients with ESCLC was 4.6% in 2000 compared with 1.5% in 1973. Median survival is now estimated at 8-13 months. Five-year survival is poor at 1-2%. Median survival of patients with LSCLC is 15-20 months, compared with 12-17 months in the 1980s; 20-40% of patients will survive to 2 years and 10-13% will survive to 5 years with limited-stage disease.<sup>1</sup>

## NEW DIRECTIONS AND CHALLENGES

Several new cytotoxic agents continue to be evaluated in SCLC. Amrubicin in the first-line setting in combination with cisplatin achieved a response rate of 88% and median OS of 14 months in a Japanese study.<sup>25</sup> North American and European trials are underway to determine the efficacy of amrubicin in other ethnic groups.

Immunotherapy and targeted agents have generally been unsuccessful in changing the outcome of SCLC. Interferon therapy has not show benefit but did increase toxicity. Thalidomide has failed to show any benefit when added to chemotherapy and caused thrombotic events.<sup>26,27</sup> Oblimersen, a B-cell lymphoma-2 (Bcl-2) antisense oligonucleotide, demonstrated a trend towards a worse outcome as initial therapy for ESCLC.<sup>28</sup> In relapsed SCLC, imatinib and gefitinib have not been successful. Bevacizumab and sorafenib both seem to have some activity in

sensitive relapsed SCLC from Phase II data.

Although the incidence of SCLC is declining, survival outcomes remain dismal. Systemic chemotherapy for SCLC has not significantly advanced in the last 20 years. Unlike the case in several other tumour sites, the understanding of molecular pathways has not yet led to the use of targeted agents that provide a clear survival advantage. However, combinations of targeted agents with chemotherapy and the investigation of new targeted therapies is ongoing. It is to be hoped that the two decades of minimal progress merely herald an imminent explosion of new clinical breakthroughs to parallel the progress made in NSCLC.

## REFERENCES

1. Govindan R, Page N, Morgensztern et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol* 2006;28:4539-44.
2. Jemal A, Seigel R, Ward E et al. Cancer Statistics 2009. *CA Cancer J Clin* 2009;59:225-49.
3. Shepherd FA, Crowley J, Van Houtte P et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of tumor, node, metastasis classification for lung cancer. *J Thorac Oncol* 2007;2:1067-77.
4. Yu JB, Decker RH, Detterbeck FC et al. Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. *J Thorac Oncol* 2010;5:215.
5. Eberhardt W, Stamatis G, Stuschke M et al. Prognostically orientated multimodality treatment including surgery for selected patients of small-cell lung cancer patients stages IB to IIIB: long-term results of a phase II trial. *Br J Cancer* 1999;81:120.
6. Sundstrom S, Bremnes RM, Kaasa S et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol* 2002;20:4665-72.
7. Murray N, AT Turrisi. A review of first-line treatment for small-cell lung cancer. *J Thorac Oncol* 2006;1:270-278.
8. Ettinger DS, Berkey BA, Abrams RA et al. Study of paclitaxel, etoposide, and cisplatin chemotherapy combined with twice-daily thoracic radiotherapy for patients with limited-stage small-cell lung cancer: a Radiation Therapy Oncology Group 9609 phase II study. *J Clin Oncol* 2005;23:4991.
9. Pugol JL, Carestia L, P Daures. Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen versus a regimen without this alkylating agent. *Br J Cancer* 2000;83:8.
10. Skarlos DV, Samantas E, Kosmidis P et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. *Ann Oncol* 1994;5:601.
11. Puglisi M, Dolly A, Faria A et al. Treatment options for small cell lung cancer – do we have more choice? *Brit J Cancer* 2010;10:629-38.
12. Hanna N, Bunn PA Jr, Langer C et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006; 24:2038.
13. Artal-Cortes A, Gomez-Codina J, Gonzalez-Larriba JL et al. Prospective randomized phase III trial of etoposide/cisplatin versus high-dose epirubicin/cisplatin in small-cell lung cancer. *Clin Lung Cancer* 2004;6:175.
14. Evans WK, Feld R, Murray N et al. Superiority of alternating non-cross-resistant chemotherapy in extensive small cell lung cancer. A multicenter, randomized clinical trial by the National Cancer Institute of Canada. *Ann of Intern Med* 1987;107:451.
15. Bozcuk H, Artac M, Ozdogan M et al. Does maintenance/consolidation chemotherapy have a role in the management of small cell lung cancer (SCLC)? A meta-analysis of the published controlled trials. *Cancer* 2005;104:2650.
16. Pignon JP, Arriagada R, Ihde DC et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618.
17. Warde P and D Payne. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol* 1992;10:890.
18. Turrisi AT, Kim K, Blum R et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265-271.
19. Auperin A, Arriagada R, Pignon JP et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999; 341:476-84.
20. Slotman B, Faivre-Finn C, Kramer G et al. Prophylactic cranial irradiation in extensive stage small-cell lung cancer. *N Engl J Med* 2007;357:664-72.
21. Von Pawel J, Schiller JH, Shepherd FA et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999;17:658.
22. O'Brien ME, Ciuleanu TE, Tsekov H et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol* 2006; 24:5441.
23. Inoue A, Sugawaka S, Yamazaki K et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan lung cancer study group trial 0402. *J Clin Oncol* 2008;26:5401-06.
24. Ettinger DS, Jotte R, Lorigan R et al. Phase II study of amrubicin as second-line therapy in patients with platinum-refractory small-cell lung cancer. *J Clin Oncol* 2010;28:2598-2603.
25. Inoue A, Ishimoto O, Fukumoto S et al. A phase II study of amrubicin combined with carboplatin for elderly patients with small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0405. *Ann Oncol* 2010; 21:800.
26. Pujol JL, Breton JL, Gervais R et al. Phase III double-blind, placebo-controlled study of thalidomide in extensive-disease small-cell lung cancer after response to chemotherapy: an intergroup study FNCLCC cleo04 IFCT 00-01. *J Clin Oncol* 2007; 25:3945.
27. Lee SM, Woll PJ, Rudd R et al. Anti-angiogenic therapy using thalidomide combined with chemotherapy in small cell lung cancer: a randomized, double-blind, placebo-controlled trial. *J Natl Cancer Inst* 2009; 101:1049.
28. Rudin CM, Salgia R, Wang X et al. Randomized phase II Study of carboplatin and etoposide with or without the bcl-2 antisense oligonucleotide oblimersen for extensive-stage small-cell lung cancer: CALGB 30103. *J Clin Oncol* 2008;26:870.

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