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Health related quality of life (HRQOL) in randomised controlled trials for non small-cell lung cancer (NSCLC) patients – what is the added clinical value

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HRQOL outcomes can be important in NSCLC, but few systematic reviews have examined the global impact and added insights of HRQOL data, over routine clinical data, from RCTs of NSCLC patients. Therefore a systematic review was performed, in keeping with the Cochrane methodology. The review examined the reported quality and added insights of HRQOL data in published studies. Articles were selected and assessed according to pre-defined eligibility criteria, such as only RCT, minimal 100 patients and only patient based assessments. Articles were identified mainly by MEDLINE, Cochrane library, Cancerlit. Three reviewers (AB, FE, VV) independently extracted and evaluated the data. As no universally agreed review checklist exists for evaluating reporting of HRQOL RCTs they were then evaluated within a broad framework of a recently developed RCTs HRQOL minimum standard checklist for evaluating HRQOL outcomes in cancer clinical trials.

29 RCTs were identified, with 8445 patients mostly staged III and IV. Treatment involved mainly chemotherapy alone (n=24); four studies examined radiotherapy alone; one study examined chemotherapy plus radiotherapy. Most studies (n=23) assessed HRQOL as a secondary endpoint with only six as a primary endpoint. The most commonly used measure was the EORTC QLQ-30, which was used in more than 50% of trials. Of the 27 RCTs testing for survival differences, no significant differences were seen for 15 (56%) of these trials. However, in nine of these 15 trials (60%), HRQOL data provided additional information, for example, highlighting improvements in the levels of fatigue, improvements in levels of physical functioning, or information on psychological wellbeing that helped in understanding the consequences of NSCLC interventions. In the remaining 12 trials (44%), where survival differences were seen, HRQOL data also revealed significant differences between treatment arms in six (50%) of these trials. Frequently, however in most trials investigators did not take into account multiple testing of HRQOL endpoints, which has the risk of raising the likelihood of finding more significant results by chance effects.

In summary, careful use of HRQOL data from RCTs does appear to add insights and help understand the consequences of treatment regimens in NSCLC and this therefore should help clinicians and their patients make more informed treatment decisions.

Debate

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Concurrent targeted and chemotherapy treatments is the best way to go

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The evidence supporting the concurrent use of chemotherapy with targeted therapy is becoming overwhelming. I will start with the use of Herceptin as a model for targeted therapy.

The pivotal survival data for Herceptin was obtained in combination with standard front-line chemotherapeutic regimens. The study showed a 45% improvement in response rate from 20-29 months when Herceptin was added on to chemotherapy vs. chemotherapy alone. It is interesting to note that the TTP in this trial was 7.1 months, as opposed to that of 3.5 months observed in the Vogel front-line monotherapy trial. Current Herceptin data strongly advocates its use combined with chemotherapy, demonstrating a response rate of 49% compared with 35% in front-line monotherapy; for TTP, 7.1 vs 3.5 months; survival for the FISH+, 26.8 vs 22.9 months.

Furthermore, pre-clinical combination data for Herceptin *in vitro* and *in vivo*, shows synergy with multiple agents, and additivity with many others. This data has now been strongly confirmed in multiple clinical trials. TTP on paclitaxel alone in the pivotal trial (NEJM 344(11), 2001) was 3.0 months; and Herceptin monotherapy (Vogel) was 3.5 months. The current doublet combinations of paclitaxel, docetaxel, vinorelbine, capecitabine and gemcitabine yield TTPs from 5 to 9 months. The recent triplet combinations of taxanes plus cis- or carboplatin plus Herceptin yield TTPs of 12.7, 13.5, and 17.0 months. The median survival on the randomised triplet versus doublet combination trials for Herceptin, paclitaxel and carboplatin, has not yet been reached (although the curves to date show a positive trend).

In the adjuvant setting, all four Herceptin trials are not only based in combination therapy, but mainly in new combinations employing synergistic (or at least additive) agents. In practice, even the more liberal experts use Herceptin therapy in combination for aggressive disease, reserving monotherapy for patients with bone or skin metastases only.

For the other agents in development, strong synergy is shown for Iressa, Tarceva, Gleevec and C225. From this debater's perspective, the failure of the Iressa pivotal lung trial reflects not any negative interaction between chemotherapy and Iressa, rather, it was a result of sub-optimal single agent benefit of Iressa in a non-bio marker-enriched population.

This year's ASCO has now revealed a highly significant prolongation in median survival, PFS, ORR and duration of response for Avastin in combination with CPT-11/5FU/LV in colorectal cancer versus chemotherapy alone.

Moreover, the C225 data in relapsed colorectal cancer post CPT11 showed a significant advantage for C225 treatment in combination with CPT11 versus C225 alone.

Finally, combinations of key targeted therapies with either hormones or therapies directed at other pathways show synergy or additivity in *in vitro* and *in vivo* models, rather than single agent or sequential use.

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Concurrent targeted and chemotherapy treatments is the best way to go. CONTRA

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Preclinical experiments show additive activity and sometimes synergy between a large array of novel biological targeted therapies and several chemotherapeutic agents, most notably platinum analogs and taxanes. This, added to the expected limited cytotoxic activity of many of the targeted agents, prompted early investigation of these agents in combination with chemotherapy and radiation, even before knowing single agent activity. Although additive activity may seem likely in breast cancer treated with Herceptin, it has not been shown by randomized trials. Only recently in a randomized study Cetuximab and irinotecan combination was shown to produce significantly more responses and longer time to progression than Cetuximab alone in advanced colorectal patients refractory to irinotecan. This is the only study that proved that a combination of an antibody against EGFR is superior to the antibody alone in a very specifically selected population of patients. Again in colorectal cancer, in first-line treatment, Avastin added to chemotherapy prolonged survival of about 5 months compared to chemotherapy alone. Avastin however failed to show increased time to progression in combination with capecitabine in advanced breast cancer, compared to capecitabine alone. More strikingly, recently 2 large randomized studies performed in advanced non-small cell lung cancer, compared 2 different schedules of chemotherapy (cisplatin-gemcitabine or carboplatin-paclitaxel) in combination with placebo or 2 different doses of Iressa. Both studies failed to prove any superiority of the addition of Iressa to chemotherapy. Two similar studies have been completed with Tarceva in this disease, and results will become available soon. The results of the INTACT studies (Iressa and chemotherapy) have clearly reduced the enthusiasm. These negative results point to the fact that effects of combinations may different depending probably on the targeted therapy, the chemotherapy and the disease type. Where in some cases combinations may prove most effective, in other instances sequential administration may prove more efficacious. Given the poor predictivity of the preclinical models, the best place of targeted therapies will have to be carefully sorted out in the clinic, possibly by developing novel testing strategies and making best use of surrogate markers when available.