Circulating tumor cells are prognostic in SCLC, but still lack clinical application

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Editorial:

A Comment on: R. Tay et al. Prognostic value of circulating tumour cells in limited-stage small cell lung cancer: analysis of the Concurrent ONcedaily VErsus twice-daily RadioTherapy (CONVERT) randomised controlled trial, Annals of Oncology

Running head: CTC in SCLC

Small cell lung cancer

Around 19% of all cancer-related deaths are due to lung cancer, the leading cause of mortality worldwide [1]. Small-cell lung cancer (SCLC) affects approximately 13% of patients diagnosed with lung cancer. The mainstay of treatment is platinum-based chemotherapy. Recently, a modest survival improvement was observed when combining chemotherapy with immune checkpoint inhibitors [2]. For very limited disease (confined to a lobe without lymph node involvement), surgery may be an option, but most patients present with limited-stage or metastatic disease. For fit patients with limited-stage disease, concurrent chemoradiotherapy is nowadays the standard [3]. Tumor response is usually high, but due to the high relapse rate, the five-year survival rate is only about 20% [4].

CTC in Small Cell Lung Cancer

Studies indicate that circulating tumour cells (CTC0 are prognostic for survival in SCLC patients, and decreasing CTCs during treatment correspond well to tumor response [5–7]. Many studies have reaffirmed these findings and showed that CTC can be used to monitor disease status [8–11]. CTC enumeration is, therefore, a promising biomarker for chemotherapy efficacy in SCLC. However, no studies have been performed to show that CTC during follow-up is better than the routine blood chemistry and chest X-rays.

CTC in the CONVERT trial

In this issue of *Annals of Oncology*, Tay et al used the Manchester data from the CONVERT trial to determine the optimal CTC cut-off value in LS-SCLC to stratify the 75 included patients in a low- and high-risk group for recurrence[12]. They argue that CTC are not used clinically because no optimal cut-off was ever established, especially not for limited-stage patients. Patients were randomized for either concurrent once or twice daily

chemoradiotherapy. As expected, no difference in CTC counts were observed between these groups. An optimal cut-off value was established at 15 CTC/7.5mL blood, and tested for its prognostic value compared to two previously used cut offs (2 and 50 CTC/ 7.5mL blood). Once again, baseline CTC, irrespective of the cut-off, were prognostic for shorter survival with larger HRs for increased CTC counts, indicating an enumeration-based effect. CTCs were not correlated to tumor size or stage. This could be due to the limited sample size and because most patients had stage III disease, but might also indicate that in LS-SCLC CTC are more reflective of tumor aggressiveness. This remains to be proven by further studies.

Although the study was well designed, some flaws should be mentioned. As CTCs outperformed ECOG performance score (PS) in the multivariable regression analysis, Tay et al concluded that CTCs were prognostic when patients had a good performance score. However, no patients with a PS of 0 had CTCs above the optimal cut off of 15 CTCs. Furthermore, the included number of patients with a PS of 2 was very low and subjected to selection bias due to the inclusion criteria of the CONVERT study. Therefore, it is undetermined whether CTCs really outperform PS. Perhaps these two prognostic factors can be used in tandem for even better survival estimates on an individual level.

Before generalising the results, one has to realize that the included patients had a skewed distribution in the overall CONVERT study from the general population. Only 14% of the patients who were treated in the CONVERT trial were older than 70 years, while this is about 45% in the general population. Moreover, only patients with PS 0 – 1 were included in the study, while patients with PS 2 were only eligible for inclusion based on the estimation of their treating physician. Finally, no CTCs were detected in around 40% of patients with LS-SCLC and no sequential sampling was performed for monitoring disease status.

Clinical use of CTC

Tay et al argue that the threshold of 15 CTCs could be used to stratify patients in low- and high-risk groups for recurrence of disease, though external validation remains to be performed. Due to the limited treatment options and the high risk of recurrence (even patients with CTCs<15 have a median progression-free survival of 19 months), it seems unlikely that treatment for limited-stage SCLC will be adjusted based on CTC status.

Changes in CTCs after treatment are of value in determining the efficacy of therapy and could be used clinically to guide (early) treatment [5–7, 9, 10]. So, for clinical use, a better approach would be to make a shared decision with the patient based on a comprehensive risk assessment including CTCs at baseline and changes in CTCs count after one cycle of treatment.

Other applications of baseline CTCs in clinical practice will be new treatment stratifications and in shared decision-making when one knows that inevitably the end-of-life approaches soon. Quality of life and perhaps the choice *not* to treat may be balanced against side effects and too short-lasting benefits (70% of patients with CTCs≥15 per 7.5mL died within 1 year despite treatment).

A way to proceed with CTCs is to evaluate their intrinsic cellular abnormalities as a surrogate for the whole tumour. The same Manchester group identified earlier specific copy number alteration (CNA) patterns that could discriminate chemorefractory from chemosensitive SCLC patients [13]. Although CNA is not the preferred method to detect the known resistance mechanisms to therapy due to its low sensitivity, it is a first step in understanding those mechanisms. Unfortunately, CTC counts may be insufficient for this analysis, and heterogeneity of CTCs decreases the accuracy of the prediction. This highlights an important

issue for biomarker studies, namely the need for a sufficient number of (viable) CTCs for single-cell sequencing or culturing. Often CTCs are pre-apoptotic and the most viable cells come in clusters.

Hurdles in CTC detection

At this time, the Cell Search system, which identifies CTCs based on expression of the epithelial cell adhesion molecule (EpCAM) - is still the only FDA-approved system. However, other methods differentiating cells based on size or sorted weight are in development [14–16].. Within the CANCER-ID program of the European Union (http://www.cancer-id.eu/) the characterization of CTCs is currently improved and the scoring automated [17, 18]. Moreover, the isolation of CTCs for further functional and genomic analysis could provide more detailed predictive information [14, 15, 19–21].

Closing statement

CTCs are a strong independent prognostic biomarker. In limited-stage SCLC, a cut-off of 15 CTCs per 7.5 mL peripheral blood is an optimal independent prognostic marker irrespective of other clinical variables. More research in this field is necessary to determine the clinical role of CTCs.

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