Short Communication

iMedPub Journals
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Journal of Neoplasm

2017
Vol.2 No.3:23

Are Liquid Biopsies Applied Across Every Type of Solid Tumours?

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Received: September 04, 2017; **Accepted:** September 30, 2017; **Published:** October 06, 2017

Citation: De Macedo JE, Machado M (2017) Are Liquid Biopsies Applied Across Every Type of Solid Tumours? J Neoplasm. Vol.2 No.3:23.

Abstract

Liquid biopsies have for long received enormous attention due to its clinical immediate application in daily practice. This short review focuses in how the detection of circulating tumour cells (CTCs) and/or circulating tumour DNA and RNA (ctDNA/RNA), from peripheral blood, have prognostic and predictive impact across the most common type of solid tumours. In the era of Precision Medicine liquid biopsies have revolutionized the era of translational research wilt direct benefit in the quality of care of our patients and with high public interest.

Keywords: Liquid biopsies; Precision medicine; Solid tumours

Introduction

Emerging data has been invading, in a daily bases, our lives with new evidence concerning the application of liquid biopsies in many solid tumours. Many are the advantages of liquid biopsies in relation to tissue biopsies, widely well known for those in the field of this new era of translational research [1]. Liquid biopsies consist in fact in searching for and collecting circulating tumour cells (CTCs) and/or circulating tumour DNA and RNA (ctDNA/RNA), from peripheral blood [2]. The identification of specific oncogenic mutations can make the whole difference concerning the weapons that clinicians can use and it's timing of application, or procedures to be applied earlier, before classical diagnosis. Recently, last May 2017, the College of American Pathologist, the Association of Molecular Pathology as well as the European Society of Pathology, have validated the guidelines for next generating sequencing (NGS) as the standard of care in some guidelines. The aim of this short communication is to inform clinicians, of the different applications of liquid biopsies already recommended, studies that lead either to its routine use as in a daily bases or used in clinical trials allowing validation in the most common malignant solid tumours.

Application in Solid Tumors

Breast Cancer has for long been a great concern for clinicians to detect progression in the metastatic context before traditional exams. A recent study, which included 30 patients with metastatic breast cancer in systemic treatment, demonstrated that when imagiological tests, such as X-ray and analytic testing with CA15 [3] when compared to ctDNA, were in favour of ctDNA. In fact ctDNA is a good biomarker with a superior sensitivity and with direct clinical application, by detecting early response to treatment and progression, when compared to classical evaluation (clinical, analytic and imagiological) [3]. In an even earlier study, in 2004, 177 patients with metastatic breast cancer were tested before treatment and in follow-up for CTCs in a prospective multicentre study. On that study, CTCs proved to be a positive prognostic factor, and an independent predictor of progression-free-survival (PFS) and overall survival (OS) in metastatic breast cancer [4]. The DETECT study proved that cell search test is one viable test with prognostic impact in the detection of metastases, PFS and OS in metastatic breast cancer [5]. In a prospective study with non-metastatic breast cancer detection of CTCs predicted early recurrence and decreased OS in chemo-naive patients. In other words in the non-metastatic setting identification of CTCs also has prognostic relevance [6].

Concerning metastatic castration-resistant prostate cancer (mCRPC), the determination of CTC has demonstrated predictive and prognostic benefit in survival in patients submitted to treatment. One study enrolled 276 patients with progressive disease starting a new line of systemic treatment. They were monitored during follow-up. Once again, CTCs proved to be an independent predictor of OS. As a consequence of this study the Food Drug Administration (FDA) has validated its evaluation in CRPC patients [7]; CTCs were validated as a prognostic and also as a predictive factor. Some meta-analysis and systemic reviews of the published literature investigated the relationship between CTC and survival in prostate cancer patients. Enough evidence supported the notion that CTCs are important biomarkers, with prognostic impact in therapeutic decisions in prostate cancer patients [8]. Recently, studies have demonstrated that the detection of androgen receptor (AR) mutations, such as AR splice variants (AR-Vs), being AR-V7 the most common, its status (AR gain or

AR mutations) in CTCs or cfDNA detected by NGS, have demonstrated that the may be predictive of response or attribute a worse prognosis, in mCRPC [9]. In fact, AR-V7 status plays a relevant role in determining response to treatment with enzalutamide and abiraterone, but more prospective studies need to be performed [10]. AR point mutations such as L702H and T878A demonstrated resistance to abiraterone, and F877L point mutation demonstrated resistance to enzalutamide. Other important biomarkers have also been identified such as full-length AR (AR-FL), and AR copy number gain have also been detected either in cfDNA as well as in CTCs11. Recurrent gene fusion between the androgen-regulated gene TMPRSS2 and members of the ETS transcription factor family, most commonly ERG, are present in about 50% of prostate cancer cases. TMPRSS2-ERG has also been identified in CTCs, and the presence of this fusion gene is a critical event in the development of prostate cancer [11].

Colorectal cancer (CRC) has been no exception along the last years. CTCs have also proved to be a positive independent prognostic and predictive factor when evaluated for tumour response, PFS and OS in patients with metastatic CRC (mCRC) submitted to treatment, when compared to imagiological evaluation [12]. The study referenced, allowed the FDA to validate the test "CellSearch" to be now commercially available. Nevertheless, further studies have been promoted and the detection of KRAS mutations in cfDNA obtained from a simple blood withdrawal, in patients already submitted to treatment with an anti-EGFR therapy, have detected these acquired mutations in sub-clones of disease, before computerized tomography (CT) imaging [13]. This is another advantage of this modern technology which allows the detection of resistance to therapy, also in mCRC. Recent meta-analysis, has shown that mCRC have a heavy burden of cfDNA detected in blood stream and bear a strong prognostic value. On the other hand, tumour specific mutations detected in cfDNA have an extreme importance in choosing target therapies in mCRC [14]. Not only in specific anti-EGFR therapies have liquid biopsies shown its importance, as has the detection of Multidrug resistance-associated protein 1 (MRP1) expression in CTCs shown resistance to chemotherapy in mCRC, such as irinotecan based chemotherapy [15]. Also the detection of thymidylate synthase expression in CTCs has also predicted resistance to 5-fluorouracil therapy in mCRC [16].

Gastric cancer in the metastatic context has for long, been somehow left behind in this field. But as all others, CTCs detection in blood plasma has also been useful as prognostic, for monitoring response to treatment and also for predicting relapse [17]. Nevertheless, recent advances in the era of target therapy have occurred. In patients with negative tissue samples for HER2, concerning the TOGA study, amplification of HER2 was identified in CTCs. They showed a similar response to trastuzumab-based therapies, as those with positive HER2 tissue samples [18].

Epstein-Barr virus (EBV) DNA samples have been withdrawn from asymptomatic participants and also from patients with positive results for nasopharyngeal cancer, in a prospective study [19]. The authors concluded that EBV DNA detected in blood samples is a good biomarker for screening asymptomatic patients, and this study also demonstrated a high sensitivity and specificity in the results [19].

Lung cancer has for long been a disease, where the acquisition of a new tumour samples, either for diagnosis, detection of resistance to therapy [20], has been a challenge for clinicians (oncologists, pulmonologists and intervention radiologists among others). In September 2014, European Medicines Agency (EMA) has approved the clinical use of detection of cfDNA for determination of EGFR mutations, primary or secondary [20], as an option when tumour samples are unavailable or painless and difficult to obtain [21]. It has been approved with effect in all European Union member countries. A prospective study has just at last minute, validated that the baseline presence of more than or equal to a total of five CTCs in advanced NSCLC, will confer poor prognosis for these patients [22].

Lung cancer has been in some way a pioneer, within most common cancers, where advances have been more emancipated during the last years. After a long period, where science seemed to be static in time, lung cancer has leapt in time. cfDNA has been proven to be a good prognostic, predictive factor for long. It has allowed screening to be performed within a wider screen at a genetic level, enabling early detection, determine clonal heterogeneity and evaluate residual disease after surgery. In the metastatic context, evaluate response to treatment, resistance to therapy (primary and secondary) and relapse [1].

New and Future Perspectives

Many of the studies referred above, have proved that liquid biopsies, number of CTCs or cfDNA detected before treatment, have demonstrated to be a predictive factor with prognostic value. In fact, Bettegowda et al. have already proven since 2014 a correlation between quantification of cfDNA, stage and tumour burden either in colon, breast or lung cancer [23].

Owing to many studies occurring worldwide and with the recent necessity of a uniform validation, an OncoNetwork Global Consortium has been created. By this way, all scientists will use the same language and the same techniques to make science and its development in translational research, a unique language. It's owing to these international efforts that patients, will fortunately, benefit of new modernized investigational techniques, which will fortunately improve the quality of care of our patients. Medicine is taking a 360° clock-wise turn, favoring the era of Precision Medicine.

References

1. De Macedo JE, Machado M (2017) Is the determination of ctDNA a scientific "spy" that foresees cancer? World J Respirol 7: 35-38.
2. Batth IS, Mitra A, Manier S, Ghobrial IM, Menter D, et al. (2017) Circulating tumour markers: Harmonizing the yin and yang of CTCs and ctDNA for precision medicine. Ann Oncol 28: 468-477.

3. Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, et al. (2013) Analysis of circulating tumor dna to monitor metastatic breast cancer. N Engl J Med 368:1199-1209.

4. Cristofanilli M, Budd GT, Ellis MJ, Stopeck A, Matera J, et al. (2004) Circulating tumor cells, disease progression, and survival in metastatic breast cancer N Engl J Med 351:781-791.

5. Müller V, Riethdorf S, Rack B, Janni W, Fasching P, et al. (2012) Prognostic impact of circulating tumor cells assessed with the cell search systemtm and a DNA test breast tm in metastatic breast cancer patients: The detect study. Breast Cancer Res 14: R118.

6. Lucci A, Hall CS, Lodhi AK, Bhattacharyya A, Anderson AE, et al. (2012) Circulating tumour cells in non-metastatic breast cancer: A prospective study. Lancet Oncol. 13: 688-695.

7. De Bono JS, Scher HI, Montgomery RB, Parker C, Miller MC, et al. (2008) Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res 14: 6302-6309.

8. Ma X, Xiao Z, Li X, Wang F, Zhang J, et al. (2014) Prognostic role of circulating tumor cells and disseminated tumor cells in patients with prostate cancer: a systematic review and meta-analysis. Tumor Biol 35: 5551-5560.

9. Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, et al. (2014) AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer N Engl J Med 371: 1028–1038.

10. Conteduca V, Wetterskog D, Sharabiani MTA, Grande E, Fernandez-Perez MP, et al. (2017) Androgen receptor gene status in plasma DNA associates with worse outcome on enzalutamide or abiraterone for castration-resistant prostate cancer: a multi-institution correlative biomarker study. Ann Oncol 28: 1508–1516.

11. Van Soest RJ (2017) Liquid biopsies and plasma DNA: Paving the way for personalized medicine in metastatic castration-resistant prostate cancer. Ann Oncol: 1408–1409.

12. SCohen SJ, Punt CJ, Iannotti N, Saidman BH, Sabbath KD, et al. (2008) Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer. J Clin Oncol 26: 3213-3221

13. Misale S, Yaeger R, Hobor S, Scala E, Janakiraman M, et al. (2012) Emergence of KRAS mutations and acquired resistance to anti - EGFR therapy in colorectal cancer. Nature 486: 532–536.

14. Spindler KG, Boysen AK, Pallisgård N, Johansen JS, Tabernero J, et al. (2017) Cell-Free DNA in metastatic colorectal cancer: A systematic review and meta-analysis. Oncologist 22: 1–7.

15. Abdallah EA, Fanelli MF, Souza E Silva V, Machado Netto MC, Gasparini Junior JL, et al. (2016) MRP1 expression in CTCs confers resistance to irinotecan-based chemotherapy in metastatic colorectal cancer. Int J Cancer 139: 890–898.

16. Abdallah EA, Fanelli MF, Buim ME, Machado Netto MC, Gasparini Junior JL, et al. (2015) Thymidylate synthase expression in circulating tumor cells: A new tool to predict 5-fluorouracil resistance in metastatic colorectal cancer patients. Int J Cancer 137: 1397–1405.

17. Uenosono Y, Arigami T, Kozono T, Yanagita S, Hagihara T, et al. (2013) Clinical significance of circulating tumor cells in peripheral blood from patients with gastric cancer. Cancer 119: 3984–3991.

18. Mishima Y, Matsusaka S, Chin K, Mikuniya M, Minowa S, et al. (2017) Detection of HER2 amplification in circulating tumor cells of HER2-Negative gastric cancer patients. Target Oncol 12: 341–351.

19. Allen Chan KC, Woo J, King A, Lo D, Zee B, et al. (2017) Analysis of plasma epstein–barr virus DNA to screen for nasopharyngeal cancer. N Engl J Med 377: 513-522.

20. De Macedo JE (2016) New era of epidermal growth factor receptor-tyrosine kinase inhibitors for lung cancer. World J Respirol 6.

21. https://www.astrazeneca.com/media-centre/press-releases/2014/iressa-chmp-positive-opinion-blood-based-diagnostic-testing-european-label-26092014.html#!

22. Lindsay CR, Faugeroux V, Michiels S, Pailler E, Facchinetti F, et al. (2017) A prospective examination of circulating tumor cell profiles in non-small-cell lung cancer molecular subgroups. Ann Oncol 28: 1523–1531.

23. Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, et al. (2014) Detection of circulating tumor DNA in early- and late-stage human malignancies. Sci Transl Med 6: 224ra24.