Integration of cytological score on circulating cancer cells in cancer risk models for clinical use

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I. INTRODUCTION

Recent advances in medical diagnosis, tissue biopsy remains the gold standard for cancer detection and diagnosis. Nevertheless, while efficacious in many practical instances, biopsy is an invasive, non-quantitative technique of analysis, and does not achieve early detection of cancers. Despite the consolidate use of the circulating molecular biomarkers to monitor patient’s disease, they fail as diagnostic biomarker for the high rate of false positive/negative. In this scenario, the circulating tumour cells may be considered a promising candidate for the blood-based cancer diagnosis and monitoring.

A. Hypothesis

Circulating tumour cells (CTCs) would be eligible for a diagnostic cytological evaluation if they were not a rare population. Our hypothesis consists in the use of optimized protocol, previously described, (1,2,3,4,5), to favour the \textit{in vitro} survival of proliferating cells to obtain short-term blood-derived cultures (BDCs) enriched for CTCs. The resulting preparation could be used as cytological preparation to early cancer detection and further analysis.

B. Goals

1. short-term expanded CTCs were studied for antigenic and genomic profiles compared with the heterogeneity of the corresponding primitive tumour
2. evaluation of the impact cytology features of CTCs on cancer diagnosis
3. making therapeutic decision based on integration of follow-up data with molecular characterization and proliferation of CTCs

C. Ethical aspects

All Patients involved signed the informed consensus included in the prospective observational clinical study CHARACTEX (CHARacterization of Circulating Tumor cells and EXpansion) approved by the local Ethics Committee n.2013.34 [1]

II. METHODS

Within 4 hours from blood collection, after a passage over a Ficoll-Hypaque gradient to separate a specific density phase, the cells were seeded in chamber slide to obtain cytological preparations from BDCs. We use a clustering algorithm (Ward’s method) to evaluate the differences on cytopathology feature landscapes in BDCs across cancer patients by a scoring system. Pathological variables considered were: a. rate of lympho-monocytes (Vc1) b. endothelial cells (Vc2), c. cellular structural abnormality (atypical cells) (Vc3), d. mitotic figures (Vc4), e. homotypic cell clusters (Vc5) (cellular aggregations characterized by an unique cell type), f. heterotypic cell clusters (Vc6) (cellular aggregations characterized by different cell types), g. mononuclear macrophages (Vc7) h. multinucleated macrophages (Vc8). Individual scores for each variable were estimated following scoring parameters (i.e. 1-5 target cells/100 cells corresponding to score 1; 5-10 target cells/100 cells corresponding to score 2; >10 target cells/100 cells corresponding to score 3)

III. RESULTS

1. short-term CTCs lines were representative of the primitive tumour heterogeneity for genomic and antigenic profiles .
2. cytology of BDCs distinguished with a high accuracy and specificity healthy and cancer patients. Diagnostic correlation between blood-derived cytological and corresponding tumors specimens was very high with low value of rate of false positive and negative.
3. integrating clinical data with morphology/molecular analysis on CTCs permitted us to update in real-time the clinicians on the dynamic changes occurring during the progression of the disease.

IV. DISCUSSION

Further analysis on BDCs in collaboration with other Centre is in progress for a collegial evaluation on cytology of CTCs to develop a representative atlas useful, by a deep learning process, to an automated recognition of this biomarker.

V. CONCLUSIONS

The results of this study highlighted that it is possible to use available and valuable circulating tumour cells to early diagnosis and to treat the right patient in the right time with the right target therapy

REFERENCES

[1] MALARA N et al NATURE PRECISION ONCOLOGY . 2018