Detecting disseminated solid tumor cells in hematopoietic samples: methodological aspects

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Abstract—Detection of tumor cell dissemination in solid tumor patients recently became essential to determine the prognosis of the disease and to monitor response to the therapy. Accurate detection of disseminated tumor cells in hematological samples requires tumor-specific target molecules, which allow sensitive and specific assays and, further, enable the quantification of tumor cells. Currently, numerous applications are in use, including immunological and molecular biological approaches. Theoretically, both ways are sensitive enough to detect less than one tumor cell in 1 million hematopoietic cells. With the improved sensitivity, however, the likelihood that unspecific events will be amplified is also increased. Moreover, biological and analytical variables may fundamentally influence the findings in a particular case. Basic methods, significant pitfalls and the most recent developments in this field are discussed in this overview.

Key words: Disseminated tumor cells; immunology; PCR; bone marrow.

INTRODUCTION

Tumor cell spreading and metastasis formation is a frequent phenomenon in malignant solid tumor patients. In the course of the disease, single tumor cells or small cell groups may enter the circulation leaving the original tumor site. Some of them are capable of growing in a new microenvironment when special conditions prevail, while others will die by active processes. A given part of disseminated tumor cells, however, may persist at distant sites without formation of bulky metastases for longer times. The quantity and tumorigenic potential of these disseminated cells is of basic clinical importance, since these may significantly contribute to the long term outcome of the disease. Recent results suggest therapy

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stratifications based on the detectability of minimal tumor cell dissemination at initial diagnosis [1–3] or during follow-up [4–6]. Moreover, specific targeting and elimination of minimal amounts of disseminated tumor cells by new treatment strategies will soon be available according to recent biotechnological improvements [7–9]. To indicate and to monitor the benefit of such adjuvant therapies, accurate methods are necessitated which possibly lead to a re-evaluation of the diagnostic issue concerning rare tumor cells.

Peripheral blood and bone marrow efficiently reflect tumor cell dissemination in general and, therefore, they are analysed with increasing frequency. Isolated or disseminated tumor cells (DTC) usually can no longer sensitively be detected by classical histological or cytological examinations. Therefore, the adoption of more appropriate immunological or molecular biological methods is necessary. In this paper, we focus on the methodological aspects of reliable tumor cell identification. Crucial technical requirements are discussed that should be taken into consideration when applying a specific method or when judging laboratory findings. The most promising latest improvements on this continuously evolving field are also referred.

THE IMPACT OF DISSEMINATED TUMOR CELLS DETECTED IN HEMATOLOGICAL SAMPLES

The term minimal tumor cell dissemination covers several conditions with clinical impact in which, by special methods, isolated tumor cells can be detected in the hematopoietic samples of cancer patients. The following main issues might be of fundamental significance: (i) prognosis at initial diagnosis: in invasive solid tumors, early tumor cell dissemination may already occur prior to the diagnosis without causing manifest metastases detectable by radiological imaging or conventional microscopy; (ii) therapy monitoring: as a sign of disease progression/recurrence, neoplastic cells can appear in the hematopoietic system of those patients, whose samples proved to be negative for neoplastic contamination at the time of the initial diagnosis. In reverse, patients with previous massive bone marrow involvement, but responding well to induction chemotherapy may still carry residual tumor cells in the bone marrow following several treatment cycles. The term minimal residual disease (MRD) covers this latter situation; however, it is often used in general for all conditions presenting with minimal tumor cell dissemination; (iii) validation of graft purging efficiency: autologous stem cell products may contain contaminating tumor cells. As megatherapy followed by autologous stem cell transplantation became an important alternative in the treatment of solid tumor patients, highly sensitive techniques are of great practical use to guarantee that the autologous graft is free of tumor cells.