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Evolutionary game theory and oligometastatic patient: considering the role of interventional oncology

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Abstract. – The possible role of evolutionary game theory (EGT), to pursue a tailored therapeutic strategy, has recently gained widespread interest within the clinical setting of oncological patients.

The potentially revolutionary shift of paradigm suggested by EGT points to the fact that, for metastatic patients, the optimal therapeutic strategy should be aimed at reducing the survival fitness of tumor cells compared with normal cells, thus allowing natural selection to help control the overall tumor burden, instead of trying to kill all tumor cells.

A specific subset of metastatic patients, the so-called oligometastatic patients, has not been adequately considered so far in the light of EGT theoretical approach.

A modern and comprehensive definition of oligometastatic patient should consider at least three main parameters: the total number of lesions, the timing of their appearance and their biological heterogeneity.

A valid therapeutic option for oligometastatic patients could be to integrate together both systemic and local therapies, such as interventional oncology.

The potential advantage of implementing interventional oncology in the clinical practice, for example in oligorecurrent or oligoprogressive patients, could be to delay or even to avoid unnecessary shifts in systemic therapies.

Another important point to consider is the potential role that the treatment of a single metastatic site may have in terms of immune system activation towards other untreated metastatic sites; such phenomenon is known as abscopal effect.

Key Words:
Evolutionary game theory, Oligometastatic patient, Oligometastases, Interventional oncology.

Short Report

The possible role of evolutionary game theory (EGT), to pursue a tailored therapeutic strategy, has recently gained widespread interest within the clinical setting of oncological patients1.

EGT is a theoretical framework addressing the nature of strategic interactions among "players", "competitors", and "cooperators" in a given "environment" leading to a "final reward".

Such theory, applied to the oncological field, can be interpreted as follows: the final reward (survival fitness) for the single player (tumor cell) depends on the behavior of other competitors (other tumor cells) and cooperators (normal cells) within the environment (patient)[2].

The potentially revolutionary shift of paradigm suggested by EGT points to the fact that, for metastatic patients, the optimal therapeutic strategy should be aimed at reducing the survival fitness of tumor cells compared with normal cells, thus allowing natural selection to help control the overall tumor burden, instead of trying to kill all tumor cells[3].

First attempts to obtain a mathematical frame for EGT in metastatic patients were designed considering chemotherapy as main treatment strategy.

In particular, these efforts were focused on choosing the best drug sequence trying to anticipate tumor evolutionary adaptations to chemotherapy[4].

The relationship between tumor and microenvironment was highlighted by Hanahan and Weinberg[5].

It is of paramount importance to underline that such topic requires a non-reductive glob-

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al approach to adequately explore the intricate time-dependent complexity of this interplay[6].

In order to properly address the intricacy of this system there is an urgent need for defining new metrics to assess tumor response which may take into account both ecological (size) and evolutionary (molecular mechanisms) changes[7].

A specific subset of metastatic patients, the so-called oligometastatic patients, has not been adequately considered so far in the light of EGT theoretical approach.

A modern and comprehensive definition of oligometastatic patient should consider at least three main parameters: the total number of lesions, the timing of their appearance and their biological heterogeneity.

Regarding the total number of lesions in 1995 Hellman and Weichselbaum were the first authors to introduce the concept of oligometastases as a clinically significant state defined by the presence of a limited number of organs interested by distant metastases[8].

Since then, several authors have tried to propose a commonly shared definition, however, the currently accepted definition of oligometastatic patients involves no more than five metastases[9].

Later on, other researchers shifted the focus from the number of lesions to the timing of their appearance introducing the concept of oligorecurrence, when the oligometastases arise after a primary therapy[10], and of oligoprogression when the oligometastases arise during a primary therapy[11].

The concepts of number and timing need, however, to be furtherly integrated with another element of paramount importance: biological heterogeneity.

In fact, it has been widely demonstrated that different metastatic lesions within the same patient may vary greatly in terms of genetic signature, biological behavior and therefore clinical relevance[12].

For the aforementioned reasons, a valid therapeutic option, for oligometastatic patients could be to integrate together both systemic[13] and local therapies such as interventional oncology[14].

In fact, such combination would allow to pursue a truly tailored strategy thus applying a Darwinian approach[15].

Interventional Oncology is a new and broad discipline, defined by some authors as "the fourth pillar of oncology", which includes at least four main fields: interventional radiotherapy, interventional radiology, interventional chemotherapy and interventional endoscopy[16].

The potential advantage of implementing interventional oncology in the clinical practice, for example in oligorecurrent or oligoprogressive patients, could be to delay or even to avoid unnecessary shifts in systemic therapies.

In fact, there is supporting evidence, even from prospective trials, that by treating all metastatic sites in oligometastatic patients, it is possible to achieve long-term progression-free survival, without significant treatment-related toxicity[17].

This kind of approach may even trigger an "*in situ* vaccination", also in the absence of a pre-existing antitumor immunity, thus enhancing the possible role of combination with immunotherapy[18].

Another important point to consider is the potential role that the treatment of a single metastatic site may have in terms of immune system activation towards other untreated metastatic sites; such phenomenon is known as abscopal effect[19].

Conclusions

Evolutionary game theory (EGT) represents an interesting theoretical model which could lead to significant paradigm shifts, in clinical practice, if correctly exploited within the setting of oligometastatic patients. Interventional oncology should be further investigated in order to be adequately embedded within such frame.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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