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My mission is possible: discussing ethical concerns about genomics and precision medicine

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Summary. Although there is considerable evidence that precision anticancer drugs may be more effective than "one size fits all" approach, doubts persist about their cost, availability, and overall benefit for patients. With increasing frequency, patients with metastatic malignancies are undergoing next-generation sequencing (NGS) procedures to determine if there is a viable mutation that could guide their first or next line of treatment. However, this could be prohibitive for many disadvantaged patients. Furthermore, efficacy studies are often structured around surrogate endpoints of dubious long-term predictive validity. Moreover, it is necessary to add that it is often a therapy with significant toxicities, especially in over-treated patients. There is no doubt that precision medicine represents the near future of medical oncology, however, questions need to be asked, out of the spotlight and much closer to our patients.

La mia missione è possibile: discutere questioni etiche sulla genomica e la medicina di precisione.

Riassunto. Nonostante esistano considerevoli prove che l'oncologia di precisione possa di gran lunga rappresentare uno spazio di cura superiore rispetto al tradizionale approccio "one size fit all", ancora oggi persistono controversie riguardo al loro costo, alla loro disponibilità e al beneficio complessivo per il paziente. Con crescente frequenza, i pazienti con neoplasie metastatiche sono sottoposti a procedure di sequenziamento di nuova generazione per determinare la presenza di una mutazione driver in grado di guidare l'oncologo nella scelta della loro prima o successiva linea di trattamento oncologico. Tuttavia, questo potrebbe essere proibitivo o non accessibile per pazienti svantaggiati dal punto di vista sociale, economico e culturale. Inoltre, gli studi sull'efficacia di questo approccio *tailored* sono spesso strutturati attorno a endpoint surrogati di dubbia validità predittiva a lungo termine, con scarsissimi dati relativi a qualità della vita o misure di beneficio riferite dal paziente stesso (*patient-reported outcomes*). A tutto questo è necessario aggiungere che spesso si tratta di terapie con tossicità potenzialmente significative e in pazienti pluritrattati. Non c'è dubbio che la medicina di precisione rappresenti il futuro prossimo dell'oncologia medica, tuttavia, può essere naturale porsi alcune domande, lontane dai riflettori e molto più vicine ai nostri assistiti.

While there is increasing evidence that precision cancer medicines can be more effective than "one-size-fits-all" oncology medicines, questions persist as to their cost, availability, and overall patient benefit. Next-generation sequencing (NGS) has the potential to accelerate precision medicine in oncology by informing efficient and improved clinical treatment decision-making. However, discussions on the utility of NGS in clinical practice are ongoing. Given the high uptake of NGS testing and the lower rates of application of test results to guide treatment, the clinical impact of NGS may not be fully optimized. This discrepancy highlights the ongoing need for real-world evidence to better understand and further optimize the evolving role of NGS in the context of the overall management of the cancer patient.

With increasing frequency, patients with metastatic malignancy undergo NGS in order to determine if there is an actionable mutation that can guide their next line of treatment. However, this technology could be cost prohibitive for many underserved patients.

In this issue, we reported the paper from Esposito et al.[1] about mutational oncology of non-small cell lung cancer (NSCLC), and the current therapeutic options based on the molecular profile of NSCLC with all the related negotiation conditions of authorized and reimbursed drugs in Italy.

High-dimensional data created using genomics and other "omics" technologies are central to many of the predictive, diagnostic, and therapeutic applications of personalized medicine[2]. However, the substantial increase in individual health information required by this approach is also a major source of ethical, legal, and social concerns regarding personalized medicine. The ability to use genomic information in the clinic strongly depends on health information technologies and on the economic resources available, even for the single patient with the risk of exacerbation of existing disparities in healthcare.

Easily: if patients are unable to access a new technology, then they are also unable to enjoy the benefits of that technology. At this level, however, many

patients are still likely to end up taking medications with higher direct costs compared with the standard therapy.

There are some questions to remark.

Are we sure that these drugs always guarantee a gain in terms of efficacy? What is the measure of their effectiveness? Are we guarantors of the surrogate endpoints that come from many of the clinical trials? What is our position in the face of studies that have already failed in the personalization of treatments based on genomic profiling[3]? What kind of information are we able to give to patients when we offer these treatments? In which setting? Is it always right to propose them?

With great humility, primarily as medical oncologists, we must say that today we still do not know how to answer many (or all) of these questions. One possible explanation may be that unidentified factors might exist across specific tumor subtypes that could render single drug-targeted therapy ineffective.

More ethically, the presence of biological data showing that a targeted drug affects a molecular alteration needs to be taken in the context of clinical experience and clinical conditions of cancer patients.

As we usually say, "one size do not fit all"[4], but off-label use of molecularly targeted agents should be discouraged, and enrolment in clinical trials should be encouraged to assess predictive biomarkers of efficacy.

A further question: given what we know today, can these data always be translated into the adjuvant setting of the disease?

A key example is the use of Osimertinib in resected epidermal growth factor receptor (*EGFR*) mutation-positive NSCLC. Osimertinib represents the standard-of-care therapy for previously untreated *EGFR* mutation-positive advanced (NSCLC)[5]. In the ADAURA Study[6], patients with stage IB to IIIA *EGFR* mutation-positive NSCLC treated with Osimertinib showed a disease-free survival significantly longer than placebo. Based on these data, on December 18, 2020, the Food and Drug Administration approved Osimertinib for adjuvant therapy after tumor resection in NSCLC patients whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, after Orphan Drug designation and Breakthrough Therapy designation for this indication.

As Richard Pazdur (director of the FDA's Oncology Center of Excellence and acting director of the Office of Oncologic Diseases in the FDA's Center for Drug Evaluation and Research) said: «Today's approval demonstrates how additional research on therapies approved in later stages of cancer can eventually improve treatment options for patients in earlier stages»[7].

In this way the second paper reported by Marchetti et al.[8] underlines the importance of adapting pathologic pathways in order to guarantee the execution of diagnostic investigations, in particular molecular tests, in an increasing proportion of NSCLC patients.

Also, in this case, starting from the ADAURA study, we must underline several points of discussion (or real alerts) about evidence, ethics, and economics concerns.

As reported by Gyawali et al.[9], ADAURA was designed to identify an improvement in DFS rather than overall survival (OS). Although DFS has been identified as a surrogate that can correlate well with OS for NSCLC, this conclusion is based on data of conventional cytotoxic chemotherapy, with limited treatment options at relapse. By contrast, these variables are far more likely to become dissociated with targeted therapies for molecularly selected populations in whom treatment even later in the natural history of the disease is associated with a high probability of a dramatic and prolonged response and we have also seen specific examples in which dramatic benefits in DFS have not translated to an OS benefit for adjuvant *EGFR* TKI therapy, or of progression-free survival translating to OS benefit in the setting of metastatic *EGFR* NSCLC.

Despite the tolerability of targeted adjuvant therapy, the impact on patients and society is considerable. Daily treatment for up to 3 years represents a significant therapeutic burden, particularly as some of these patients would have already recovered without Osimertinib. Although Osimertinib is considered to be a generally well tolerated drug, several side effects have been reported. Such negative effects, even if of a low degree, can be quite debilitating when a therapy is given for several years. Such adverse effects, even if low grade, can be quite debilitating when a therapy is given over several years.

It is also necessary to consider the economic impact of a therapy costing more than $ 200,000 per patient annually in the United States and with a high price worldwide.

As Bishal said: «Contrary to the metastatic context, where a therapy can improve the quality of life by reducing the tumor burden, adjuvant therapy can only have harmful effects on the quality of life. That loss of quality of life for years can only be ethically justified if there is compelling evidence of benefit from starting the same therapy at the time of relapse among those who have demonstrated need».

This is our mantra.

Conflict of interests: the author has no conflict of interests to declare.

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