LES COLLOQUES DE L'INSTITUT SERVIER

2017 COLLOQUIUM

PRECISION MEDICINE AND TARGETED THERAPIES: REALITIES AND PERSPECTIVES

Is tumour sequencing necessary for every cancer patient?

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Springer Healthcare

Notes are linked to the references page.

The rise of targeted molecular therapies in the late 1990s revolutionised the prognosis of patients with certain types of cancer. International initiatives in high-throughput sequencing of tumours in the early 2000s showed that the majority of targetable genetic alterations were common to many types of cancer, heralding the introduction of personalised medicine, and then precision medicine, in oncology. The scientific community looked toward the day when treatment could be individualised to each cancer patient based on the genetic map of his or her tumour. In recent years, high-throughput sequencing has become feasible in clinical practice in terms of rapidity and cost, making it possible to genetically map a tumour. At the dawn of the France Genomic Medicine Plan 2025, it is therefore relevant to ask the question: should the tumour of every cancer patient be sequenced? Here we review the literature and discuss some of the challenges of precision cancer medicine so that an opinion can be formed on this issue.

MODALITIES OF CANCER TREATMENT

Localised tumour and metastatic cancer: two radically different situations

The practice of oncology is confronted with two very different situations: in the first, the tumour remains localized in the tissue where it originated while in the second, the cancer cells have migrated to other parts of the body and the cancer has become metastatic.

A localised tumour, amenable to radiotherapy and surgery, is curable. Pharmacotherapy such as chemotherapy and hormone therapy can be given in the adjuvant or neoadjuvant setting, either after or before surgery or radiotherapy, and these methods are therefore the mainstay of treatment for a localised tumour.

In the metastatic setting, with the exception of certain cancers such as testicular cancer, a cure is achieved in only 5% of cases. The strategy of the oncologist will be to stabilize the disease as long as possible with the hope that it will evolve towards chronicity. Pharmacotherapy is then given over the long term. Surgery and radiotherapy still have their place in the therapeutic strategy, but less so than in the case of a localised tumour.

A history of traditional cancer treatments

Historically, surgery was the first cancer treatment, even before physicians had a clear idea of the nature of this disease.

Radiotherapy was next to arrive in our therapeutic arsenal. France can be proud of having played a leading role in this field thanks to Marie Curie's work on radioactivity. 2017 marks the 150th anniversary of her birth. It was

Professor Emile Roux, director of the Pasteur Institute, who, in late 1909, proposed the creation of a Radium Institute dedicated to medical research on cancer and its treatment with radiotherapy. The Radium Institute would later become Institut Curie.

Chemotherapy developed in the aftermath of the Second World War. An Italian ship transporting mustard gas was destroyed by American bombardment. Many sailors were killed by the mustard gas, and those who survived experienced a collapse of their white blood cell counts. The observation of this elective toxicity suggested that mustard gas derivatives could be used in the treatment of leukamias which are characterised by an excess of white blood cells.

TARGETED THERAPIES

In contrast to chemotherapy that kills all dividing cells, and therefore not only cancer cells but also the cells responsible for renewal of the intestinal lining, blood cells or hair growth, targeted therapies are only effective on the cells that express their target.

These therapies have emerged from advancements in the biology of cancer cells

A normal cell becomes cancerous as a result of DNA modifications that allow it to become independent of the signals that normally regulate its growth and division, to escape the process of programmed cell death and to acquire the ability to divide indefinitely.

Significant progress was made in the 1980s and 1990s in understanding the biology of cancer cells. These advances have given rise to targeted therapies which are based on identification of a target molecule of interest, such as an alteration involved in cell multiplication or the process of metastasis, which may lead to the development of drugs capable of blocking the target. Thus, the development of targeted therapies is quite different from that of chemotherapy: they result from the identification of a target, whereas chemotherapies are discovered after in vitro screening of many compounds found in nature, such as the taxanes that come from the yew tree.

Efficacy that can be remarkable

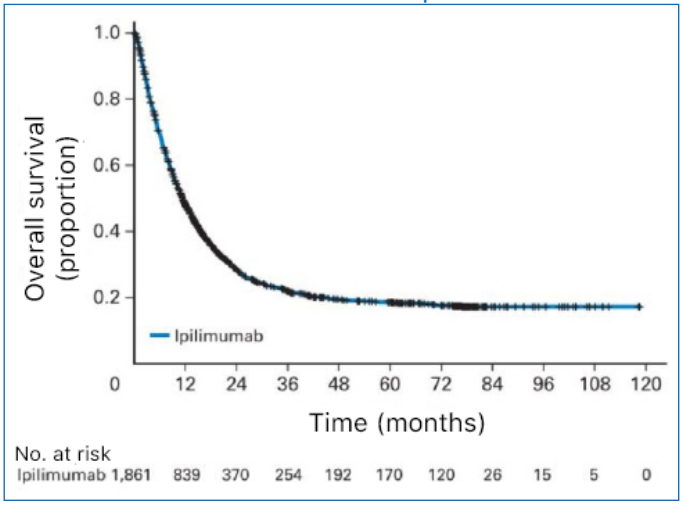
The 1990s saw the advent of the first targeted therapies. These drugs were shown to be extraordinarily effective. For instance, about 15-20% of breast cancer patients carry an amplification of the HER2 gene (human epidermal growth factor receptor 2). It was shown that overactivity of the HER2 gene is linked to a more aggressive form of breast cancer. The use of a treatment targeted to HER2 receptors (trastuzumab) procured a two-fold reduction in the risk of recurrence after surgery in localised HER2-positive breast cancer. In metastatic disease, this same targeted therapy given in combination with chemotherapy led to an increase in median survival from less than two years to more than six years. We have been following patients treated for metastatic breast cancer for more than 15 years.

IMMUNOTHERAPY

Tumour cells grow in the body by escaping the immune system. Immunotherapy aims to counteract this growth by stimulating the immune system to effectively fight against cancer cells[1].

The first such drug, ipilimumab, was marketed in 2011. Twenty percent of patients with metastatic melanoma treated for 10 years with this agent are still alive today, while their median survival was one year (see Fig. 1). Some of these patients, who are no longer on treatment, due mostly to the toxicities of immunotherapy, are nonetheless in complete remission.

Figure 1. Survival curve of patients with metastatic melanoma treated with ipilimumab[1]



Immunotherapies produce favorable outcomes in many types of cancer. These treatments are available for melanoma, lung cancer and will soon be available for head and neck cancer, and bladder cancer, among others. Only a minority of patients respond to immunotherapy, but when they do, the response is very long-lasting.

TARGETED THERAPIES: A NOVEL PARADIGM

Sequencing the tumour of all cancer patients is now possible

The clinical development of chemotherapy has always been based on tumour type and histology. Patients' treatments are therefore classically chosen according to these same criteria. In targeted therapies, it is the presence or absence of the molecular anomaly that theoretically is important to predict efficacy, but despite this fact, targeted therapies have followed the same clinical development path as chemotherapies, that is to say, organ by organ. Thus, trastuzumab, a monoclonal antibody targeting HER2, is approved for patients with breast adenocarcinoma with overexpression of HER2 protein or amplification of the HER2 gene[2]. However, these different molecular anomalies are only tested in certain specific tumour types even though they are present in almost all cancers[3]. For instance, it has been shown that, in stomach cancer, 20% of patients carry this same HER2 gene amplification, and trastuzumab is effective in this indication with an increase in overall survival. A mutation (and not an amplification) of HER2 has also been found in some patients with lung cancer and a clinical response to treatment with another HER2 receptor inhibitor lapatinib has been demonstrated[4].

Today we are capable of sequencing the tumour of any cancer patient. The power of gene sequencers has grown exponentially. The first sequencing of DNA from a cell took seven years of study and had a cost of around three billion dollars. Today it is possible to do the same thing in a few days for around ten thousand Euros. Advances in high-throughput analysis technologies make it possible to establish a molecular profile in a clinically feasible time frame and at a reasonable cost.

The question then becomes whether it is pertinent to develop targeted therapies based on tumour location, as is done for chemotherapy or whether they should be developed instead based on tumour biology? This strategy is what is meant by personalised medicine: a specific treatment for each patient based on the molecular profile of his or her tumour. This represents a new paradigm, in which targeted therapies are prescribed based on the profile of the tumour, according to an algorithm that does not necessarily comply with how these agents are authorised to be used. However it is still necessary to demonstrate that this approach improves patient outcomes[2].

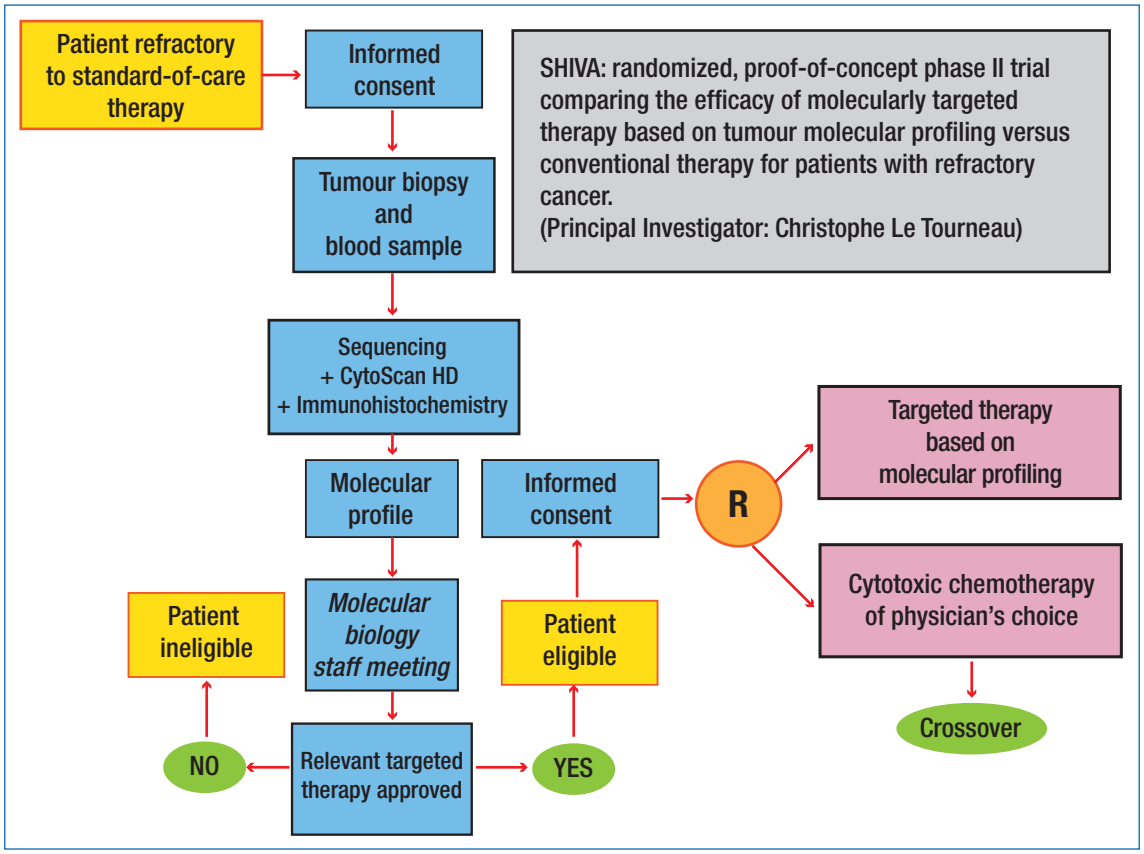
THE SHIVA TRIAL

To address this question, Institut Curie initiated the SHIVA trial, a multicenter proof-of-concept phase II trial evaluating the efficacy of targeted therapy based on tumour molecular profiling independently of cancer histological type versus conventional therapy in patients with refractory cancer (see Fig. 2).

The molecular profile of the tumour was established using high-throughput sequencing on a biopsy sample from a metastatic site using high-throughput sequencing. Based on a predefined treatment algorithm, patients carrying a molecular alteration corresponding to one of 11 study drugs were randomised between:
• an experimental arm treated with the targeted therapy matched to the molecular profile of the tumour,
• a control arm with standard treatment of the oncologist's choice.

To better control for heterogeneity, randomisation was stratified according to three signaling pathways (hormone receptor, PI3K/AKT/mTOR and RAF/MEK) and according to the Royal Marsden Hospital prognostic score. The SHIVA trial was conducted at 8 French centers: Institut Curie (Paris and Saint-Cloud), Centre Léon Bérard (Lyon), Centre René Gauducheau (Nantes), Institut Claudius Régaud (Toulouse), Institut Paoli-Calmettes (Marseille), Centre Georges-François Leclerc (Dijon) and Centre Alexis Vautrin (Nancy). In total, 741 patients were enrolled between October 2012 and July 2014 and 197 patients were randomised. Efficacy data for 195 patients were published in *Lancet Oncology* in September 2015[5].

Figure 2. Flow chart of SHIVA trial[2]



Of 195 patients who had been randomised, 99 received targeted therapy and 96 received standard therapy. The SHIVA trial did not succeed in demonstrating that molecularly targeted therapies used outside their indications according to a predefined treatment algorithm improve progression-free survival compared with standard treatment in heavily pretreated patients with refractory cancer (see Fig. 3). Furthermore, grade 3 and 4 toxicities were more frequent in the experimental arm than in the control arm, although the difference did not reach statistical significance.

Although the SHIVA trial did not meet its efficacy endpoint in the overall population, the data suggest that this precision medicine approach based on treatment assignment according to tumour molecular profiling and not tumour location requires further analysis in the subgroup of patients who received targeted therapy matched to the RAF/MEK pathway (see Fig. 4). A second trial, SHIVA02, aims to validate this strategy in the subgroup of patients with a molecular alteration in the RAF/MEK pathway.

Figure 3. Progression-free survival according to treatment strategy in overall study population[5]

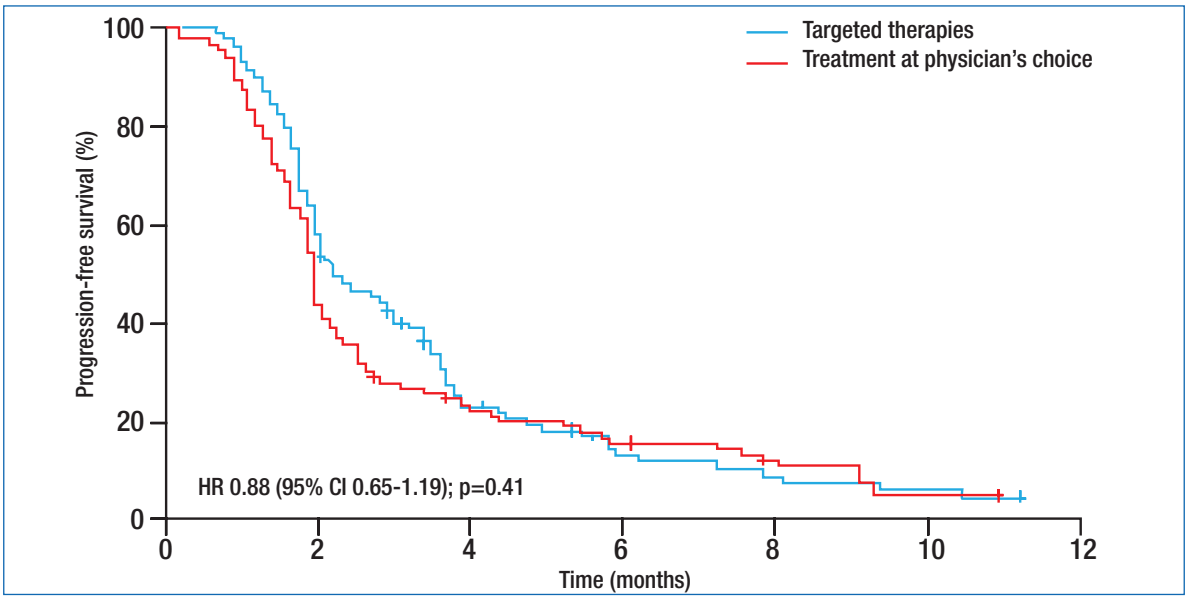
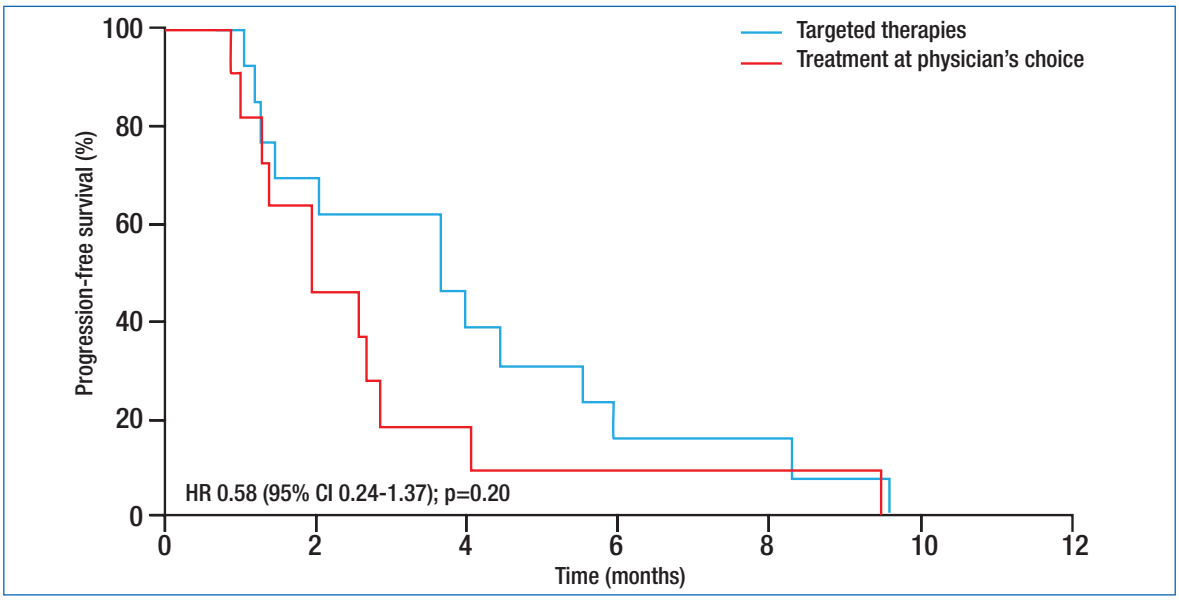


Figure 4. Progression-free survival according to treatment strategy in subgroup receiving targeted treatment for RAF/MEK pathway[5]



Current limitations of prescribing modalities for targeted therapies

A number of factors may explain the SHIVA findings. First, the decision algorithms used for the choice of therapy were probably insufficient.

Second, the techniques of sequencing and genome analysis have limitations that should induce caution. For instance, it has been shown that the sequencing platforms from Roche/454 (GS FLX), Illumina/HiSeq (HiSeq 2000) and Life Technologies/SOLiD (SOLiD 3 ECC) yield non-perfectly concordant results for identification of single nucleotide substitutions in whole genome sequences from the same human sample[6]. Likewise,

sequencing of 15 exomes (part of the genome determining the phenotype) from four families across five bioinformatics pipelines (SOAP, BWA-GATK, BWA-SNVer, GNUMAP, and BWA-Samtools) showed only 57% concordance[7].

CONCLUSION

Tumour sequencing is important for cancer patients when they are included in relevant clinical trials. On the other hand, there is no interest in sequencing the tumours of all cancer patients, especially if that leads to treating these patients off-label, because we currently have no evidence that this would offer them some benefit over current treatment approaches.

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