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Revolutions in cancer treatment:
how can they be integrated?

Multidisciplinary molecular tumour boards

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Abstract

What is a multidisciplinary molecular tumour board? Meetings of molecular tumour boards constitute a vital step in the process of interpreting genetic changes in the tumour or in the individual that may influence treatment or prognosis in cancer. They make it possible to translate knowledge of molecular biology into appropriate treatment recommendations for every patient. The meetings should be attended by specialist doctors and scientists, and in particular by medical oncologists, surgeons, radiotherapists, research doctors, geneticists and pathologists. It should also be possible at the meetings to establish the indications for access to large-scale genomic tests, manage compliance with regulatory aspects of care (patient information and consent) and ensure that the genetic test results, which have consequences for patients and their families, are handled appropriately. Our experimental multidisciplinary molecular tumour board was launched in 2015 to improve the management of patients with lung, colon and rare cancers, and implemented in Pompidou and Tenon hospitals in France. Our results show that the molecular tumour board is capable of meeting the requirements of this concept.

THE MULTIDISCIPLINARY MOLECULAR TUMOUR BOARD: A RECENT CONCEPT

The multidisciplinary molecular tumour board is a recent concept in the treatment of cancer, which emerged in the mid-2010s. Multidisciplinary molecular tumour boards are a response to the need for the healthcare team to have a multifaceted "view" of a patient's results at certain times during their treatment. Joint interpretation of these results by people working in different specialties (specialist doctors, oncologists, surgeons, radiotherapists, geneticists and pathologists) helps guide decision-making on which investigations to undertake and which treatments to provide, withhold, modify or add.

Initiatives of this kind are not yet widespread, but more are being established and the number of multidisciplinary molecular tumour boards is increasing rapidly.

A CLEAR NEED

The rationale for having these molecular tumour boards is based on two key numbers:
- the 9% of patients with metastatic cancer who have targetable genomic alterations under current standards of care; this is the sum of the prevalences of all the targetable rare genomic alterations that have been reported, and
- the 27% of patients with genomic alterations for which there is convincing clinical evidence of a drug response beyond the registered indication.[1,2]

When the two groups are added together, they account for more than one-third of patients. Since a patient may have a number of different genetic alterations, the aim of the multidisciplinary molecular tumour board is to define which one should be targeted and which treatment is likely to target it. This is a necessary step in providing the best possible treatment for cancer.

A NECESSARY STEP

The multidisciplinary molecular tumour board meets a need in the characterisation of the tumour. Clinical decisions are being influenced by the rapid advances in technology, in particular:
- the increase in sequencing capacity, with next-generation sequencing,
- the significant reduction in the cost of these investigations,
- access to large panels (> 400 genes; whole exome sequencing [WES], whole genome sequencing [WGS]) that have been integrated into care through the commercial availability of sequencing procedures ("100,000 genomes"[3] and Genomic France 2025[4]),
- the development of an increasing number of targeted therapies.[5]

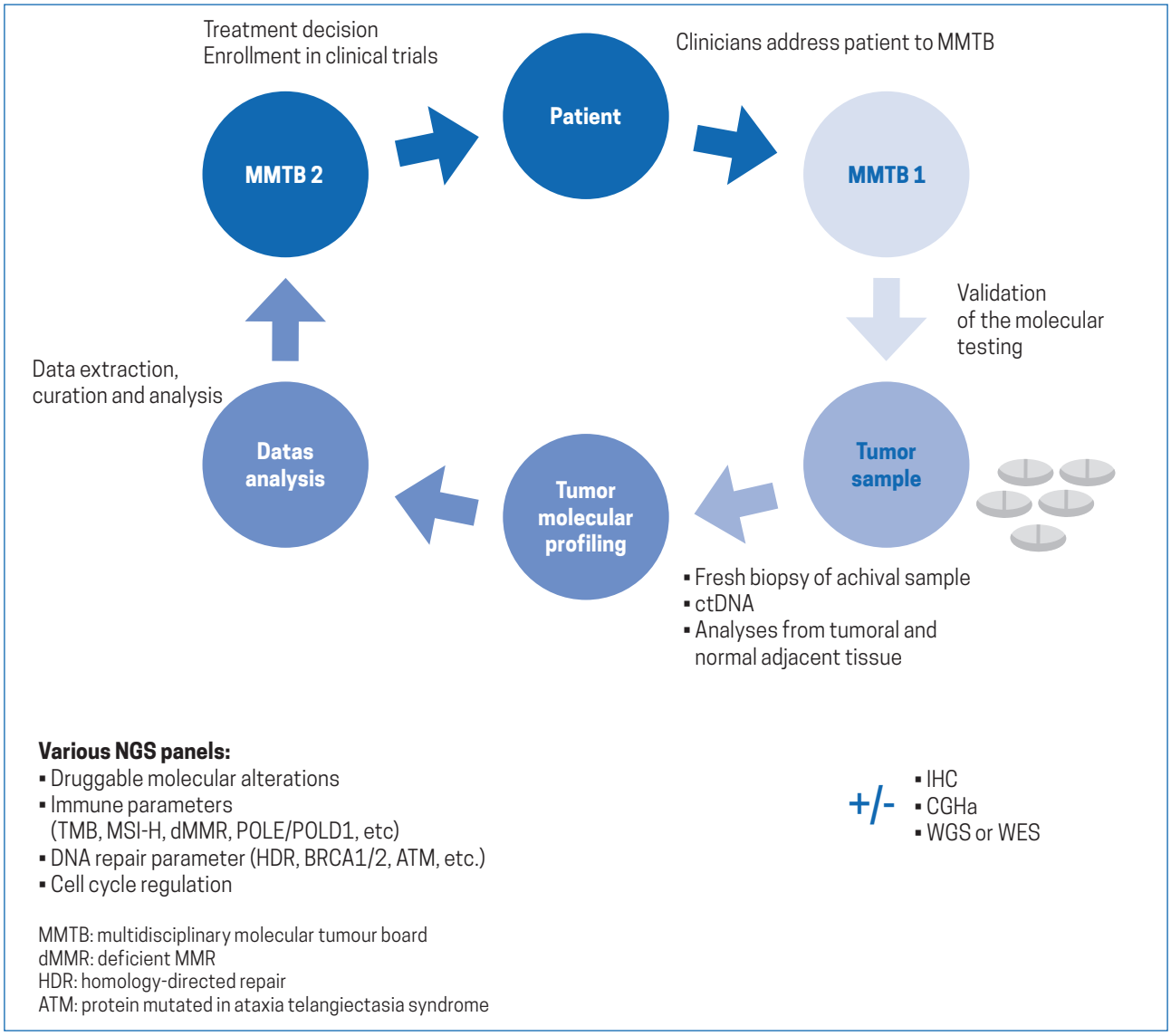
Clinicians need to explain to the patient what has been found in terms of constitutional genetic alterations in their tumour or genome, and make adjustments to their treatment. This represents a shift in the paradigm of treatment, and the consequent problem of a widening gap between clinical knowledge and increasingly complex genetic information.[5] The multidisciplinary molecular tumour board can remedy this disparity, by translating the information from molecular profiling into rational treatment decisions using a precision medicine paradigm.[5,6]

THE MULTIDISCIPLINARY MOLECULAR TUMOUR BOARD: HOW CAN IT BE DEFINED?

Because there is currently limited literature on this subject, we have no real definition of this new concept. Similarly, no quality requirements or directives on the composition of the multidisciplinary molecular tumour board have been published by any learned society. By consensus, the multidisciplinary molecular tumour board is simply focused on the interpretation of genetic alterations and treatment recommendations. A literature review carried out by Velden et al[5] revealed some major differences between boards, for example in the number and specialty of the participants in a multidisciplinary molecular tumour board. The number of participants at each meeting varied between 6 and 40 members, with participants coming from between 2 and 10 different specialties.[5]

The multidisciplinary molecular tumour board forms part of the implementation of precision medicine, by coordinating the workflow on tumour samples when looking for targetable molecular alterations (**Figure 1**).[6] Borcoman et al[6] reviewed the key functions of multidisciplinary molecular tumour boards, to identify the methodological approach that is likely to be most effective. This appears to be centred on the patient. The starting point in this process is identifying the patient's clinical needs, and the mutations that need to be addressed (*EGFR, KRAS*, etc.). The pre-indication multidisciplinary molecular tumour board selects which test to carry out – large panel, exome sequencing, genome based on ctDNA, sequencing or expression profile – to classify the tumour and identify targets for treatment. It also determines which sample will be used for the tests – primary tumour, recurrent tumour, newly progressing tumour, fresh biopsy, cancer tissue from a metastasis, normal adjacent tissue, lymphocytes etc. The purpose of the pre-indication review by the board is to correctly identify the molecular profile that can guide treatment decisions. When using large panels to identify somatic variants, it is necessary to sequence the individual's normal DNA, making it possible to find constitutional genetic alterations or even a predisposition to cancer. Once the variants have been characterised, the multidisciplinary molecular tumour board should meet again to interpret the results and reach conclusions on further investigations and clinical decision-making.[6] Borcoman and colleagues also described the challenges that need to be considered and offer perspectives for broadening the use of precision medicine in routine oncology practice.[6]

Figure 1. Functioning of a multidisciplinary molecular tumour board (MMTB), a patient-centred process.
Reproduced from reference [6], Borcoman et al, Molecular screening programs in different countries: what we learned and perspectives. Curr Opin Oncol. 2019;31:445-453. Available at: https://journals.lww.com/co-oncology/Abstract/2019/09000/Molecular_screening_programs_in_different.13.aspx



CHALLENGES INVOLVED

In practice, every multidisciplinary molecular tumour board faces a number of challenges when choosing appropriate patients to consider, techniques, and investigation modalities, and when interpreting the results. The interpretation of constitutional variants is the most difficult challenge of all, because, in the absence of an infallible bioinformatic algorithm, such interpretation requires the expertise of a biologist, as well as knowledge of how treatments are used in practice (**Table 1**).

Table 1. The various options to be discussed during a multidisciplinary molecular tumour board

The question	Choices
Which patients to sequence?	Adequate physical fitness: no organ failure; patient wishes to participate in a trial of treatment.
Which tumour to analyse?	Primary tumour, secondary tumour before or after treatment, tissue fixed and embedded in paraffin or frozen tissue, circulating tumour DNA (ctDNA).
Which technique to use?	Gene panel, exome + RNA sequencing, genome.
How to interpret the variants?	Actionable somatic variants and constitutional variants, willingness to participate in a trial of treatment.
Clinical usefulness?	Treatment options: targeted drug alone or in a combination, inclusion in a treatment trial, prescription not covered by the marketing authorisation, description and documentation of the response.
Ethical considerations to take into account?	Equal access to these new techniques, management of the family.

SECONDARY AND INCIDENTAL CONSEQUENCES OF LARGE GENE PANELS

Large genome panels provide considerable information about a person's predisposition to cancer. A study by Mandelker et al[7] conducted a study in 1040 patients (65.3% men) with different types of cancer and testing a panel of 76 genes. Overall, 205 patients (19.7%) had deleterious pathogenic variants (14 *BRCA1* and 45 *BRCA2* mutations) conferring a predisposition to cancer.[7] These variants were present not only in patients with breast or prostate cancer, but also those with pancreatic cancer, renal cell carcinoma and colorectal cancer.[7] A study by Schrader et al[8] involving 1566 patients (with an average age of 58 years) who all benefited from a mutation profile using a panel of 341 genes, showed susceptibility to cancer in about 10% of the patients with cancer.

These two studies both found genetic predispositions to cancer that are not part of the expected spectrum for those cancer types, suggesting that the management of cancers will change as our understanding of the genetic determinants evolves.

OUR EXPERIENCE

Over one and a half years, the multidisciplinary molecular tumour board at HEGP / Hôpital Tenon (Paris) reviewed a total of 328 patients: 162 with lung cancer, 57 with colon cancer, 61 with rare tumours, 25 with brain tumours, four with adrenal tumours, 26 with sarcomas and 6 with miscellaneous tumours. Of these, 138 cases (42%) were selected for exome sequencing and RNA-seq (sequencing of RNA or ribonucleic acid). The median time taken to obtain a result was 21 days. In 109 patients, tumour tissue was analysed by exome sequencing and/or RNA-seq (19 samples of colon cancer, 48 of lung cancer, 19 of brain tumours and 23 from other rare tumours including 12 sarcomas). In all, 107 exomes were based on frozen tissue samples, 10 exomes on paraffin-embedded samples, and 107 RNA-seq tests were carried out.

Prior to the analysis, all the patients had an oncogenetic consultation and agreed to receive their secondary data on predisposition to 59 genes (cardiovascular diseases and predispositions to cancer). Targetable mutations were found in 81 patients. The signalling pathways with alterations were: *HER/RAS/MAPK* and *PTEN/PI3K/AKT/STK11*. Genetic alterations were also found in the DNA repair systems and cell cycle control systems *ATR/ATRX/ATM/BRCA1/BRCA2* and in the chromatin organisation system *ARID1A/ARID2/EZH2*. Six targetable rearrangements (fusion genes) involving *RET, ROS1, RAF1 NRG1, STAT6, NF1* were identified.

Sixteen patients received targeted treatment after exome sequencing. Eight patients were included in a treatment trial. This analysis made it possible to correct two diagnoses and identify a melanoma and a Ewing sarcoma, the first tumour to be treated successfully using immunotherapy. Finally, our patients also received information about their predispositions, mostly for genes that predispose to cancers (e.g. *BRCA2*).

CONCLUSION

Faced with the complexity of implementing precision management of cancer, in terms of both patient selection and evaluating treatment options, the involvement of a multidisciplinary molecular tumour board during the course of patients' cancer treatment represents a significant innovation and a useful tool. Nevertheless, although more and more multidisciplinary molecular tumour boards have been established in recent years and the positive results of these meetings are communicated quite regularly, there is still a need for more initiatives of this kind and for learned societies to publish recommendations precisely defining their mission and their composition.

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