BIOLOGICAL MARKERS

Tailoring treatment and trials to prognosis

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As we learn more about the biology of cancer, we may be able to apply prognostic biomarkers to select patients at high risk or low risk of disease recurrence or progression. This will allow *a priori* stratification of patients in clinical trials and will help to tailor treatment to patients.

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The dominant focus of precision or personalized cancer medicine has been on the discovery of predictive, companion diagnostics for the new era of targeted therapeutics. The central idea has been that the pool of patients more likely to benefit could be enriched by identifying a tumour biomarker that predicts response (or lack of response) to therapy.[1,2] Nevertheless, these successes remain relative rarities as the vast majority of anticancer drugs are not associated with clinically validated predictive biomarkers.

If biology is king, then it is logical to also consider how prognostic molecular biomarkers, which describe the progression and outcome of a cancer, could be used to tailor treatments to patients, perhaps delivering more-intensive therapy to patients with a poor prognosis, or to ensure that there is a balance across both arms of a prospective randomized trial in terms of patients with good or poor prognosis. Significant progress has been made in the characterization of prognostic biomarkers through the application of robust molecular methodologies, improved study design (especially with regard to statistical power) and better access to well-curated biobanks that are often linked to large clinical trial databases.[3–7]

> “...prognostic molecular biomarkers are being ... used to alter treatment selection in the clinical setting...”

A major issue that has been associated with the discovery and use of clinically relevant prognostic biomarkers has been the high false-positive rate in studies that are looking to identify them. This false-discovery rate depends on the tumour recurrence rate within the population of patients studied, the number of genes studied (relating directly to the number of multiple comparisons), the variability of gene expression and the size of the hazard ratios deemed clinically relevant. Therefore, for the identification of true prognostic biomarkers, it is preferable to have a large sample size of patients, and for the identified biomarker to be independently verified in a similar large cohort of patients.

In this article, we will describe how prognostic biomarkers can be incorporated into therapeutic algorithms and discuss the benefits of their *a priori* inclusion as stratifying factors, using colorectal cancer as an example.

Many attempts have been made to identify biomarkers that predict clinical outcome in colorectal cancer, particularly for stage II disease. The QUASAR study represented an opportunity to validate a range of prognostic biomarkers that had previously been identified.[3,4] In this trial, patients with colon or rectal cancer who had been resected (90% had stage II disease), were randomly assigned to receive chemotherapy with fluorouracil and folinic acid ($n = 1{,}622$) or to observation only ($n = 1{,}617$). This was the first study to show that adjuvant chemotherapy with fluorouracil and folinic acid gave a statistically significant survival benefit (absolute 5-year improvement, 3.6% [$P = 0.04$]) for patients with stage II colorectal cancer. Although many proposed biomarkers of prognosis were assessed in the QUASAR patient cohort, only mismatch repair deficiency (MMR-D) has been confirmed and incorporated into international treatment guidelines. The confirmation of MMR-D as a prognostic biomarker required data from QUASAR and several other large randomized clinical trials and a meta-analysis, which together reported a hazard ratio for death of 0.65 (95% CI 0.59–0.71) and conclusively proved that the presence of tumoural MMR-D is associated with a favourable outcome irrespective of treatment.[3,7,8]

> “...opportunity to bring descriptors of tumour behaviour to the fore in ... clinical trials must not be missed”

In a study related to the QUASAR trial, a quantitative gene-expression assay was used to assess the recurrence risk following chemotherapy. First, a prognostic signature comprising 12 genes was identified through analysis of 761 candidate genes by reverse-transcription PCR, in the context of stage, tumour grade, nodes examined and MMR status, and this gene signature was used to calculate a recurrence score (RS). The RS was validated using data obtained from primary colon tumour blocks from 1,436 patients in the QUASAR trial with stage II colon cancer, who had a median follow-up of 6.6 years. In the primary analysis of relapse-free interval, the RS predicted recurrence risk (hazard ratio per 25 units = 1.58, 95% CI 1.15–2.15; $P = 0.004$), disease-free survival ($P = 0.01$) and overall survival ($P = 0.04$). In multivariate analyses, RS retained prognostic significance ($P = 0.008$) independent of MMR status, tumour stage, nodes examined, grade, and lymphovascular invasion.[5] On the basis of these results, a new staging algorithm was produced based on tumour stage, molecular biomarkers, MMR status and RS (Figure 1). Applying this algorithm to the patients in this study indicated that patients with T3 primary tumours and tumour

MMR-D (about 15% of patients) have a sufficiently low risk of recurrence (<5%) to suggest that the absolute benefit from post-operative chemotherapy is minimal (from 95% without chemotherapy to 96% with chemotherapy), and that these patients can, therefore, be spared treatment. This risk is similar for patients with T3 tumours, MMR-proficient disease with a low RS, whereas clinicians would be more inclined to offer adjuvant chemotherapy to stage II patients with T4 and T3 tumours, MMR-proficient disease with a high RS. These examples show that prognostic biomarkers have a role in the clinic to help guide treatment selection. Therefore, is it possible that they could also be useful in the design and analysis of clinical trials?

In clinical trial analysis, it is important to discriminate whether apparent differences between treatments might be due to random allocation of more patients with a good prognosis to one treatment than to the other treatment. Prognostic biomarkers can be used in this analysis, since any information about the major determinants of prognosis helps to address this question, and, consequently, assists in producing a more-accurate picture of the relationship between different treatments and patient outcome. Stratification of clinical trials is the partitioning of subjects and results by a factor other than the treatment. For example, a trial of a treatment for which male and female patients might respond differently would usually ensure that each treatment group contained the same proportion of males and females. Individuals can be stratified by demographic information, such as sex, body weight or age, or by clinical criteria, such as tumour stage, previous or simultaneous medication or site of treatment centre. With the identification of new prognostic biomarkers, these could provide another factor by which participants could be stratified.

It might be argued that if good statistical methods are used to analyse data retrospectively from clinical trials, there is no need for randomization to be stratified by prognostic features. Moreover, there is the possibility that the organizational complexity of stratification might deter clinicians from entering patients into trials.[9] However, retrospective analyses rebalancing prognostic factors in trials of novel anticancer agents, in which the primary end point was missed in the intention-to-treat population, do not provide a sufficiently compelling narrative to either the regulatory authorities or the wider clinical community. For example, in the PETACC 3 trial,[10] which—despite accruing 2,000 patients—showed that irinotecan, when added to infusional fluorouracil and leucovorin (LVFU2) as adjuvant therapy, did not improve disease-free survival or overall survival in patients with stage III colon cancer compared with LVFU2 alone. Retrospective analysis showed there was a statistically significant excess in the frequency of patients with poor prognosis T4 tumours in the irinotecan and LV5FU2 group compared to the LV5FU2 group (17% versus 13%; $P = 0.006$).[10] This imbalance was sufficiently biologically important to have contributed to the negative overall result, but had no bearing on how the clinical community viewed the outcome of this trial, and adjuvant use of irinotecan was consigned to the dustbin.

As well-characterized validated prognostic molecular biomarkers are being added to staging algorithms and used to alter treatment selection in the clinical setting, it seems odd not to consider using these biomarkers upfront in the trial stratification process. This stratification will ensure 'biological' balance and that any novel therapy is given a level playing field to prove its worth. The community of cancer physicians and patients is becoming more used to performing molecular tests to determine the best therapeutic course of action, and the opportunity to bring descriptors of tumour behaviour to the fore in randomized clinical trials must not be missed.

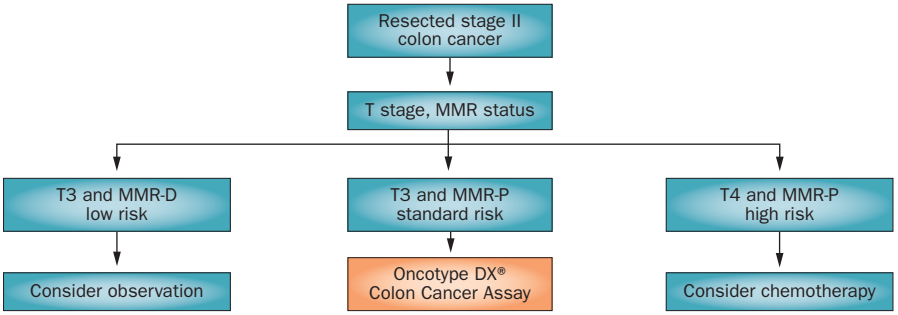

Figure 1 | Molecular prognostic and pathology algorithm for colon cancer. Abbreviations: MMR-D, mismatch repair deficient; MMR-P, mismatch repair proficient; T, tumour.

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Competing interests
D. J. Kerr declares associations with the following companies: Genomic Health, Oxford Cancer Biomarkers. See the article online for full details of the relationships. Y. Shi declares no competing interests.

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