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Osimertinib in central nervous system progressive EGFR-mutant lung cancer: do we need to detect T790M?

Recently, we reported the efficacy of 160 mg of osimertinib in *EGFR* 790M-positive non-small-cell lung cancer patients with brain metastasis or leptomeningeal (LM) disease (with or without brain metastasis) who progressed on prior epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) treatment. This study demonstrated median progression-free survival of 7.6 versus 8.0 months and median overall survival of 16.9 versus 13.3 months, respectively, in the brain metastasis versus LM cohort, which are quite promising data.[1] Facchinetti et al.[2] raised the issue of the importance of detecting T790M, because patients who experienced metastases only in the brain or LM metastasis without extracranial progression achieved favorable clinical outcomes even better than those without T790M in either tissue, circulating free DNA (cfDNA), or cerebrospinal fluid. Given the pharmacological resistance of first- or second-generation EGFR TKI treatment attributed to poor penetration into the central nervous system, we fully agree with their opinion. Actually, in our study, cfDNA analysis showed that about half of the patients had T790M-negative or unknown status at the time of study entry, which is consistent with a previous study.[3] Considering our current data and retrospective study results,[4] osimertinib should be the treatment of choice regardless of T790M status in clinical practice in patients who develop central nervous system metastasis, especially LM, for which therapeutic options are very limited. However, the reasons why only T790M-positive patients were included in our study are as follows. First, to recruit a more homogeneous population of patients in terms of molecular aberrations; second, to investigate the difference in treatment efficacy between brain metastasis and LM; and third, to evaluate the efficacy of 160 mg of osimertinib in patients who failed prior third-generation EGFR TKI treatment, including 80 mg of osimertinib. Although osimertinib has been approved as first-line therapy in *EGFR*-mutant non-small-cell lung cancer globally, first- or second-generation EGFR TKIs are still widely used because of reimbursement issues. As a result, repeat biopsy of either tissue or cfDNA to detect T790M mutation remains a standard approach. However, based on our study results, for those patients who developed LM during first- or second-generation EGFR TKI treatment, osimertinib should be strongly recommended to improve their clinical outcomes. An upcoming clinical trial of 80 mg of osimertinib in *EGFR*-mutant patients with LM regardless of T790M status will further provide clinical evidence.

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The potential influence of human Y-chromosome haplogroup on COVID-19 prevalence and mortality

We read with interest the paper by Montopoli et al. about the association between androgen deprivation therapies (ADT) in prostate cancer patients and protection against coronavirus disease 2019 (COVID-19). The *TMPRSS2* regulated expression by the androgen receptor (AR) in non-prostatic tissues might explain the increased susceptibility of men to develop severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. ADT, based on luteinizing hormone-releasing hormone (LHRH) agonist/antagonists or AR inhibitors, might reduce SARS-CoV-2

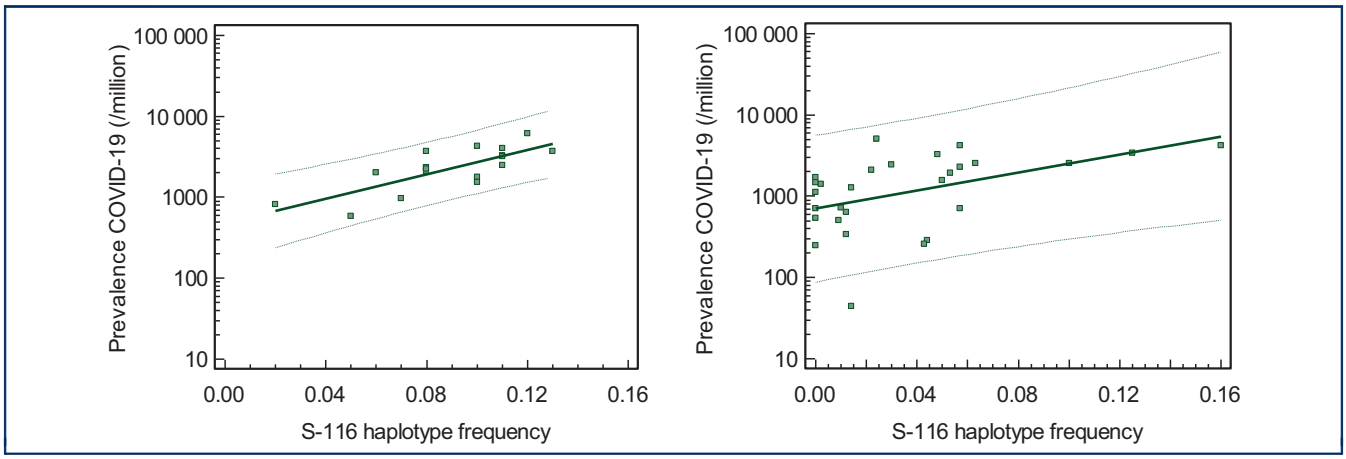

Figure 1. **R1b-S116 haplotype frequency versus COVID-19 prevalence (30 April 2020) in the Netherlands and Flanders (A) [log (prevalence) = 2.8684 + 7.543 X (R1b-S116 haplotype frequency), $r^2 = 0.601$] and in a group of 28 countries (B) [log (prevalence) = 2.848 + 5.561 X (R1b-S116 haplotype frequency), $r^2 = 0.390$].**

infections or complications in high-risk male populations.[1] The outbreak of the pandemic shows a marked geographical variation in the prevalence and mortality of COVID-19. Some Western European regions (e.g. Bergamo in Italy, Noord-Brabant in the Netherlands, Limburg in Belgium) were severely affected. As a potentially protective role of the double X chromosome in females was suggested,[2] we postulated that Y-chromosome polymorphisms might also partly explain the variable prevalence and mortality.

The phylogenetic resolution of the Y-chromosome haplogroup (YHG) tree is now sufficiently high to be able to detect geographic patterns on a micro-regional scale.[3,4] A critical role for genetic variation in chromosome Y in regulating susceptibility to influenza A virus infection and in augmenting pathogenic immune responses in the lung has been demonstrated in a murine model.[5] We have compared the prevalence of Y-chromosome haplotypes in the Netherlands and Dutch-speaking Belgium (Flanders) with the prevalence and mortality of COVID-19 using individualized data of 12 Dutch and 5 Flemish provinces. In parallel, prevalence and mortality of COVID-19 were compared with epidemiological data on Y-chromosome haplotypes and several polymorphisms [angiotensin-converting enzyme 1 (*ACE1*), human homeostatic iron regulator protein (*HFE*), and complement component *C3*] in 28 (mainly European) countries. Infection-related data reported on 30 April 2020 by Belgian and Dutch health authorities, as well as Johns Hopkins, were analyzed. COVID-19 prevalence (Figure 1A) and mortality frequency in the Dutch and Flemish provinces strongly correlated with the R1b-S116 haplotype frequency ($r^2 = 0.601$ and 0.453, respectively). Similarly, in European countries, a marked correlation was noted: COVID-19 prevalence (Figure 1B) and mortality showed a strong correlation with the R1b-S116 haplotype frequency ($r^2 = 0.390$ and 0.493, respectively). Even in separate multivariate regression models for COVID-19 prevalence and mortality frequency including the listed candidate markers, R1b-S116 remained a significant factor (next to *ACE1* polymorphism for COVID-19 prevalence). Remarkably, among Italians, the heavily affected Bergamo area is characterized by a very high R1b-S116 haplotype frequency (0.179). Among European countries, a linear positive correlation was found between R1b-S116 allele frequency and basic reproduction numbers [calculated from a susceptible-infectious-recovered COVID-19 model ($r^2 = 0.281$)].

On the one hand, the Y-chromosome influences immune and inflammatory responses, resulting in a genetically programmed susceptibility to diseases with a strong immune component. On the other hand, the R1b-S116 haplotype frequency might also be regarded as a population marker, which stands for cosegregated genes and associated epigenetic control. Further research should focus on the interaction between the AR, *TMPRSS2*, and the pattern of Y-chromosome haplotype distribution in different COVID-19 patient population groups.

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Genetic and hormonal influence on SARS-CoV-2-infection susceptibility

Re: The potential influence of human Y-chromosome haplogroup on COVID-19 prevalence and mortality

We read with interest the correspondence by Delanghe et al.,[1] suggesting that genetic variants, and in particular Y chromosome polymorphisms, might explain outcome variations between genders. During the coronavirus disease 2019 (COVID-19) pandemic one prominent difference became apparent: men are more vulnerable to severe outcomes than women.[2] We recently published an observational study putting forward the hypothesis that male hormones may explain the increased male susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Our analysis was focused on SARS-CoV-2-infected prostate cancer patients of the Italian region of Veneto.

Importantly, as highlighted by Delanghe et al.,[1] the spread of the pandemic shows a marked geographical heterogeneity in the prevalence and mortality. Several factors can contribute to this phenomenon; the geographical distribution of genetic variants is one of them. Indeed, Delanghe et al.[1] reported a positive correlation between COVID-19 prevalence and mortality frequency and the frequency of the R1b-S116 haplotype in Europe. Noteworthy, several genes located on the Y chromosome have been associated with human diseases such as hypertension, coronary artery disease, and also infections. Indeed, several immune-related genes are on the Y chromosome and might modulate the immune response.[3]

Data from our study suggest that male hormones may be associated with increased SARS-CoV-2 susceptibility. It is important to highlight that the androgen receptor (*AR*) gene locus is located on the X chromosome, and that *AR* polymorphisms exist, which are linked to variable AR transcriptional activity. However, the association between *AR* genetic variants and COVID-19 severity has not been demonstrated yet.[4]

Other studies have investigated the influence of genetic factors in the spreading of SARS-CoV-2. *ACE2* and *TMPRSS2* are interesting target genes, as they are crucial for SARS-CoV-2 entry in infected cells.[5] Importantly, *ACE2* is located on the X chromosome and *TMPRSS2* is regulated by androgen levels. Asselta et al.[6] analyzed genetic variants of *ACE2* and *TMPRSS2* genes in the Italian population, looking for genetic factors underlying COVID-19 severity. According to their analysis, specific *TMPRSS2* genetic variants (one exonic variant and two distinct haplotypes) might be associated with more severe disease manifestations, and could also explain sex-related differences.[6]

Nevertheless, available data on the COVID-19 pandemic are not sufficient to confirm the existence of genetic modulators of SARS-CoV-2 infection outcomes. For this reason, there is an urgent need for large studies linking genetic variants with disease susceptibility and outcomes.

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