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RESEARCH HIGHLIGHT

Androgen-deprivation therapy in men with metastatic prostate cancer: less may not necessarily be more

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In a pivotal phase 3 randomized controlled trial, Hussain *et al.* tested the hypothesis that, with respect to survival, intermittent androgen deprivation therapy (ADT) is non-inferior to continuous in men with newly diagnosed metastatic prostate cancer. While the trial findings were statistically inconclusive, the study suggests, but does not prove, that intermittent may do more harm than good, although findings are not definitive. While outcomes of ongoing trials are awaited, the trial by Hussain *et al.*, in conjunction with an earlier trial in men with non-metastatic prostate cancer by Crook *et al.*, does provide important new guidance regarding the choice of ADT in men with androgen-sensitive prostate cancer.

ADT is one of the most effective palliative therapies for patients with metastatic prostate cancer, but not without drawbacks. While not as toxic as chemotherapy, ADT carries a significant risk of morbidity, including sexual dysfunction, fatigue, anemia, accelerated bone loss and fractures, sarcopenia, increased risk of diabetes, and possibly, of cardiovascular events.[1,2] In addition, despite an initial response rate of more than 90%, most patients develop resistance to ADT, resulting in a median survival of 2.5–3 years. Preclinical data suggest that continuous use of ADT may accelerate the emergence of resistance to this therapy, and that re-exposure of prostate cancer stem cells to androgens can re-induce differentiation and increase their apoptotic potential.[3] These ADT-associated shortcomings, in addition to treatment expense, have spurred the development of strategies to minimize the exposure to ADT, including the use of intermittent ADT. While several smaller randomized controlled clinical trials have compared the use of intermittent with continuous ADT, no definitive information is available for patients with metastatic prostate cancer. To fill this evidence gap, a large multinational randomized controlled trial led by Hussain *et al.*[4] was designed in 1993, and outcomes have been published recently in the *New England Journal of Medicine*. In a coprimary end point, the authors tested the hypotheses that (i) intermittent ADT is not inferior to continuous ADT with respect to survival in men with metastatic, hormone-sensitive prostate cancer; and (ii) compared to continuous therapy, intermittent ADT improves quality of life. The primary finding from the study was inconclusive, that is, intermittent ADT was not proven to be as good as continuous ADT, and there was instead a trend to inferiority. While intermittent ADT was associated with better erectile function and mental health, this benefit did not persist beyond 3 months. Due to the inconclusive finding of this non-inferiority trial its findings may be difficult to interpret and apply to clinical practice. Therefore, we explore this trial in more detail.

The study by Hussain *et al.*[4] enrolled 3040 men from the Unite States, Canada and UK who had newly diagnosed prostate cancer with lymph node, visceral or bone metastases and a prostate-specific antigen (PSA) $>$ 5 ng ml^{-1}. Men received a 7-month induction course with a luteinizing hormone releasing hormone agonist and anti-androgen (goserelin and bicalutamide, or equivalent) to select androgen-dependent disease, defined by a PSA $\leqslant$4 ng ml^{-1} at induction end. One thousand five hundred and thirty-five men fulfilled this criterion and were then randomized but not blinded to intermittent or continuous ADT, stratified by performance status, prior hormone therapy and extent of disease. Men assigned to continuous therapy continued, whereas men assigned to intermittent therapy discontinued ADT at completion of the 7-month induction course. The thresholds for re-commencement of ADT in the intermittent group were: a rise of PSA to baseline or $\geqslant$20 ng ml^{-1} or investigator discretion (PSA $>$10 ng ml^{-1} or symptomatic disease). For the statistical analysis, the authors assumed a median survival in men receiving continuous ADT of 35 months and considered a 7-month shorter survival with intermittent clinically unacceptable, and therefore, a hazard ratio of 1.20 was set as a one-sided test of the null hypothesis.

Median age of the randomized population was 70, pre-treatment PSA 42 ng ml^{-1}, 96% had an Eastern Cooperative Oncology Group performance status of 0–1 and 50% had extensive (*vs.* 50% minimal) disease, and one-third of men had bone pain at the beginning of the induction period, with no difference in men assigned to intermittent (n=770) and continuous (n=765) ADT. Median follow-up was 9.8 years.

Median duration of protocol therapy after randomisation was only 17 months in the continuous group and 19 months in the intermittent group. Those in the intermittent group received ADT for a median 47% of time, and at 15 months, 78% of men in the intermittent group had resumed ADT. Median survival was 5.8 years in the continuous group and 5.1 years in the intermittent group, and 73% to 80% of deaths were related to prostate cancer. The hazard ratio for death was 1.10, representing a 10% increased risk of death with the use of intermittent ADT, with a 90% confidence interval of 0.99–1.23. Because the upper limit of the 90% confidence interval exceeded the predefined threshold of 1.20, the hypothesis that intermittent ADT was not inferior to continuous therapy

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could not be rejected, as the statistical analysis did not rule out the possibility that intermittent therapy was associated with a ⩾7-month shorter survival. Since the lower limit of the confidence interval (0.99) crossed unity, intermittent ADT was not, in strict statistical terms, inferior to continuous therapy. However, since nearly the entire confidence interval favoured continuous therapy, there remains the concern that intermittent therapy may compromise survival. Subgroup analysis according to disease extent, PSA and performance status, although limited by small numbers, showed no significant differences in survival. Data on quality of life were available from 1162 men; at 3 months, men assigned to ADT reported less impotence and better quality of life, but these differences did not persist beyond 3 months. However, patients were not blinded and an emotional response to receiving a treatment break cannot be ruled out. The study was not powered to detect between group difference in high-grade adverse events, with 11 cardiovascular and 2 musculoskeletal events reported in the intermittent, and 15 and 3 in the continuous group.

In summary, because the confidence interval limits crossed both unity and the prespecified delta, the findings by Hussain *et al.*[4] were statistically inconclusive. Thus, the results do not imply that intermittent therapy is inferior; rather, the possibility that intermittent therapy is inferior cannot be discounted. Conversely, the trial has not shown that continuous therapy is superior. However, while not significant, median survival was 7 months shorter in the group receiving intermittent therapy, a timeframe which the authors predefined as being clinically unacceptable. Interestingly, in the subgroup analysis, it appeared that predominantly the men with minimal (as opposed to extensive) disease benefitted from continuous therapy, although this finding requires confirmation.

This trial may have been inconclusive for a number of reasons. Firstly, the median survival in both groups (5.1–5.8 years) was longer than the predicted (3.5 years) survival used for statistical modelling, and hence, statistical power diminished. In addition, follow-up may have been to short, with survival curves separating only after 4–5 years, and the PSA trigger level for therapy resumption in the intermittent ADT group may have been too conservative. Unfortunately, serum testosterone levels were not measured during the trial. Given that testosterone recovery in the off-treatment period is variable, and given that a rise in testosterone would be predicted not only to correlate with improved quality of life measures but also with re-sensitization of prostate cancer cells to subsequent ADT therapy, analysis by testosterone levels would have been informative. Strengths of the trial include the large number of disease-specific events, because only patients with metastatic disease, preselected for androgen-dependent disease were selected.

The trial does not necessarily contradict the results of another recent pivotal phase 3 randomized controlled trial by Crook *et al.*[5] that reported that intermittent ADT was not inferior to continuous ADT with respect to survival. This trial recruited men without evidence of metastatic disease, and patients assigned to intermittent ADT were on therapy only 27% of the time. As expected with earlier stage prostate cancer, median survival was longer (9 years), and prostate cancer-specific mortality (14.2%) lower in this trial[5] compared to the randomized controlled trial in men with metastatic prostate cancer by Hussain *et al.*[4] While the trial by Crook *et al.*[5] showed non-inferiority for overall survival, intermittent therapy was associated with a non-significant increase (9%) of prostate cancer-specific mortality, with a trend towards reduced overall survival in those with a Gleason score of 8–10. Because of the relatively low number of prostate cancer-related deaths, the trial may have been underpowered to show inferiority of intermittent therapy. Interestingly, this was offset by an 8% increase of non-prostate cancer deaths in the continuous ADT group, and, although causality was not proven, it is tempting to speculate that this increase was related to ADT-mediated toxicities. In addition, although testosterone recovery to baseline in the off-treatment period occurred in only 35%, intermittent ADT was associated with improvements in measures of quality of life, such as better sexual and physical function and less fatigue,[5] although the clinical meaningfulness of such statistical improvements is more difficult to delineate. Similar to the trial by Hussain *et al.*,[4] the trial by Crook *et al.*[5] was not powered to detect between group differences in serious ADT-associated adverse events between groups such as minimal trauma fractures or cardiovascular events.

So where do the results of these trial leave us? Collectively, these two pivotal trials[4,5] do not support the hypothesis from preclinical data[3] that intermittent ADT delays the emergence of castrate resistance disease, but they do inform about patient characteristics predicting suitability for either continuous or intermittent ADT. Clearly, treatment needs to be individualized for a men with prostate cancer, based on potential benefits, and risks with intermittent versus continuous ADT, and the patient should be, where appropriate, involved in decision making.[6] Evidence, reviewed elsewhere, suggests that toxicities of ADT are more significant in men with underlying comorbidities, such as cardiometabolic disease and reduced bone mass.[1] Conversely, men at higher risk of prostate cancer-specific death are more likely to derive benefit from ADT and less likely to succumb to competing causes of mortality that may be accelerated by ADT. In addition, men will be individually different in their tolerance of ADT-associated decrements in quality of life, such as hot flushes, fatigue and sexual dysfunction. Based on the trial by Crook *et al.*,[5] intermittent ADT therapy should be considered for most men with non-metastatic disease, especially in older men with a Gleason score of 7 or less, associated comorbidities, poor tolerance to ADT and slow PSA rises in the off-treatment period. However, based on the results by Hussain *et al.*,[4] intermittent ADT should be used with caution in men with metastatic disease. Men with metastatic disease would be expected to derive less benefit from intermittent ADT because of shorter off-treatment time with less potential for testosterone recovery, and reduced life expectancy. Importantly, if ADT is commenced, patients should be monitored and treated for ADT-associated comorbidities according to evidence-based guidelines[7] to minimize the risk of ADT-associated adverse events. Indeed, a recent prospective study has demonstrated that implementation of such guidelines can mitigate ADT-associated cardiovascular risk and bone loss.[8]

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