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The potential role of curcumin in prostate cancer: the importance of optimizing pharmacokinetics in clinical studies

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Curcumin, a commercially available nutritional supplement, has been studied for use as a chemopreventive agent and an anti-cancer therapy in prostate cancer (1). The anti-tumor activity of curcumin and its analogues are well-documented from preclinical studies using prostate cancer models, including its effects on androgen receptor (AR) signaling and numerous downstream targets (e.g., VEGF, PTEN, NF-κB) (2–7). Curcumin was shown to down-regulate AR expression, limit AR binding to the androgen response element of the prostate specific antigen (PSA) gene, and reduce the expression of PSA in LNCaP cells (2). Pyridine analogues of curcumin were shown to have an inhibitory effect on CWR-22Rv1 AR activity and cell growth (5). Curcumin was also effective at delaying tumor growth and suppressing AR expression in a LNCaP xenograft model (3,8). A phase I clinical study also showed that an 8,000 mg dose could be given safely to humans with minimal toxicity (9). Given the minimal toxicity and promising preclinical activity, the rationale of adding curcumin to standard of care therapy (e.g., docetaxel) would become an attractive therapeutic option for patients with metastatic castration resistant prostate cancer (mCRPC) if clinical efficacy could be established.

The single arm phase II study described by Mahammedi *et al*. in *Oncology* administered docetaxel (75 mg/m^2 IV infusion, once every 21 days for 6 cycles) in combination with curcumin (6,000 mg orally, once daily) to 30 patients with mCRPC without prior chemotherapy treatment (10). An objective PSA response (defined as reduction in serum PSA of at least 50%) was obtained for 59% of patients (n=17), while 40% of patients with measurable or evaluable lesions (6 of 15 patients) had a partial response. The study, however, did not conduct a pharmacokinetic analysis to characterize the exposure-response relationship associated with curcumin plasma concentrations. The severe toxicities observed on study were attributable to the docetaxel component of therapy and 89% of patients were compliant with daily curcumin administration. The study also measured two biomarkers

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associated with neuroendocrine differentiation (NED), chromogranin A (CgA) and neurospecific enolase (NSE). The findings suggested a correlation between baseline CgA and baseline PSA, and some rationale for further use of NSE as a biomarker of treatment response. The median overall survival (OS) of the study was 18 months, with a statistically significant association of abnormal NSE values and higher OS (10). The patient sample size is too small to determine a relative benefit of this study.

The median OS of curcumin in combination with docetaxel did not differ significantly from the landmark phase III TAX-327 study that assessed docetaxel monotherapy every 3 weeks (OS: 18.9 months) (11). Though Mahammedi *et al.* compared the response rate to that of the SWOG-9916 trial that examined docetaxel in combination with estramustine (PSA response rate: 50%), the median OS did not differ significantly from this study either (OS: 17.5 months) (12). The lack of improvement in OS calls into question the clinical efficacy of the synergistic combination of curcumin with docetaxel. However, the investigators initiated a follow-up multicenter, randomized phase II study that is currently ongoing comparing the docetaxel and curcumin combination to docetaxel monotherapy as first-line treatment for mCRPC (Clinicaltrials.gov identifier: NCT02095717). Whether this study can demonstrate a favorable time to disease progression remains to be seen; it is also uncertain if pharmacokinetic assessments are being conducted (as suggested by Mahammedi *et al.*) to correlate with clinical outcome.

The lack of a correlative pharmacokinetic analysis is a major limitation to the study presented by Mahammedi *et al.* Curcumin is poorly absorbed and undergoes extensive phase II metabolism (e.g., glucuronidation and sulfation) (13). Despite the administration of high doses, the measurements of free curcumin plasma concentrations are consistent with very low exposures by comparison (AUC_{0-24} of 13.74±5.63 nMole·h/mL) (9). Although a majority of curcumin is glucuronidated or sulfated in plasma, the concentrations of these metabolites are still consistent with poor bioavailability (14). An analysis of the conjugated metabolites showed significant interpatient variability in maximum plasma concentrations (C_{max}) and steady state concentrations 2 to 6 hours post dose (0 to 125 ng/mL and 22 to 41 ng/mL respectively) (14). The formation of phase II metabolites and limited bioavailability hinder the reproducibility of pharmacokinetic data across a patient population and reduce the likelihood of significant responses to therapy. Additionally, more recent preclinical assessments show that curcumin potently inhibits OATP1B1, OATP1B3, and CYP3A4 in human liver microsomes, suggesting a decrease in hepatocyte-mediated uptake and metabolism of docetaxel (15). The measurement of curcumin and docetaxel plasma concentrations is necessary to validate a clinically significant drug exposure and subsequent improvements in clinical response. The correlation of curcumin therapy to clinical benefit is unclear with the omission of a pharmacokinetic analysis by Mahammedi *et al.*

Much research has been focused on optimizing curcumin's pharmacokinetic profile. One approach has included the use of piperine to inhibit hepatic and intestinal glucuronidation, which was shown to increase the bioavailability of free curcumin by 2,000% in humans (16). A large effort to improve curcumin pharmacokinetics has involved the development of nanoformulations incorporating the use of liposomes, cyclodextrins, polymers and other unique systems of delivery (17). Curcumin-based nanoparticle formulations could

circumvent issues of poor oral absorption (likely via intravenous administration), better control the exposure in plasma, and possibly improve deposition into tumor tissue. One example includes an anti-PSMA conjugated curcumin loaded poly(lactide-coglycolide) (PLGA) nanoparticle, which has demonstrated target selectivity to prostate cancer cells expressing PSMA both *in vitro* and *in vivo* (18). Another formulation that co-encapsulates docetaxel and curcumin in lipid-polymer hybrid nanoparticles was shown to inhibit tumor growth in mice bearing PC-3 prostate cancer xenografts, suggesting the synergy of the treatment combination (19).

Curcumin derivatives might also provide a promising alternative to nanoformulations. A notable curcumin analog is ASC-J9, which was discovered via structure-activity relationship (SAR) studies (20). ASC-J9 has been shown to inhibit tumor growth in mice with CWR-22Rv1 xenografts and degrade both full-length and splice variant ARs (6,21). More recently, ASC-J9 was shown to degrade ARs with the F876L mutation in C4–2 and DU-145 cells, and suppress prostate cancer stem/progenitor (S/P) cell invasion via the alteration of EZH2/STAT3 signaling in mice with CWR-22Rv1 CD133+ S/P xenografts (22,23). The preclinical data of ASC-J9 suggests anti-tumor activity against commonly reported pathways of treatment resistance in patients with mCRPC (24). Additionally, the incorporation of ASC-J9 into PLGA nanoparticles induced the apoptosis of estrogen dependent breast cancer cells (MCF-7 cells) at lower doses than the pure compound (25). While the preclinical studies of these novel curcumin formulations and derivatives are promising, their clinical benefit has yet to be determined.

The study by Mahammedi *et al.* did not provide a strong rationale for developing combination docetaxel and curcumin therapy in patients with mCRPC. Despite not demonstrating a significant improvement in OS, the study inadvertently emphasized the importance of generating exposure-response data in clinical studies and the notable deficiencies of curcumin as a therapeutic agent. The success of curcumin as an anti-cancer therapy will depend on the development of an enhanced formulation and/or analog to generate a favorable pharmacokinetic profile and improved efficacy, followed by biomarker-driven studies to validate its mechanism of action and identify the subset of patients most likely to respond to the treatment regimen. The future clinical utility of curcumin will likely be determined following continued efforts to optimize the compound's delivery and structure activity relationship.

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