模型引导下免疫检查点抑制剂的研发

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摘要: 免疫检查点抑制剂作为一种新型的抗肿瘤治疗药物, 因其对多种肿瘤卓越的疗效及良好的安全性得到广泛认可。基于定量药理学的发展应运而生的模型引导的药物研发 (model-informed drug development, MIDD), 能加速新药临床试验的进程, 提高新药研究过程中决策的正确率, 尤其是针对研发难度较大而需求甚广的免疫检查点抑制剂类新药。本文主要以帕博利珠单抗为例, 阐述MIDD方法在免疫检查点抑制剂研发过程中的具体应用, 包括研发早期有效给药方案的拟定, 研发晚期评估临床疗效和验证给药方案的可行性, 再至上市后给药方案的再评估及变更, 为MIDD指导抗肿瘤新药的研发提供参考。

关键词: 模型引导的药物研发; 建模; 模拟; 定量药理学; 免疫检查点抑制剂; 帕博利珠单抗

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Model-informed drug development for immune checkpoint inhibitors

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Abstract: With a deepening understanding of cancer treatment, immune checkpoint inhibitors are recognized widely as a novel fundamental remedy for various malignancies with effectiveness and safety. With the development of pharmacometrics, model-informed drug development (MIDD) has emerged to accelerate the process of clinical research for new drugs and improve the accuracy of decision-making in new drug research, especially for immune checkpoint inhibitors. As a typical illustration, the research development of pembrolizumab is presented in this review to highlight the application of MIDD, which may provide a reference for the development of other new antitumor drugs.

Key words: model-informed drug development; modeling; simulation; pharmacometrics; immune checkpoint inhibitor; pembrolizumab

免疫检查点抑制剂 (immune checkpoint inhibitors, ICIs) 是一种备受关注的肿瘤免疫治疗药物。ICIs通过抑制免疫检查点的活性, 阻断免疫抑制通路, 解除机体免疫耐受状态并增强机体自身对肿瘤细胞的识别与清除能力, 发挥强大抗肿瘤效应, 从而显著改善癌症患者的治疗效果和生活质量[1]。鉴于ICIs广阔的临床应用前景, ICIs新药研发迅速成为了抗肿瘤治疗领域的研究热点[2]。而模型引导的药物研发 (model informed drug development, MIDD) 作为一种先进的药物研发方法, 以药动学−药效学−疾病进程的建模和模拟 (modeling and simulation, M&S) 为基础, 在新药研发各阶段均能起到指导性作用[3]。在ICIs新药研发过程中采用模型引导的药物研发方法, 能有效降低研发成本, 提升研发效率, 从而使ICIs能更好地应用于肿瘤患者的临床治疗。本文根据文献报道, 对模型引导的ICIs新药研发进行综述, 旨在为抗肿瘤新药的研发提供借鉴。

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1 免疫检查点抑制剂

自2011年首个CTLA-4抑制剂伊匹单抗在美国获批上市后, 以程序性死亡受体1 (programmed cell death protein 1, PD-1) 抑制剂和程序性死亡受体-配体1 (programmed cell death-ligand 1, PD-L1) 抑制剂为主的7个ICIs相继获得美国食品与药品监督管理局 (Food and Drug Administration, FDA) 的批准并在临床上广泛使用[4]。近年来, ICIs在黑色素瘤、非小细胞肺癌、泌尿道上皮细胞癌等癌症的治疗中展示出强大的抗肿瘤活性, 并相继获得FDA的批准用于临床治疗[5-7], 成为一类作用机制新颖、对恶性肿瘤疗效显著且发展前景方兴未艾的药物, 为化疗或靶向治疗失败的肿瘤患者带来了新的希望。

尽管基于ICIs的肿瘤免疫疗法发展迅猛, 且肿瘤患者对ICIs有着巨大且迫切的需求, 但ICIs的新药研发过程颇具挑战性。首先, 与小分子化疗药物相比, ICIs作为抗肿瘤治疗性单克隆抗体, 具有独特的药动学/药效学 (pharmacokinetics/pharmacodynamics, PK/PD) 特征。传统的新药研发方法及毒性评估试验无法完全适用于ICIs, 亟需新的药物研发模式来指导ICIs研发过程中各阶段临床试验的设计等, 满足ICIs的研发需求[8]。其次, 多个ICIs新药在研发过程中获得FDA的加速审批资格[9], 使该类药物的研发时间显著缩短, 且更侧重于早期的临床试验[10]。有鉴于此, 相比研发效率相对较低且以经验性临床试验为主导的传统药物研发流程, 基于药动学-药效学-疾病进程的建模和模拟的新药研发模式, 更加受到研究人员的重视与青睐[3,11,12]。

2 模型引导的药物研发

建模和模拟技术的出现可追溯至20世纪90年代, 已在新药研发领域中屡见不鲜[13-16], 而“模型引导的药物研发”是近十年中逐渐形成的, 是新药研发领域划时代的进步。其本质是以数学建模和模拟及统计分析为基础, 通过构建相应的模型, 对大量临床前及临床试验数据进行定量描述、分析, 以预测药物在体内的药动学、药效学行为, 并对其中信息的不确定性进行量化, 从而为新药开发和药物治疗提供合理决策依据[17]。自20世纪60年代末Sheiner和Jelliffe首次提出应用数学模型开展个体化用药的概念以来[18,19], 随着定量药理学理论的发展以及在新药研发中的广泛应用, MIDD[11]的概念应运而生。

MIDD的核心要素是通过建模和模拟, 整合临床前及临床试验数据、分析药物-疾病-人体三者的关系, 以加速新药研发的进程, 提高新药研究过程中的重大决策的正确率, 指导整个新药开发进程的开展[3]。基于不同的建模和模拟技术和应用场景, MIDD常用的模型种类包括但不限于: 群体药代动力学 (population pharmacokinetics, PopPK) 模型、药动学/药效学 (PK/PD) 模型、暴露-效应模型、基于生理的药代动力学模型、疾病进展模型、基于模型的荟萃分析等[3]。

MIDD作为一种先进的药物研发方法, 遵循“学习-确认循环” (learn and confirm cycle)[20]的研发模式: 通过已有信息构建模型, 并进行预测, 随后通过开展真实研究所获得的数据, 进一步验证模型分析结果的准确性。在此过程中可不断优化、更新和完善模型, 并贯穿于新药研发的每个阶段。与传统模式相比, MIDD在指导药物研发、上市以及药物的全生命周期管理中均发挥了重要的作用。

鉴于国内对MIDD方法应用尚处于起步阶段, 为规范和引导MIDD相关方法的合理使用, 提高药物研发效率, 2020年12月31日, 我国首个有关MIDD的技术指导文件——《模型引导的药物研发技术指导原则》, 由国家药品监督管理局药品审评中心正式发布[21]。该指导原则通过借鉴国内外相关文献资料, 详细阐述MIDD的一般性考虑和原则性要求, 重点强调MIDD对新药研发过程和决策的指导意义。在新药研发过程中, MIDD依靠建模和模拟技术, 通过精准的定量试验设计以加速临床试验流程和改进新药研发模式, 从而直接降低新药开发成本, 节省研究时间, 提高研发效率, 最终使更多的患者获益[22,23]。

3 模型引导的免疫检查点抑制剂的研发

3.1 概述

MIDD在ICIs新药研发各阶段中的主要应用, 如图1所示, 可简要概括为以下三个方面: ① 在药物研发的早期阶段: MIDD能帮助研发人员确定新药的有效剂量, 优化后续的临床试验研究方案, 为后续阶段临床试验的进一步开展提供指导。应用MIDD进行ICI早期研发的实例见表1[24-30]; ② 在药物研发的晚期阶段: 研究人员采用MIDD方法评估新药的获益风险比及探究影响药物PK/PD的各种内在和外在因素, 与实际临床研究相结合, 综合分析并验证推荐给药方案的可行性, 支持药品说明书的制定。应用MIDD进行ICI晚期研发的实例见表2[31-38]; ③ 药物上市后阶段: MIDD作为一种可靠的决策支持手段, 可对大量的上市前和上市后的临床研究数据进行进一步的评估分析, 为上市后的药物再评价及给药方案调整变更等提供依据, 达到合理用药的目的[3,39]。应用MIDD进行ICI上市后研发的实例见表3[30,40-46]。

为了更好地阐明MIDD在ICIs研发流程中的价值, 下面主要以帕博利珠单抗为范例, 详细论述MIDD依据“学习-确认循环”在ICIs药物研发过程中的具体应用。

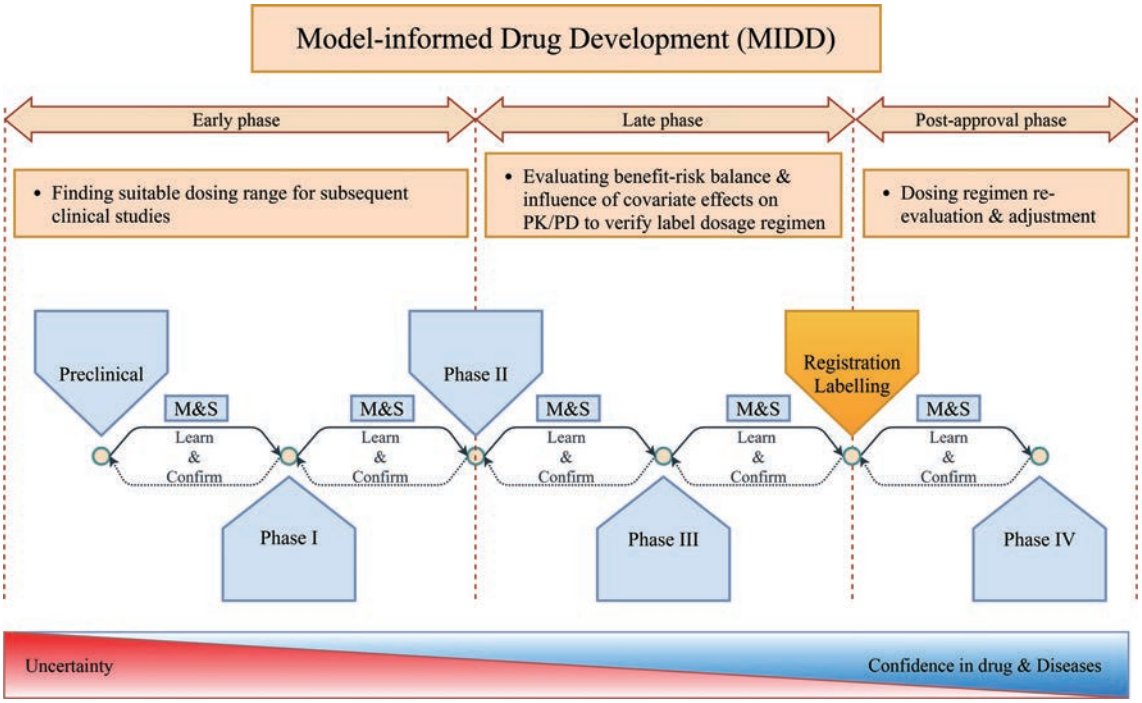

Figure 1 Application of model-informed drug development (MIDD) in different stages of immune checkpoint inhibitors (ICIs) drug development. M&S: modeling and simulation; PK/PD: Pharmacokinetics/pharmacodynamics

Table 1 Application of MIDD in early phase of drug development - effective dose determination of subsequent clinical research in human. PopPK: Population pharmacokinetics

ICIs	MIDD exemplification
Ipilimumab	A phase 2, dose-ranging study showed that about 95% patients with 10 mg·kg^{-1} Q3W were expected to achieving the target trough concentration of 20 μg·mL^{-1}, which lending support to further investigations of ipilimumab efficacy and safety by 10 mg·kg^{-1} Q3W[24].
Nivolumab	Significantly lower tumor progression rate and higher objective response rate were observed in patients with dosing regimen of 3 mg·kg^{-1} Q2W, while peripheral receptor occupancy was saturated at 3 mg·kg^{-1}, according to a large phase 1b study. Dosing regimen of 3 mg·kg^{-1} Q2W was recommended in several further clinical researches[25].
Pembrolizumab	① A translational PK/PD model from mouse to man exhibited that receptor occupancy is saturated at 2 mg·kg^{-1} Q3W with maximum 60%, and the probability of achieving a >30% reduction in tumor size reached a plateau[26]. ② In terms of the phase 1 clinical study, 2 mg·kg^{-1} Q3W was needed to reach 90% probability of 95% target engagement and meet 95% saturation of *ex vivo* target engagement in blood[27], comparing to lower single dose. The aforementioned two studies supported that 2 mg·kg^{-1} Q3W was the preferred dosing regimen.
Avelumab	In the phase 1 dose escalation trial, receptor occupancy was over 95% at 10 mg·kg^{-1} Q2W and significant correlation between clearance of avelumab and body-size metrics could not be proved by covariate analysis[28].
Durvalumab	The exposure-efficacy and exposure-safety analysis indicated that 10 mg·kg^{-1} Q2W regimen was an appropriate dose for durvalumab[29], which could completely saturate serum receptors in over 90% patients and maintain target trough concentration (50 μg·mL^{-1}) throughout the dosing interval by PopPK model simulation results [30].

3.2 帕博利珠单抗

帕博利珠单抗是一种高效、高选择性的IgG$_4$-κ人源性单克隆抗体, 可与PD-1受体结合, 从而阻碍PD-1与其自身配体的相互作用, 解除PD-1通路介导的免疫应答抑制, 从而抑制肿瘤免疫逃逸, 恢复患者自身免疫系统的抗肿瘤作用[47]。FDA于2014年9月4日通过快速审批通道, 批准帕博利珠单抗用于伊匹单抗或V-raf鼠肉瘤病毒癌基因同源体B (BRAF)抑制剂治疗后发生突变的晚期黑色素瘤患者。此后, 帕博利珠单抗陆续获批用于治疗不能手术或转移性黑色素瘤、转移性非小细胞肺癌、头颈部鳞状细胞癌等癌症[48]。

3.2.1 早期阶段 在帕博利珠单抗研发过程的早期阶段, 确定其有效剂量并为后续阶段的临床试验找寻合适的给药剂量成为研究人员的第一要务。

研究人员首先以临床前研究的小鼠实验数据为基础, 构建帕博利珠单抗的小鼠PK/PD肿瘤生长抑制模型, 预测帕博利珠单抗的血药浓度与小鼠肿瘤内的靶受体结合率之间的关系; 然后将模型从小鼠外推至人体, 预测帕

Table 2 Application of MIDD in late phase of drug development - confirmation and verification of availability of recommended dosing regimen. PopPK/PD: Population pharmacokinetics/pharmacodynamics; IgG: Immunoglobulin G

ICIs	MIDD exemplification
Ipilimumab	PopPK analysis was conducted in phase 2 clinical study to reveal that linear PK characteristics was emerged in dose range from 0.3 to 10 mg·kg^{-1}. Besides, clearance of ipilimumab increased with increasing body weight, which implied that a body weight-normalized dosing regimen was rational for ipilimumab treatment[31].
Nivolumab	Volume of distribution and clearance could be elevated with increasing body weight by PopPK model. Other covariates did not have clinically relevant effect on PK, which suggested that dose adjustment was not required[32].
Pembrolizumab	① Multiple intrinsic and extrinsic covariates had no clinically relevant impact on pembrolizumab PK characteristics, which supported 2 mg·kg^{-1} Q3W in various patient subpopulations without dose adjustment, as the PopPK analysis was performed[33]. ② PopPK/PD model of tumor size dynamics was developed to find that increasing exposure could not clinically increase tumor response rate. Dosing range in 2−10 mg·kg^{-1} Q3W could induce maximal response similarly, which was in favor of 2 mg·kg^{-1} Q3W as effective dose[34].
Atezolizumab	① A linear pharmacokinetics was displayed in the dose range of 1−20 mg·kg^{-1}, including label dosage of 1 200 mg. Dosage adjustment was not needed because none of statistically significant covariates was found in this PopPK research [35]. ② A similar exposure-safety and PK profile of atezolizumab in pediatric and young adult patients was demonstrated in the PopPK study, which suggested a weight-based regimen of 15 mg·kg^{-1} Q3W as an appropriate dosage in the pediatric population[36].
Avelumab	Dose adjustment was not necessary because no corresponding covariate was found out affecting time-varying clearance in the PopPK model[37].
Durvalumab	On the basis of PopPK modeling and simulation results, both patients with solid tumors and hematologic malignancies had similar exposure when identical dosing regimen was given. Moreover, IgG level was identified as a critical covariate to affect PK in patients with multiple myeloma[38].

Table 3 Application of MIDD in post-approval phase of drug development - re-evaluation and adjustment of current dosing regimen. FDA: Food and Drug Administration

ICIs	MIDD exemplification
Nivolumab	FDA approved label dosage alteration from 3 mg·kg^{-1} Q2W to 240 mg Q2W and finally 480 mg Q4W based upon PopPK modeling development by data from previous clinical researches and analysis of the benefit-risk ratio among various dosing regimen[40].
Pembrolizumab	PopPK modeling analysis of exposure and clearance from various dosage supported FDA approval from 2 mg·kg^{-1} Q3W to 200 mg Q3W[41,42] then 400 mg Q6W[43].
Atezolizumab	As for the PopPK modeling and simulation result, the predicted exposures, efficacy and safety for 840 mg Q2W and 1 680 mg Q4W were similar as the approved regimen of 1 200 mg Q3W, which provided reliable decision-making evidence for approval of aforementioned two alternative dosing regimens[44].
Avelumab	PopPK analysis showed that no significant difference of exposure in the weight-based dose of 10 mg·kg^{-1} Q2W and flat dose of 800 mg Q2W. In addition to the similarity of benefit-risk profiles between these two regimens, it provided the basis for FDA approval of 800 mg Q2W[45].
Durvalumab	Comparison of 1 500 mg Q4W, 750 mg Q2W and referential dose of 10 mg·kg^{-1} Q2W was carried out by PopPK analysis. The result reflected that three dosing regimens had comparable exposure and no dose adjustments were needed in accordance with any patient or disease characteristics, which verified the feasibility of approving the above-mentioned two flat dose regimens[30,46].

博利珠单抗对人体肿瘤的抑制生长率[26]。研究结果显示: 当小鼠帕博利珠单抗的血药浓度 > 10 μg·mL^{-1}时, 帕博利珠单抗与受体在肿瘤内的最高结合率约为60%, 且不随血药浓度的增加而上升。此外, 对于多种不同的肿瘤生长模式而言, 与基线值相比 2 mg·kg^{-1} Q3W 以上的剂量能使肿瘤直径降低 40% 以上; 且在 2 mg·kg^{-1} Q3W 时, 肿瘤体积降低 > 30% 的概率已经到达平台, 再增加剂量亦不能明显降低肿瘤体积。另外, 缩短给药间隔为Q2W亦无法显著降低肿瘤体积, 从而支持了 2 mg·kg^{-1} Q3W 作为帕博利珠单抗的治疗方案。

为了在人体上进一步验证 2 mg·kg^{-1} Q3W 是有效剂量, 2011 年, 首个在晚期实体瘤患者中评估帕博利珠单抗的安全性、药代动力学及药效动力学的 I 期临床研究 (KEYNOTE-001) 正式实施[47,49]。

该研究是一项多中心、多队列、随机 I 期临床试验。其中首个队列试验 (队列 A) 确定了帕博利珠单抗的有效剂量。队列 A 试验分为两部分, 第一部分 (A & A-1 部分) 17 位受试者纳入研究, 采用了经典 3+3 剂量爬坡试验研究设计, 其中 9 位受试者 (A 部分) 分别按 1、3 及 10 mg·kg^{-1} 三个不同的剂量方案给药。首剂给药后 28 天给予第二剂帕博利珠单抗, 随后每 2 周给药一次; 另外 7 名受试者 (A-1 部分) 则从首剂开始采取 10 mg·kg^{-1} Q2W 的给药方案, 通过体外血浆白细胞介素-2 (interleukin-2, IL-2) 激发率作为帕博利珠单抗与肿瘤 PD-1 受体结合率的替代指标, 评估不同剂量帕博利珠单抗对 PD-1 的受体占有效果。

第一部分试验结果显示: 尽管3个剂量组均未见剂量限制性毒性的发生, 无法确定最大耐受剂量 (maximum tolerated dose, MTD), 但是确定了帕博利珠单抗对IL-2激发率产生90%抑制效应时的血药浓度 (IC_{90}) 约为10 μg·mL^{-1}, 即帕博利珠单抗10 μg·mL^{-1}时与PD-1受体结合程度为90%。单次给药后21天内, 帕博利珠单抗剂量的增加 (1～10 mg·kg^{-1}) 并不会导致IL-2激发率出现显著变化、改变靶点的结合率。同时, 以上试验还表明: 10 mg·kg^{-1} Q2W的给药方案是安全的。此外, 血药浓度在10 μg·mL^{-1}时, 帕博利珠单抗与靶受体的结合基本饱和, 且帕博利珠单抗对靶受体的抑制可持续3周。

为进一步分析帕博利珠单抗的PK/PD特征, 确定后续阶段临床试验的有效剂量, 第二部分的试验 (A-2) 沿用“学习-确认循环”模式。试验中选取13名受试者, 进行剂量爬坡实验: 3周内从低剂量 (0.005～0.06 mg·kg^{-1}) 上升至高剂量 (2或10 mg·kg^{-1}), 随后以2 mg·kg^{-1} Q3W或10 mg·kg^{-1} Q3W的方案进行给药。A-2部分所得的PK/PD数据与第一部分 (A & A-1部分) 的PK/PD数据相结合, 构建最终PK/PD模型, 通过比较各个PK/PD参数的预测准确性, 分析帕博利珠单抗的PK/PD特征, 以预测不同给药方案下的PK/PD行为。

A-2部分的PK数据进一步表明: 当给药剂量在1 mg·kg^{-1} Q3W及2 mg·kg^{-1} Q3W时, 帕博利珠单抗的稳态谷浓度均大于10 μg·mL^{-1}。结合第一部分实验的结果可知: 1 mg·kg^{-1} Q3W及2 mg·kg^{-1} Q3W对靶点的结合率均在90%以上。

从构建的PK/PD模型可推断: 当帕博利珠单抗的给药方案为1 mg·kg^{-1} Q3W并达到稳态, 靶点结合率达到95%的概率在50%～60%之间; 当给药方案为2 mg·kg^{-1} Q3W并达到稳态时, 靶点结合率达到95%的概率可至90%[27]。试验中帕博利珠单抗在体内的靶点结合率高达90%～95%, 而小鼠肿瘤内的受体结合率最高仅为60%。两者存在明显差异, 可能的原因包括: ① I期临床试验选用IL-2激发率作为靶点结合率替代指标, 可能无法完全体现帕博丽珠单抗在肿瘤内的靶点结合情况; ② 人类与小鼠之间存在种属差异。基于以上研究结果, 研究人员进一步确定了2 mg·kg^{-1} Q3W作为后续临床研究的给药方案。

图2简要概括了早期阶段研究确定2 mg·kg^{-1} Q3W为帕博利珠单抗有效剂量的过程。

3.2.2 晚期阶段 晚期阶段临床研究中MIDD的应用重心是筛选影响PK/PD的因素, 以及临床疗效的再评估, 进一步验证现有的给药方案。通过对可能影响帕博利珠单抗暴露的内在及外在因素进行筛选, 系统评价帕博利珠单抗PK/PD的影响因素, 验证给药方案的适用性, 也为肝、肾功能受损等特殊人群的给药方案提供依据。

Ahamadi等[33]开展了一项针对帕博利珠单抗药动学影响因素的研究, 该研究涵盖了KEYNOTE-001、KEYNOTE-002、KEYNOTE-006三个临床试验, 包括晚期黑色素瘤、NSCLC及其他多种晚期实体瘤受试者。研究中采用PopPK分析方法, 分析不同的协变量对帕博利珠单抗PK的影响, 并采用AUC的几何均数

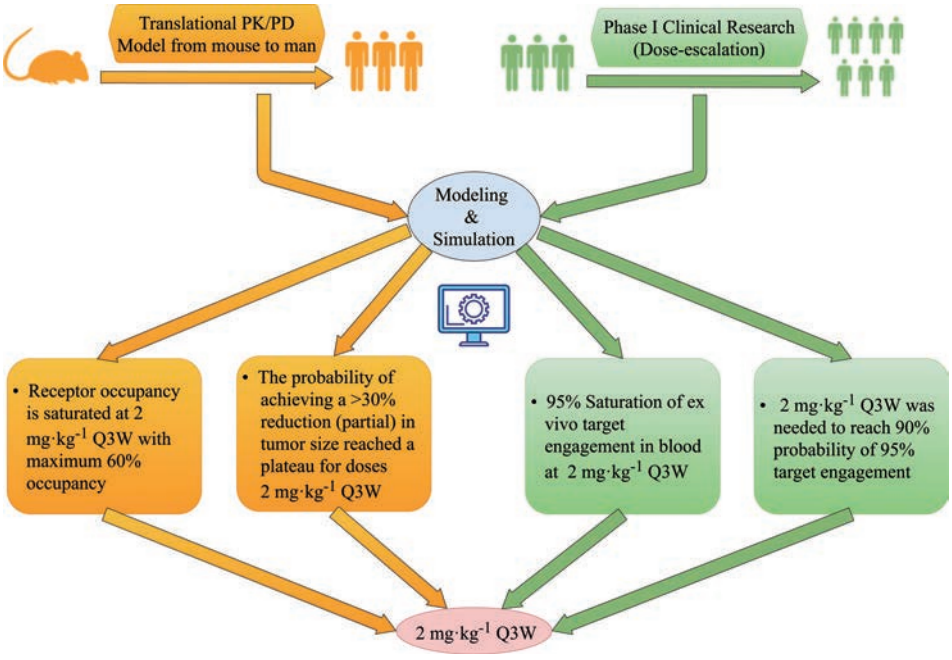

Figure 2 The effective dose confirmation of pembrolizumab

比值 (geometric mean ratio, GMR) 评价各协变量的临床意义。当一个协变量能导致AUC的GMR下降至1/2或上升至5倍时, 该协变量被视为能对帕博利珠单抗的药动学产生具有临床意义的影响。结果显示: 除体重外, 其他因素包括性别、年龄、肝肾功能、肿瘤种类及肿瘤负荷等均未对帕博利珠单抗的PK产生有临床意义的影响 (图3), 无需根据上述因素进行剂量调整, 进一步支持了2 mg·kg^{-1} Q3W的给药方案。

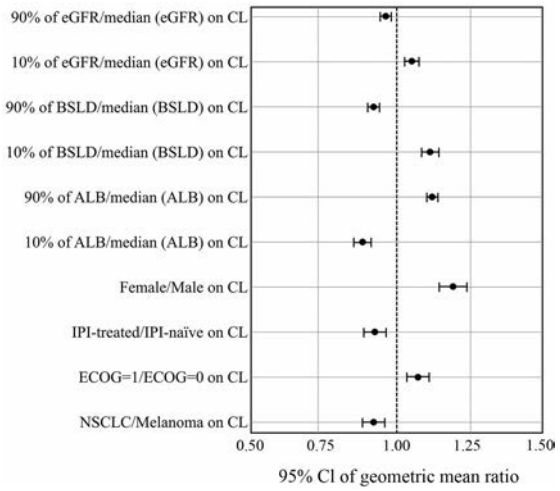

Figure 3 Various covariates have no clinically relevant impact on pembrolizumab exposure [33]. eGFR: Estimated glomerular filtration rate; CL: Clearance; BSLD: Baseline tumor burden; ALB: Albumin; IPI: Ipilimumab; ECOG: Eastern cooperative oncology group; NSCLC: Non-small cell lung cancer

在早期研究阶段, 研究人员曾利用转化PK/PD肿瘤生长抑制模型, 以预测帕博利珠单抗对人体肿瘤的抑制生长率。随着临床试验的开展, 受试者的数量也在不断增加, 为建立肿瘤生长动力学模型提供了便利。Chatterjee等[34]通过纳入KEYNOTE-001、KEYNOTE-002、KEYNOTE-006三个临床试验的受试者数据, 应用PopPK/PD分析方法, 构建肿瘤生长动力学模型, 探索帕博利珠单抗的暴露与肿瘤体积大小之间的量效关系。研究表明: 提高帕博利珠单抗的暴露量并不能导致肿瘤缓解率的提升, 在2～10 mg·kg^{-1} Q3W的剂量范围内均能产生最大临床效应, 进一步支持2 mg·kg^{-1} Q3W作为临床的使用剂量。2014年9月, 帕博利珠单抗获得FDA的批准, 用于经一线治疗失败的不可切除或转移性黑色素瘤的治疗, 推荐给药方案为2 mg·kg^{-1} Q3W[49,50]。

3.2.3 上市后阶段 由于不同患者之间的药代动力学行为可有差异, 大部分抗肿瘤药物剂量方案的制定都是以体重为基础。但是, 由于单抗类药物的体内分布与清除受体重的影响较小[51-53], 且ICIs通常拥有较宽的治疗窗[54], 即使从按体重给药变为固定剂量给药, 临床疗效亦不会明显降低。然而, 固定剂量与按体重给药相比, 能够有效减少药物的浪费、提高用药的便利性[55]。因此, 固定剂量给药对于ICIs而言是一个更优的给药方案选项。

Freshwater等[41]开展了一项帕博利珠单抗给药方案再评估的研究。研究首先基于Ahamadi等[33]根据KEYNOTE-001、KEYNOTE-002、KEYNOTE-006共计1 622例受试者的数据, 开展了PopPK分析。研究中异速增长模型描述体重 (weight, WT) 与清除率 (clearance, CL) 和分布体积 (volume of distribution, V_c) 的关系, 表明了按体重给药与固定剂量给药相比并无明显的优势。

研究者再将KEYNOTE-10、KEYNOTE-055、KEYNOTE-024、KEYNOTE-164、KEYNOTE-045和KEYNOTE-052等临床试验的数据纳入分析, 并对模型进行再评价。随后利用构建的PopPK模型, 以0～6周给药的稳态AUC ($AUC_{ss,\ 0\text{-}6\ weeks}$) 作为评估参数, 对不同给药方案下的药物暴露进行预测评估。结果表明: 体重为基础 (2 mg·kg^{-1} Q3W) 的治疗方案中, 体重较小的患者与体重较大的患者相比, 暴露量往往较低, 而固定剂量 (200 mg Q3W) 则相反。而对于这两种方案而言, 低体重患者的个体暴露范围与高体重患者基本重叠, 两种给药方案的PK变异性非常相似。以受试者体重中位数为77 kg计算, 尽管154 mg Q3W的固定剂量与2 mg·kg^{-1} Q3W给药方案的预测AUC暴露相同, 但为确保个体患者暴露与原方案相似, 尤其是体重较高的患者, 故上调剂量并取整, 选择了200 mg Q3W为推荐给药方案。

进一步研究发现: 以上两种方案的药时曲线基本相似, PK参数的分布也十分接近, 在不同肿瘤类别之间的AUC和清除率亦无显著差异。此外, 以黑色素瘤患者的治疗为例, 若以2 mg·kg^{-1} Q3W的方案给药, 6.2个月的平均疗程期间需要使用8剂帕博利珠单抗。由于帕博利珠单抗的药品规格仅为50 mg和100 mg两种, 每位患者单次给药将造成至少27 mg的浪费, 整个疗程将有216 mg的药物耗损, 但以固定剂量给药则不会造成损失。综合以上因素分析, 200 mg Q3W与2 mg·kg^{-1} Q3W两种剂量方案下获益风险相似。2018年2月, FDA最终批准帕博利珠单抗用法用量变更为固定剂量200 mg Q3W[42]。

Lala等[43]研究者采用PopPK分析方法, 进一步对400 mg Q6W、200 mg Q3W和2 mg·kg^{-1} Q3W三种剂量方案的有效性和安全性进行了风险获益评价。该研究基于5项不同肿瘤类别共计2 993名受试者的临床试验数据, 模拟并比较了三种给药方案的平均稳态血药

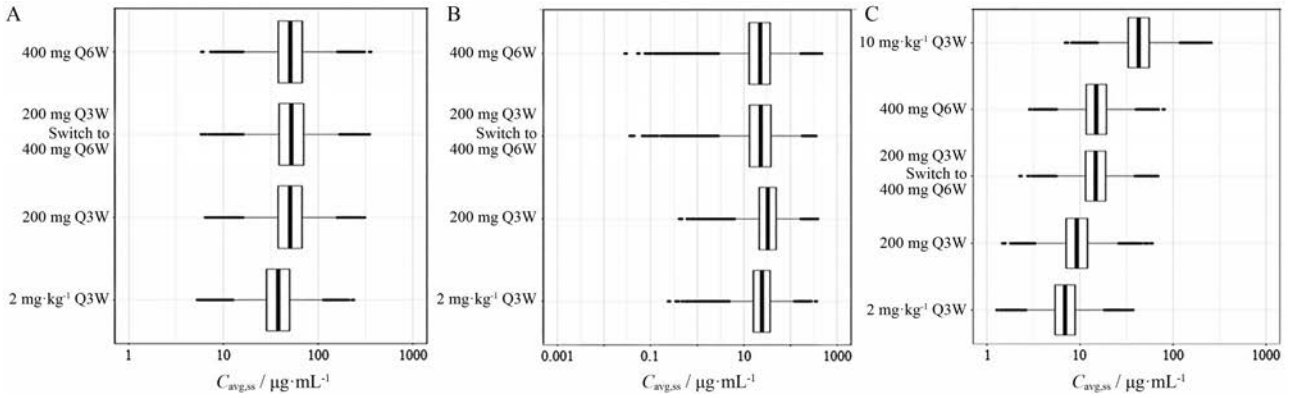

Figure 4 The comparison of $C_{avg,ss}$, $C_{min,ss}$ and $C_{max,ss}$ based upon PopPK modeling and simulation results among three different dosing regimens. A: Steady state average concentration ($C_{avg,ss}$), 2 mg·kg^{-1} Q3W ≈ 200 mg Q3W ≈ 400 mg Q6W; B: Steady state trough concentration ($C_{min,ss}$), 2 mg·kg^{-1} Q3W ≈ 200 mg Q3W ≈ 400 mg Q6W; C: Steady state peak concentration ($C_{max,ss}$), 2 mg·kg^{-1} Q3W < 200 mg Q3W < 400 mg Q6W < 10 mg·kg^{-1} Q2W

浓度、稳态峰浓度和稳态谷浓度 (图4)。三种方案的平均稳态血药浓度相近, 400 mg Q6W 的稳态谷浓度略低于其他两种方案, 但与另两种方案的95%置信区间相交叠, 无显著差异。此外, 尽管400 mg Q6W的稳态峰浓度显著高于其他两种方案, 但远低于10 mg·kg^{-1} Q2W方案, 无显著安全风险。上述结果表明: 400 mg Q6W与另外两种剂量方案之间存在相似的获益风险比, 而延长给药间隔减少患者前来医疗机构的次数, 节省患者时间, 降低医疗费用, 可为患者用药进一步提供便利。

与200 mg Q3W给药方案的变更相似, 基于以上建模模拟研究的结果, 在未开展400 mg Q6W临床研究的情况下, 2020年4月, FDA对该剂量的有效性和安全性进行评估后作出决策, 批准帕博利珠单抗使用新的400 mg Q6W固定剂量[56]。

4 结语与展望

鉴于新药研发中复杂的开发流程和高昂的成本, MIDD可以加速新药研发的进程, 优化临床试验设计方案, 显著缩短研究的时间, 并提高试验成功率, 最终使药物研发单位和患者均能受益。本文以帕博利珠单抗为例, 回顾了ICIs的研发过程, 从研发早期为后续临床试验确定有效剂量, 至晚期阶段评估临床疗效以验证现有给药方案的可行性, 再至上市后药物给药方案的再评估及变更, MIDD的应用作为可靠的决策依据, 贯穿了抗肿瘤新药研发过程的各个阶段。未来, 随着定量药理技术和方法的不断发展, MIDD必定在抗肿瘤新药研发中发挥更大的作用。

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利益冲突: 此文章研究内容无任何利益冲突。

References

[1] Li B, Chan HL, Chen P. Immune checkpoint inhibitors: basics and challenges [J]. Curr Med Chem, 2019, 26: 3009-3025.

[2] Jardim DL, Gagliato DDM, Giles FJ, et al. Analysis of drug development paradigms for immune checkpoint inhibitors [J]. Clin Cancer Res, 2018, 24: 1785-1794.

[3] Marshall SF, Burghaus R, Cosson V, et al. Good practices in model-informed drug discovery and development: practice, application, and documentation [J]. CPT Pharmacometrics Syst Pharmacol, 2016, 5: 93-122.

[4] Vaddepally RK, Kharel P, Pandey R, et al. Review of indications of FDA-approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence [J]. Cancers (Basel), 2020, 12: 738.

[5] Akinleye A, Rasool Z. Immune checkpoint inhibitors of PD-L1 as cancer therapeutics [J]. J Hematol Oncol, 2019, 12: 92.

[6] Madden K, Kasler MK. Immune checkpoint inhibitors in lung cancer and melanoma [J]. Semin Oncol Nurs, 2019, 35: 150932.

[7] Seront E, Catala G, Dermine A, et al. Immune checkpoint inhibitors as a real hope in advanced urothelial carcinoma [J]. Future Sci OA, 2018, 4: FSO341.

[8] Watson GA, Doi J, Hansen AR, et al. Novel strategies in immune checkpoint inhibitor drug development: how far are we from the paradigm shift? [J]. Br J Clin Pharmacol, 2020, 86: 1753-1768.

[9] Gill J, Cetnar JP, Prasad V. A timeline of immune checkpoint inhibitor aporovals in small cell lung cancer [J]. Trends Cancer, 2020, 6: 736-738.

[10] Ochoa De Olza M, Oliva M, Hierro C, et al. Early-drug development in the era of immuno-oncology: are we ready to face the challenges? [J]. Ann Oncol, 2018, 29: 1727-1740.

[11] Marshall S, Madabushi R, Manolis E, et al. Model-informed drug discovery and development: current industry good practice and regulatory expectations and future perspectives [J]. CPT

Pharmacometrics Syst Pharmacol, 2019, 8: 87-96.

[12] Dunyak J, Mitchell P, Hamren B, et al. Integrating dose estimation into a decision-making framework for model-based drug development [J]. Pharm Stat, 2018, 17: 155-168.

[13] Clancy CE, An G, Cannon WR, et al. Multiscale modeling in the clinic: drug design and development [J]. Ann Biomed Eng, 2016, 44: 2591-2610.

[14] Bellanti F, Della Pasqua O. Modelling and simulation as research tools in paediatric drug development [J]. Eur J Clin Pharmacol, 2011, 67: 75-86.

[15] Aarons L, Karlsson MO, Mentre F, et al. Role of modelling and simulation in phase I drug development [J]. Eur J Pharm Sci, 2001, 13: 115-122.

[16] Chen WJ, Zhou TY, Lu W. Population pharmacokinetics and its application in new drug research [J]. Acta Pharm Sin (药学学报), 2017, 52: 371-377.

[17] Barrett JS, Fossler MJ, Cadieu KD, et al. Pharmacometrics: a multidisciplinary field to facilitate critical thinking in drug development and translational research settings [J]. J Clin Pharmacol, 2008, 48: 632-649.

[18] Sheiner LB. Computer-aided long-term anticoagulation therapy [J]. Comput Biomed Res, 1969, 2: 507-518.

[19] Jelliffe RW, Buell J, Kalaba R, et al. A computer program for digitalis dosage regimens [J]. Math Biosci, 1970, 9: 179-193.

[20] Sheiner LB. Learning versus confirming in clinical drug development [J]. Clin Pharmacol Ther, 1997, 61: 275-291.

[21] Center for Drug Evaluation, NMPA. Guidelines for model-informed drug development (No.59,2020) [EB/OL]. 2020-12-31 [2021-03-09]. http://www.cde.org.cn/attachmentout.do?mothed=list&id=be346add0358a356.

[22] Liu DY, Li L, Li LJ, et al. The value and general consideration of pharmacometric study in new drug development [J]. Chin J Clin Pharmacol Ther (中国临床药理学与治疗学), 2018, 23: 961-973.

[23] Li J, Yang JB, Wang YZ. Applications of model-informed drug development (MIDD) on new drug research and development [J]. Chin J Clin Pharmacol Ther (中国临床药理学与治疗学), 2020, 25: 1-8.

[24] Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study [J]. Lancet Oncol, 2010, 11: 155-164.

[25] Agrawal S, Feng Y, Roy A, et al. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy [J]. J Immunother Cancer, 2016, 4: 72.

[26] Lindauer A, Valiathan CR, Mehta K, et al. Translational pharmacokinetic/pharmacodynamic modeling of tumor growth inhibition supports dose-range selection of the anti-PD-1 antibody pembrolizumab [J]. CPT Pharmacometrics Syst Pharmacol, 2017, 6: 11-20.

[27] Elassaiss-Schaap J, Rossenu S, Lindauer A, et al. Using model-based "learn and confirm" to reveal the pharmacokinetics-pharmacodynamics relationship of pembrolizumab in the KEYNOTE-001 trial [J]. CPT Pharmacometrics Syst Pharmacol, 2017, 6: 21-28.

[28] Heery CR, GHOS Coyne, Marte JL, et al. Pharmacokinetic profile and receptor occupancy of avelumab (MSB0010718C), an anti-PD-L1 monoclonal antibody, in a phase I, open-label, dose escalation trial in patients with advanced solid tumors [J]. J Clin Oncol, 2015, 33: 3055.

[29] Jin C, Zheng Y, Jin X, et al. Exposure-efficacy and safety analysis of durvalumab in patients with urothelial carcinoma (UC) and other solid tumors [J]. J Clin Oncol, 2017, 35: 2568.

[30] Baverel PG, Dubois VFS, Jin CY, et al. Population pharmacokinetics of durvalumab in cancer patients and association with longitudinal biomarkers of disease status [J]. Clin Pharmacol Ther, 2018, 103: 631-642.

[31] Feng Y, Masson E, Dai D, et al. Model-based clinical pharmacology profiling of ipilimumab in patients with advanced melanoma [J]. Br J Clin Pharmacol, 2014, 78: 106-117.

[32] Bajaj G, Wang X, Agrawal S, et al. Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors [J]. CPT Pharmacometrics Syst Pharmacol, 2017, 6: 58-66.

[33] Ahamadi M, Freshwater T, Prohn M, et al. Model-based characterization of the pharmacokinetics of pembrolizumab: a humanized anti-PD-1 monoclonal antibody in advanced solid tumors [J]. CPT Pharmacometrics Syst Pharmacol, 2017, 6: 49-57.

[34] Chatterjee MS, Elassaiss-Schaap J, Lindauer A, et al. Population pharmacokinetic/pharmacodynamic modeling of tumor size dynamics in pembrolizumab-treated advanced melanoma [J]. CPT Pharmacometrics Syst Pharmacol, 2017, 6: 29-39.

[35] Stroh M, Winter H, Marchand M, et al. Clinical pharmacokinetics and pharmacodynamics of atezolizumab in metastatic urothelial carcinoma [J]. Clin Pharmacol Ther, 2017, 102: 305-312.

[36] Shemesh CS, Chanu P, Jamsen K, et al. Population pharmacokinetics, exposure-safety, and immunogenicity of atezolizumab in pediatric and young adult patients with cancer [J]. J Immunother Cancer, 2019, 7: 314.

[37] Wilkins J, Brockhaus B, Wang S, et al. Population pharmacokinetic analysis of avelumab in different cancer types [J]. J Pharmacokinet Pharmacodyn, 2017, 44: 1-143.

[38] Ogasawara K, Newhall K, Maxwell SE, et al. Population pharmacokinetics of an anti-PD-L1 antibody, durvalumab in patients with hematologic malignancies [J]. Clin Pharmacokinet, 2020, 59: 217-227.

[39] de Greef R, Elassaiss-Schaap J, Chatterjee M, et al. Pembrolizumab: role of modeling and simulation in bringing a novel immunotherapy to patients with melanoma [J]. CPT Pharmaco-

metrics Syst Pharmacol, 2017, 6: 5-7.

[40] Li J, Yan F, Yang JB, et al. Application of model-informed drug development approach in dose opti-mization: insights from the modification of nivolumab dosage regimen [J]. Chin J Clin Pharmacol Ther (中国临床药理学与治疗学), 2020, 25: 408-412.

[41] Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications [J]. J Immunother Cancer, 2017, 5: 43.

[42] Hall E, Zhang J, Kim EJ, et al. Economics of alternative dosing strategies for pembrolizumab and nivolumab at a single academic cancer center [J]. Cancer Med, 2020, 9: 2106-2112.

[43] Lala M, Li TR, De Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation [J]. Eur J Cancer, 2020, 131: 68-75.

[44] Morrissey KM, Marchand M, Patel H, et al. Alternative dosing regimens for atezolizumab: an example of model-informed drug development in the postmarketing setting [J]. Cancer Chemother Pharmacol, 2019, 84: 1257-1267.

[45] Novakovic AM, Wilkins JJ, Dai H, et al. Changing body weight-based dosing to a flat dose for avelumab in metastatic merkel cell and advanced urothelial carcinoma [J]. Clin Pharmacol Ther, 2020, 107: 588-596.

[46] Baverel P, Dubois V, Jin C, et al. Population pharmacokinetics of durvalumab and fixed dosing regimens in patients with advanced solid tumors [J]. J Clin Oncol, 2017, 35: 2566.

[47] Patnaik A, Kang SP, Rasco D, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors [J]. Clin Cancer Res, 2015, 21: 4286-4293.

[48] US Food and Drug Administration. Label of KEYTRUDA® (pembrolizumab) injection [EB/OL]. 2020-06-17 [2020-10-07]. https://www. accessdata. fda. gov/drugsatfda_docs/label/2020/125514s071s090lbl.pdf.

[49] Kang SP, Gergich K, Lubiniecki GM, et al. Pembrolizumab KEYNOTE-001: an adaptive study leading to accelerated approval for two indications and a companion diagnostic [J]. Ann Oncol, 2017, 28: 1388-1398.

[50] Thu Oanh D, Ogunniyi A, Barbee MS, et al. Pembrolizumab for the treatment of PD-L1 positive advanced or metastatic non-small cell lung cancer [J]. Expert Rev Anticancer Ther, 2016, 16: 13-20.

[51] Keizer RJ, Huitema ADR, Schellens JHM, et al. Clinical pharmacokinetics of therapeutic monoclonal antibodies [J]. Clin Pharmacokinet, 2010, 49: 493-507.

[52] Mould DR, Green B. Pharmacokinetics and pharmacodynamics of monoclonal antibodies concepts and lessons for drug development [J]. BioDrugs, 2010, 24: 23-39.

[53] Garg A, Balthasar JP. Physiologically-based pharmacokinetic (PBPK) model to predict IgG tissue kinetics in wild-type and FcRn-knockout mice [J]. J Pharmacokinet Pharmacodyn, 2007, 34: 687-709.

[54] Renner A, Burotto M, Rojas C. Immune checkpoint inhibitor dosing: can we go lower without compromising clinical efficacy? [J]. J Glob Oncol, 2019, 5: 1-5.

[55] JJMA Hendrikx, JBaG Haanen, Voest EE, et al. Fixed dosing of monoclonal antibodies in oncology [J]. Oncologist, 2017, 22: 1212-1221.

[56] US Food and Drug Administration. FDA approves new dosing regimen for pembrolizumab [EB/OL]. 2020-04-29 [2020-10-07]. https://www. fda. gov/drugs/drug-approvals-and-databases/fda-approves-new-dosing-regimen-pembrolizumab.