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基于“肺火远近”理论从五脏气火探析非小细胞肺癌免疫治疗辨治策略

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［摘要］ 非小细胞肺癌（NSCLC）是临床常见恶性肿瘤。近年来，免疫检查点抑制剂（ICIs）已成为围术期及晚期的核心治疗手段，但耐药与免疫相关不良反应（irAEs）仍是制约患者远期获益的关键瓶颈。目前现代医学缺乏系统干预策略，中西医联合免疫治疗体系亦尚未建立。该研究立足《外经微言》“肺火远近”理论，以五脏气火传变阐释NSCLC免疫治疗各期各阶段动态病机。其核心病机分属“远火寒凝气衰”与“近火热灼气销”2种基本态势：远火者，诸脏火之不达，肺失温煦，气寒而凝，呈初始免疫抑制状态。结合临床分期辨析：新辅助治疗期属肺虚气弱，辅助治疗期属宗中虚陷，晚期属命门火衰。近火者，诸脏邪火上迫，肺金受灼，壮火食气，为irAEs病机基础。结合治疗阶段拆解：新辅助治疗期责肺火毒蕴，辅助治疗期属阴火上泛，晚期为肾虚火浮。而各期之中，若呈耐药倾向则责肝枢郁闭，凝为远火。然其亦可复化近火，促进病情进展。此外，君火盛衰关乎肺之治节，其与初始免疫抑制、耐药、irAEs密切相关。基于此，团队提出“调和五脏气火，以复肺中微火通熏”核心治法，针对远火之变：新辅助治疗期重在燮理肺中气火，辅助治疗期则当培土生金，晚期治宜固本培元。针对近火之害：新辅助治疗期则需固护肺金，辅助治疗期法当升阳敛火，晚期治以引火安金。若处耐药进展期，则疏枢攻毒以改善免疫状态，清金平木以缓解身心症状。此外，应在分期分阶辨治基础上，从心论治，调摄君火，安和神明。诸法并行不悖，旨在重建机体阴阳自和之态，为中医药联合NSCLC免疫治疗提供精准动态的理论依据与临床范式。

［关键词］ 非小细胞肺癌；远火；近火；五脏气火；免疫检查点抑制剂
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Syndrome Differentiation and Treatment Strategies for NSCLC Immunotherapy from Perspective of Qi-Fire in Five Zang-Organs Based on Theory of Distance of Lung Fire

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［**Abstract**］ Non-small cell lung cancer (NSCLC) is a clinically common malignant tumor. In recent years, immune checkpoint inhibitors (ICIs) have become a core treatment modality in the perioperative period and for advanced diseases. However, drug resistance and immune-related adverse events (irAEs) remain critical bottlenecks limiting long-term patient

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benefits. Currently, modern medicine lacks systematic intervention strategies, and an integrated treatment system combining traditional Chinese and Western medicine for immunotherapy has yet to be established. This study is grounded in the theory of distance of lung fire from *Wai Jing Wei Yan*, employing the transmission and transformation of Qi-fire in five Zang-Organs to elucidate the dynamic pathogenesis at various stages of NSCLC immunotherapy. The core pathogenesis of NSCLC can be categorized into two fundamental states: distant fire (characterized by cold coagulation and Qi depletion) and near fire (characterized by intense heat scorching and qi consumption). Distant fire refers to the failure of Fire from other organs to reach the lung, leading to loss of warmth, congealing cold, and Qi depletion, manifesting as an initial immunosuppressed state. Specifically, the neoadjuvant therapy, adjuvant therapy, and advanced stages pertain to lung deficiency and Qi weakness, collapse of pectoral Qi and middle Qi, and decline of the life-gate fire, respectively. Near fire refers to pathogenic fire from other organs ascending to harass and scorch the lung, and intense fire consumes qi, forming the pathogenic basis for irAEs. Specifically, the neoadjuvant therapy, adjuvant therapy, and advanced stages are attributed to lung fire-toxin accumulation, upsurge of Yin fire, and kidney deficiency with floating fire, respectively. Within each stage, a tendency toward drug resistance is attributed to constrained pivot of the liver, congealing into distant fire. However, this can also transform back into near fire, promoting disease progression. Furthermore, the prosperity or decline of the sovereign fire is related to the lung's governance and regulation, and is closely associated with initial immunosuppression, drug resistance, and irAEs. On this basis, our team proposes the core therapeutic principle of harmonizing the Qi-fire in five Zang-Organs to restore the gentle warming of the subtle fire within the lung. For the transformation of distant fire, the treatment at neoadjuvant therapy, adjuvant therapy, and advanced stages focuses on regulating Qi-fire in the lung, fortifying the earth to generate metal, and reinforcing the root and cultivating the source, respectively. For the harm of near fire, the treatment at neoadjuvant therapy, adjuvant therapy, and advanced stages necessitates securing and protecting the lung, raising Yang and constraining Fire, and directing fire downward and anchoring the lung, respectively. In the drug-resistant progression phase, unblocking the pivot and expelling toxins can be used to improve immune status, while clearing lung and pacifying wood can be adopted to alleviate physical and mental symptoms. Additionally, on the basis of stage- and phase-specific syndrome differentiation, the treatment should regulate the sovereign fire from the heart, calming the spirit and harmonizing the mind. These methods are implemented concurrently without conflict, aiming to re-establish the body's state of Yin-Yang self-harmony, thereby providing a precise and dynamic theoretical basis and a clinical paradigm for integrated traditional Chinese medicine and immunotherapy for NSCLC.

[**Keywords**] non-small cell lung cancer; distant fire; near fire; Qi-fire in five Zang-Organs; immune checkpoint inhibitor

肺癌是全球最常见的癌症及癌症相关死亡原因，2022年约有近250万例新增病例，死亡人数超180万，疾病负担沉重[1]。其中，非小细胞肺癌（NSCLC）占所有肺癌的80%~85%[2]。近年来，多项临床试验证实，免疫检查点抑制剂（ICIs）已在NSCLC治疗中取得显著进展，尤其在Ⅱ~Ⅲ期患者围术期治疗、Ⅳ期患者一线及后线治疗中展现出卓越疗效及可靠安全性[3-5]。然而，目前其临床应用仍面临耐药及免疫相关不良反应（irAEs）等问题，严重影响患者远期获益及生存质量[6-7]。

在中医视域下，ICIs具“温散”之性[8]，可调动人体正气抗邪。且团队前期发现，免疫治疗全程与机体“气火”动态流转密切相关[9]。《金匮钩玄》亦示：“气之与火，一理而已，动静之变，反化为二”，气火本属一体，生理二者动静互化，相互为用，病理亦相互累及。且肺为华盖，联系诸脏，其中火之远近，气之充馁，实可究于五脏气火盛衰传变[10]。故本团队立足《外经微言》“肺火远近”经典理论，根据各治疗时期脏腑病机侧重，化用五脏气火盛衰传变思路，系统阐释免疫治疗各时期（新辅助治疗期、辅助治疗期、晚期）、各阶段（免疫抑制、免疫耐药、免疫过激）NSCLC患者肺中气火动态演变规律。并依据“远火寒凝气衰”与“近火热灼气销”两大关键病机，提出调和五脏气火治疗大法，旨在恢复肺中“微火通熏”及免疫平衡，构建“全周期、全链条、全方位”的中西协同NSCLC免疫治疗新范式。

1 “肺火远近”理论内涵及与五脏气火相关性

“肺火远近”理论源于《外经微言》：“肺近火，则金气之柔者必销矣；然肺离火，则金气之顽者必折矣，所贵微火以通熏肺也”，其深刻揭示肺脏生理贵在得“微火”温养，既不可火近燥金，亦不可远火寒金。此“微火”之态类《素问·阴阳应象大论》所言“少火”，《质疑录》谓其“少火生人之元气，是火即为气”，少火化生阳气以温煦肺金，助其宣降，布散津液，从而维系肺体清虚柔润之性。而病理之变，则可分“近火”与“远火”两途：一曰“近火”，实为《素问·阴阳应象大论》所言食气“壮火”[11]。肺为娇脏，《慎斋遗书》称：“肺金居上，畏火者也，近火迫肺，耗气伤津，终致肺体焦枯；二曰“远火”，恰如《景岳全书》云“火得其正即为阳气，此火之不可无亦不可衰，衰则阳气亏虚也”，火衰而远，则阳气亏虚，肺金失养，宣降无能，其气凝滞，总呈顽金虚冷之态。

《素问·咳论》又曰：“五脏六腑皆令人咳，非独肺也”。肺为华盖，位处上焦，《圣济总录》称其“覆与诸脏”，故肺中气火生化，除其本身盛衰，亦赖五脏气火调和[12]。生理之际，脾之中阳升腾、肾之命门上济、肝之气火条达、心之君火下煦，诸脏调和，以“微火”之势上熏于肺，与肺中清气相贯，则肺得温养，宣降有度，功能健旺。然病理之变，此协调机转亦为传变之途，发为五脏咳证：一者，诸脏气火不达，肺中虚冷，而呈“远火”之势；二者，如《外经微言》

所言："肺居上焦，诸脏腑之火，咸来相逼"。除肺自生火毒外，余脏既生之火如阴火、浮火、木火、君火皆可上逆犯肺，而成"近火"之害[13]。

2 从五脏气火阐释NSCLC免疫治疗中肺火远近

2.1 新辅助治疗期：气火失调为远，火毒壅金为近 《外经微言》谓："肺得火则金益，肺失火则金损，故金中不可无火，亦不可有火也"。肺主气，司宣发肃降，通调水道，其功能健运调和全赖其中气火的充盛与运转[14]。而恰如《素问·评热病论》云："邪之所凑，其气必虚"。依据本团队前期构建的肿瘤"虚-寒-毒-闭-衰"五期演变学说[15]，NSCLC病起于虚损，其病机核心在于肺脏呈"远火"之变，火不化气则气虚寒凝；气不布津则痰湿内生；气不行血则瘀血内停；卫外失固则癌毒滋生。正如《杂病源流犀烛》所言："邪积胸中，阻塞气道，气不宣通，为痰，为食，为血，皆得与正相搏，邪既胜，正不得而制之，遂结成行而有块"。此正虚邪恋之态，恰似现代医学中程序性死亡配体1（PD-L1）等免疫检查点分子高表达，进而抑制T细胞功能，形成免疫抑制并介导免疫逃逸，使肿瘤细胞得以生存、增殖[16]。在此基础上，肺中气火失调又可细分："伏、竭、悬"三态：一者气火郁遏于阴浊之下，正如《金匮要略心典》所言："痞坚之处，必有伏阳"，证见胸闷、咳吐黄痰、鼻窒不通，其类丰富T细胞浸润于肿瘤之中，对ICIs治疗良好的免疫炎症型肿瘤[17]；二者气火虚极而竭，多呈气短乏力、声低懒言、畏风自汗之象，其似肿瘤基质及实质均缺少免疫细胞浸润之免疫沙漠型肿瘤[17]；三者，肺气悬于上、外，难以贯通癌毒之中，多以咳逆气促、声息难续为主，则合免疫细胞存在于肿瘤基质中，不能渗透入实质之免疫豁免型肿瘤[17]。

至于"近火"之变，NSCLC患者，尤其鳞状NSCLC多伴烟草暴露史[18]，烟草辛热燥烈，耗损气阴[19]，加之ICIs药性偏温，易助热化毒。诸火相合，直灼肺金，是"火为肺金之贼"（《外经微言》）的集中体现。研究发现，肺癌患者免疫性肺炎（ICI-P）总体发生率和重症发生率均高于其他恶性肿瘤，其中鳞癌患者较腺癌风险更高，吸烟为ICI-P的高危因素之一[20]。

2.2 术后辅助治疗期：宗中虚陷为远，阴火乘金为近 《薛生白医案》有云："脾为元气之本，赖谷气以生；肺为气化之源，而寄养于脾也"。金土二者气化相承，脾土清阳上输，则肺金得养；肺气宣降有权，则中焦枢机畅达[21]。此期，患者经历手术，虽癌灶已除，然金刃伐正，必然损伤肺体，而致肺气受损，宗气下陷[22]。然子病及母，肺气虚弱可累及中焦，加之ICIs常与放化疗攻伐之法联合应用，进一步克伐中州，土伤火弱，中气虚陷。土不生金，无力上煦华盖，肺中更呈"远火"虚冷征象，为ICIs提供应用契机。临证，此期多以气短声低，胸闷乏力，食少纳呆，畏寒喜暖，大便溏稀，脉沉弱见证。现代研究揭示，NSCLC术后，肠道菌群丰度及种群可能有所改变[23]，肠道菌群及其代谢产物通过"肠-肺"可调节肺部免疫以影响ICIs治疗效果[24]，提示调节胃肠功能可能为协同NSCLC免疫治疗的潜在策略。

此外，《脾胃论》明言："脾胃气虚，则下流于肾，阴火得以乘其土位"。中气下陷，阴火僭越中焦，循经犯肺，形成阴火乘金"近火"之局。ICIs又性属辛温，趋向升浮，加剧阴火灼肺，呈irAEs倾向，进一步销蚀肺气，诚如《外经微言》所论："故土中无火，不能生肺金之气。而土中多火，亦不能生肺金之气也"。一项荟萃分析揭示，在新辅助化免治疗的基础上，额外增加术后辅助免疫治疗，可增加irAEs的发生风险，与此相应[25]。

2.3 晚期：命门火衰为远，浮火灼金为近 《外经微言》有云："肺肾相亲，更倍于土金之相爱……肺生肾，而肾能生肺。昼夜之间，肺肾之气实彼此往来，两相通而两相益也"。肺肾乃金水相生之脏，命门之火上煦于肺，则治节有度，故谓"肺得命门而治节"（《石室秘录》）。肺中之气根于肾，则摄纳有权，故云"肾纳气，其息深深"（《医碥》）[26]。无驱动基因突变Ⅳ期NSCLC患者，病至晚期，病势由上中二焦深入下元，肾中命门真火衰微，难以上达温养肺金。肺中虚衰气火失于肾之摄纳，浮越于上而更失温煦。此与晚期肿瘤微环境中CD8阳性T淋巴细胞（$CD8^+$）耗竭T细胞占比高于早期，呈强免疫抑制状态相通[27]。肺体顽冷，气火不布则藩篱尽撤，癌毒鸱张而广泛转移，其挟阴水流注周身：上泛胸胁则为胸胁胀满、端坐呼吸、气短息微、咳唾引痛、胸水频发；中溃脘腹则成腹满疼痛、腹水内蓄、纳呆便溏，下注下焦则见癃闭肢肿、腰膝冷重而痛。若属表皮生长因子受体（EGFR）驱动基因突变阳性者，其类触及根本，直捣命门，致其升腾温化之力殆尽，故证多从寒化[28]，属"冷"肿瘤范畴，此时ICIs往往应答不佳[29]。临床以表皮生长因子受体酪氨酸激酶抑制剂（EGFR-TKI）类靶向治疗为一线首选，取其药性温通[30]，化解阴凝寒结，推动肿瘤免疫微环境由"冷"转"热"[31]。研究进一步发现，EGFR-TKI治疗后可出现PD-L1表达升高，细胞表面抗原CD4阳性的T淋巴细胞（$CD4^+$）、$CD8^+$ T细胞下调[32]。而PD-L1高表达正为第三代EGFR-TKI耐药机制之一[33]。由此可知，此"热"象并非真阳来复，实乃元阳衰惫、阴寒内盛，迫使残阳浮越于外之"真寒假热"之局，虽存后线ICIs应用之机，然其本已虚不可不知。

至于浮火灼金，此为近火之变。其责在晚期命门火衰而真阴亦竭，阴不涵阳，以致浮火上炎，刑烁娇脏，销铄肺津，灼伤肺络，煎炼肺气。且此火无根，尤易引燃，正如KEYNOTE-407研究显示，在晚期一线接受帕博利珠单抗联合化疗的鳞状NSCLC患者中，≥3级irAEs发生率高达69.8%，病情危殆[34]。

2.4 耐药进展期：肝枢郁闭为远，木火刑金为近 《四圣心源》有云："气性清凉而右降，至左升于木火，则化而为温暖"。肺气肃降于右，肝气升发于左，二者斡旋相济，共成"龙虎回环"，为一身气机升降出入之枢轴[35]。具有免疫治疗机会的NSCLC患者，本有肺体失于温煦，其气孤悬不降，更兼痰瘀浊毒等阴邪盘踞缠结，阻遏气化。《四圣心源》载："肝气之下

郁，总由太阴之弱”。肝木不能遂其条达舒展之性，郁结于中焦脐腹之间，呈郁闭之势。《杂病源流犀烛》曰：“一阳发生之气，起于厥阴，而一身上下，其气无所不乘”。肝为气机发轫之枢，其气既闭，则肺中气火郁遏不得宣通，余脏气火亦壅滞不得抵达，如此则肺中气火愈虚愈闭，正溃而邪盛，趋于耐药。现代医学认为ICIs耐药机制如抗原呈递信号传导缺陷、局部免疫功能障碍及T细胞排斥等[36]，恰似气火虚闭难启微观映象，而高增殖性肿瘤细胞、血管占比及抗原、PD-L1的丢失，则类邪毒邸张过甚，痰瘀浊毒蒙蔽[37]。

此外，肝郁既久，常从火化，木火循经上炎，肺受木火刑伐，清肃失权，病势渐进；神明为火所扰，神魂失守，情志乃伤。故此期，临床常见咳嗽咯血、痛引胸胁、声音嘶哑，并见焦虑抑郁、口苦口干、眠差、善太息等。研究亦发现，当机体长期处于情志异常、睡眠障碍、疼痛等慢性应激状态下，可激活神经-内分泌-免疫机制，高水平糖皮质激素可驱动$CD8^+$T细胞向免疫抑制及终末耗竭表型转化，可能诱导ICIs治疗耐药[38]。

2.5 免疫治疗全程：君火不及为远，君火燔灼为近 《医门法律》云：“心肺为脏阴也，以通行阳气而居上，阴体而阳用也”。心为君主之官，内藏神明，君火潜寓其中，为一身气火之统帅，统摄免疫治疗全程[39]。肺为相傅之官，主气司治节，赖君火温煦，方能行其宣肃之职，输布气血津液以荣周身，恰如《中西汇通医经精义》所言：“故心火者，乃肺之主也，心火太甚，则肺燥，心火不足，则肺寒”。

免疫治疗初始，若君火失位，不能下照于肺，则肺中气火虚弱。难以温煦诸脏，气火传输受阻，以致上焦气机郁滞、津凝痰聚、血行涩滞，痰瘀浊毒渐蒙上焦轻清之地，心肺共病而成“远火”之态。研究发现，无心血管疾病（CVD）且已证实具有免疫治疗效果（发生≥3级irAEs）的患者总生存期（OS）改善明显，而CVD患者可抵消此种获益[40]。

若ICIs治疗过程中，“君火离位”之态未得纠正，反因久病虚耗或药力攻伐而加剧，以致心神失驭，不能归明于上，则呈现“神不使”之候[30]，恰如《素问·汤液醪醴论篇》曰：“形弊血尽而功不立者何？岐伯曰：神不使也……精神不进，志意不治，故病不可愈”。此际不仅心理困扰频现，神机不运亦使药力难达病所，益趋耐药。前瞻性队列研究揭示，约48.9%NSCLC患者基线时即存在抑郁或焦虑，与无情绪压力的肿瘤患者相比，有情绪压力的患者中位无进展生存期（PFS）缩短7.6个月，客观缓解率（ORR）降低15.3%，2年总生存率（OSR）降低18.4%[41]。

又如《医贯》警示：“君火用事，肺金必受伤克”。君火过亢，则灼伤肺络，直损肺体，甚则蚕食一身之气。现代医学亦观察到，NSCLC治疗中ICIs的应用，尤其在联合放疗后，可激发炎性反应与氧化应激，导致较为严重的心脏损伤，其中尤以免疫相关性心肌炎为凶险，症见胸痛、呼吸困难、肺水肿等急性心衰征象，预后不良[42]。

3 从五脏气火构建NSCLC免疫治疗中医药联合策略

现代医学逐渐认识到：完全解除PD-1/PD-L1介导的抑制作用，可破坏干细胞样状态、介导高亲和力的干细胞样祖细胞$CD8^+$T（TSL）死亡及T细胞克隆谱失调，影响长期免疫记忆、再治疗疗效并引发irAEs。而部分阻断PD-1/PD-L1通路虽可避免TSL细胞的丢失，但以单次抗肿瘤疗效降低为代价[43]。故免疫治疗关键在于寻找最佳平衡点，此与中医“调衡”思路不谋而合。故中医调治，需统观全局，在燮理金脏之余，亦需明辨各期余脏气火状态，以平为期，终达《外经微言》述：“所贵微火以通薰肺也”。

3.1 新辅助治疗期：燮理气火，固护肺金 NSCLC新辅助治疗阶段，中医药联合重点在于协助激活免疫应答，缩小肿瘤体积，提高R0切除率，兼以改善症状。此期，团队立足于肺中“远火”状态及其衍生之“伏、竭、悬”三态，兼顾痰瘀互结、癌毒壅金的病机特点，确立以“补虚、挽竭、发郁、降逆”为调治肺中气火的核心治法，并佐以清解癌毒、化痰祛瘀。临证可根据患者症状表现或免疫状态对应辨治，具体而言：若见肺中气火虚惫者，治宜直补肺气，固护藩篱，减弱免疫抑制，以补肺汤（《永类钤方》）为主方[44]；若见气火衰极而竭者，则应温阳敛肺、补气固本，方选加味保元汤（《医学集成》）加减；若遇气火伏而不宣者，治当宣郁透热、升降气机，方予升降散，并可酌加防风、白芷等风药轻扬宣透。然若遇咳血，则须慎用辛散，遵“亡血家不可发汗”（《伤寒论》）之训，给予仙鹤草、白及等宁络止血；针对肺气孤悬、上逆不降，成“悬”者，则应降气平喘，方以定喘汤化裁。此外，此期患者肿瘤负荷较高且正气尚耐攻伐，故常在调肺中气火之剂中，辅以浙贝母、竹茹、蒲黄、茜草、白花蛇舌草、金荞麦共奏化痰祛瘀解毒之功。现代研究揭示，人参皂苷Rh_2可激活TANK结合激酶1-干扰素调节因子3-CXC趋化因子配体10（TBK1-IRF3-CXCL10）信号轴，促进$CD8^+$T细胞浸润及M1巨噬细胞极化[45]；而环黄芪醇与组织蛋白酶B（Cathepsin B）结合，抑制组织相容性复合体I（MHC-I）的溶酶体降解，促进肿瘤抗原呈递并增强$CD8^+$T细胞功能，从而与PD-L1免疫疗法形成协同作用[46]。

若因治疗或体质因素出现“近火”之变，见壮火伤阴耗气之irAEs，则可选用麦门冬汤加减滋阴润肺，以护肺金之体。研究显示，麦门冬汤加味可以提高肺癌荷瘤小鼠$CD4^+/CD8^+$的值，降低炎症因子表达，并抑制Janus激酶2/信号转导和转录激活因子3（JAK2/STAT3）信号通路[47]。

3.2 术后辅助治疗期：培土生金，升阳敛火 术后辅助治疗期治疗重在协同增效减毒，以“稳”为要，调和机体平衡，兼以调摄诸证，提升患者生活质量。针对此期“宗中虚陷为远，阴火乘金为近”之核心病机，团队宗《脾胃论》：“惟当以甘温之剂，补其中，升其阳，甘寒以泻其火则愈”之旨，确立“培土生金以治其本虚，升阳敛火以治其标热，兼以涤浊祛瘀，清除余毒”的治则。主方选用升陷汤合补中益气汤，力主升举下陷之胸中大气与中焦清阳，使清阳上达，肺金得温，以治“远火”。研究显示，升阳举陷法可有效提高$CD4^+$、$CD4^+/CD8^+$T淋巴细胞比例，激活机体免疫[48-49]。同时人参多糖可通过调节肠道菌群组成，显著改善抗PD-1免疫疗法应答情况[50]。在此基础上，亦可佐入白花蛇舌草、蛇莓、鱼腥草等解毒之品荡涤余毒。若其升提迅猛，恐元气耗散者，可酌加山萸肉、乌梅、生牡蛎以收

敛固脱；若见中脘痞闷，纳谷不馨者，可添生麦芽、枳壳、鸡内金等灵动之品以醒脾开胃、消食化滞；若见大便溏稀甚或滑脱不禁者，可酌加炮姜、煨肉豆蔻以温阳固肠止泻。

此外，甘温益气升阳之法，使下陷之清阳复位之余，亦能潜敛僭越阴火，从而缓解“近火”之害[51]。临证之际，可据阴火泛溢之处，灵活化裁：若见皮疹瘙痒，此系阴火外透肌表，可加地肤子、白鲜皮、蝉蜕以疏风止痒、凉血清热；若见中性粒细胞减少，属“壮火食气”者，可配黄芪、当归、鸡血藤等益气养血之品，资气血化源。

3.3 晚期：固本培元，引火安金 病至晚期，邪气深痼，根基已衰，其治疗难点不仅在于机体免疫耗竭之态更甚，更在于诸多兼证变证交织互结。故在力图逆转沉疴之际，尤须着力处置各类兼证，以防变证蜂起，良法难施。针对晚期“命门火衰为肺之远火，浮火灼金为肺之近火”核心病机，团队立“温肾阳以续其治节，滋肾阴以引其浮火，荡癌毒以安其娇脏”之法。主方选用济生肾气丸，意在续命门之火以存肺中残阳，化气利水以驱肺中阴霾。研究显示，肾气丸类方可诱导干扰素-γ（IFN-γ）生成，调节1型辅助性T细胞/2型辅助性T细胞（Th1/Th2）平衡，提升细胞表面抗原CD3阳性的T淋巴细胞（$CD3^+$）、$CD4^+$淋巴细胞及$CD4^+/CD8^+$，以增强机体免疫应答[52]。然此期多见若癌毒流注，多处转移，故在扶正基础上，适当佐入藤梨根、虎杖、凌霄花等以解毒散结。若遇EGFR-TKI耐药后应用ICIs者，则需明辨此乃阴盛格阳之“真寒假热”。治疗当慎用清解，宜温固下元，潜敛浮阳，可佐入煅牡蛎、煅磁石、煅海浮石等咸寒潜降之品。此外，临证之际兼夹纷繁，需灵活化裁：若见痰浊壅肺，气逆不降，可化裁苏子降气汤温化降气；若见火衰阴水为患，法当“水郁而折之”[53]，随其所在而治：咳逆倚息不得卧者，则合葶苈大枣泻肺汤泻肺行水；水流胁下，咳唾引痛者，添柴胡桂枝干姜汤和解散饮；水走肠间沥沥有声者，可化裁己椒苈黄丸分消水饮；水溢肌肤四肢浮肿者，则合防己茯苓汤通阳利水。

至于近火之患，乃肾阴枯涸，无根虚火上灼肺络，切不可纯用苦寒直折，需“引火归元，润金保肺”，可据阴亏与浮火轻重，择方而治：若以阴虚为主，虚火上炎不甚者，可用都气丸或金水六君煎滋肾纳气；若属阴虚火旺，咳痰带血者，可选百合固金汤清热宁络；若见阴亏于下而虚阳浮越于上明显者，则宜选用引火汤（《辨证录》）重滋肾阴，引火归原。

3.4 耐药进展期：疏枢攻毒，清金平木 在ICIs耐药进展期，关键在于改善免疫状态，拦截癌毒流注，调节身心症状，以重启“龙虎回环”常序，扭转气火郁闭颓势。针对此期“木无金制而愈郁”（《外经微言》）或“木火焚灼，肺金受刑”（《医方集解》）的核心病机，治疗当遵循：“耐药则疏其郁闭，化火则折其炎势，全程在流通气火”。主方选四逆散、柴胡疏肝散透达郁阳，宣畅气机，以疏启为要。在此基础上，可佐入藤梨根、虎杖、凌霄花等攻毒之品，以荡涤盘踞癌毒；再配僵蚕、桑枝、鸡血藤等通络之品，以切断癌毒传舍之径[54]。临证若见情志郁闷不舒、阳气郁遏者，可化裁桂萸温阳解郁方以温通阳气，解郁散结[55]。

至于木火刑金，灼伤肺络者，当以清降为先，选用泻白散合黛蛤散以清金制木、肃肺宁络，使娇脏免受燔灼之苦。《此事难知》又云：“金气胜则木自平”，故可添入沙参麦冬汤以清金平木。研究显示，沙参麦冬汤可降低白细胞介素-6（IL-6）、白细胞介素-1β（IL-1β）和肿瘤坏死因子-α（TNF-α）的水平，并抑制JAK2和STAT3的磷酸化，以减轻NSCLC氧化应激及炎症反应[56]。临证若见咯血者，可予咳血方（《丹溪心法》）清肝止血；若遇声音嘶哑，可加蝉蜕、木蝴蝶轻宣开音；若兼见焦虑烦躁、睡眠多梦、胸闷脘痞者，可化裁柴芩温胆汤化痰除烦[57]。

3.5 免疫治疗全程：调摄君火，主明金安 免疫治疗全程君火盛衰常变与免疫抑制、免疫耐药、免疫过激密切相关。故免疫治疗各阶段，应在分期辨证调治基础上，从心论治，重视调摄君火、安和神明。治疗须遵“温养君火以助肺中气火流转，调和神志以明主安下，清泄心热以平亢制炎”大法。可于免疫治疗各期中，予桂枝甘草汤、炙甘草汤辛甘化阳，温通君火以扭转初始免疫抑制状态。恰如《中西汇通医经精义》所言：“心火温肺，而后胸中阳和，无寒饮咳痹之证”。研究显示，炙甘草汤可调节NSCLC患者$CD3^+$、$CD3^+/CD4^+$、$CD3^+/CD8^+$，降低肿瘤标志物并显著改善症状[58]。

若因久病药伐，心神失驭，出现“神不使”之耐药倾向，则当调和神志以启复药效，改善症状。盖“情志之伤，虽五脏各有所属，然求其所由，则无不从心而发”（《类经》），故须在温复君火基础上，注重安神定志。若见情志抑郁者，可佐合欢皮、白芍养心解郁；若遇焦躁不安者，配以郁金、黄连清心解郁；若兼眠差者，宜加酸枣仁、柏子仁、珍珠母以养心安神；若因痰浊蒙蔽而神机不运者，则宜开心散（《千金方》）涤痰开窍、醒神益智。如此以达“精神内守，病安从来”（《素问·刺法论篇》）[59]。

至于各期irAEs，亦可视君火态势，予以出路：见下移小肠者，可选导赤散导热下行；上中二焦郁热炽盛者，择凉膈散清热泻火；胸膈郁热虚烦者，添栀子豉汤宣散郁火。若遇火灼肺体，耗气伤阴，甚者呈“壮火食气”危候者，则速投清营汤或犀角地黄汤合生脉散之类清心泻肺、凉营护阴。“肺火远近”理论在NSCLC免疫治疗各期中的中医病机阐释与对应方药见图1。

4 结语

本文以《外经微言》“肺火远近”理论为纲，立足团队所倡时空观、核心观、症状观、精准观、未病观[60]，首次从五脏气火传变的角度阐释NSCLC免疫治疗全程肺中气火变化及免疫状态。治疗当以调和五脏气火为要，强调多脏同调、形神并治、时时扶正、适时攻毒。此外，通过动态调控五脏气火远近态势，把握气火转化互作，以灵活防治irAEs及耐药难题。协同诸法，明晰阴阳，辨证施治，方可恢复肺金“微火通熏”生理常态及机体免疫平衡。

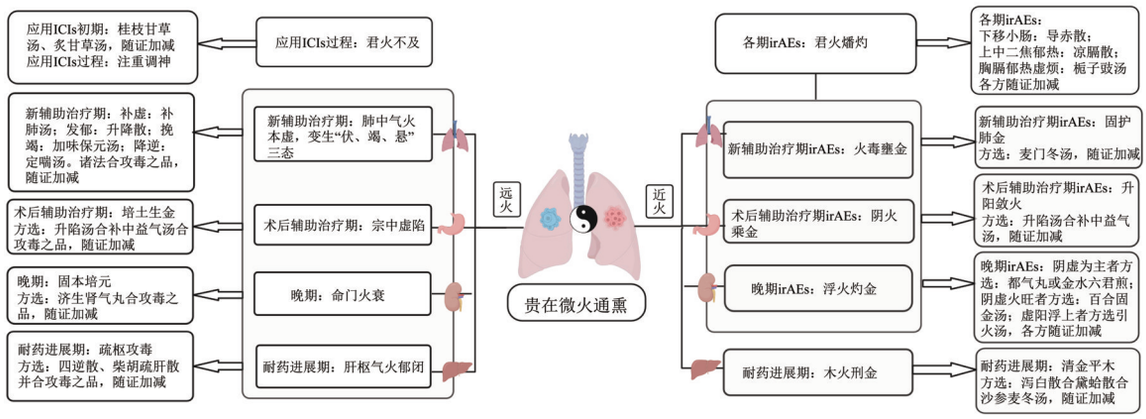

图1 “肺火远近”理论在NSCLC免疫治疗各期中的中医病机阐释与对应方药

Fig. 1 Interpretation of "distance of lung fire" theory in various stages of immunotherapy for NSCLC and corresponding traditional Chinese medicine prescriptions

［利益冲突］ 本文不存在利益冲突。

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