



· 综述 ·

广泛期小细胞肺癌免疫联合治疗研究的新进展

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[摘要] 广泛期小细胞肺癌 (extensive-stage small cell lung cancer, ES-SCLC) 是一种预后不良的高度恶性疾病, 在过去的几十年里, 尽管有许多关于新化学疗法及其组合和新生物制剂的临床试验不断开展, 但总生存率一直止步不前, 含铂类药物的EP/EC化疗方案一直是ES-SCLC的标准治疗模式, 然而化疗的效果不尽如人意, 中位生存时间和2年生存率分别只有7~10个月和10%~20%。近年来关于ES-SCLC的免疫联合疗法有了新的进展, 打破了以往的治疗瓶颈。ES-SCLC的全基因组分析显示, 大多数ES-SCLC患者 $p53$ (90%) 和 $Rb1$ (65%) 基因失活, 这些基因突变导致了基因组的不稳定性, 使肿瘤产生持久的相关抗原, 使得ES-SCLC具有较高的突变负荷, 从而奠定了免疫治疗的基础。回顾和分析最近的文献, 讨论免疫联合化疗、免疫联合放疗、免疫联合免疫、免疫联合抗血管治疗ES-SCLC方案和正在进行的临床试验, 此外就目前ES-SCLC免疫联合治疗模式的探索进行综述。

[关键词] 广泛期小细胞肺癌; 免疫药物; 免疫联合治疗; 临床试验。

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New progress in the research of immunotherapy for extensive-stage small cell lung cancer LI Guoyu¹, HE Ming²
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[Abstract] Extensive-stage small cell lung cancer (ES-SCLC) is a highly malignant disease with a poor prognosis. In the past few decades, although many clinical trials on new chemotherapy with its combinations and new biological agents were conducted, the overall survival rate has never been improved. The platinum-containing EP/EC chemotherapy regimen has always been the standard treatment method for ES-SCLC, however, the results of chemotherapy are not satisfactory, the median survival time and 2-year survival rate are only 7-10 months and 10%-20%, respectively. In recent years, there have been new advances in the combined immunotherapy for ES-SCLC, breaking the previous treatment bottleneck. The comprehensive genomic analysis of ES-SCLC shows that $p53$ (90%) and $Rb1$ (65%) are inactivated in most ES-SCLC patients. These gene mutations lead to the instability of the genome, causing ES-SCLC to have a high mutation load due to production of persistent related antigens by the tumor, thus laying the foundation for immunotherapy. We reviewed and analyzed the recent literature and discussed the combined immunotherapy regimens of ES-SCLC and ongoing clinical trials. We also reviewed the current exploration of combined immunotherapy model for ES-SCLC.

[Key words] Extensive-stage small cell lung cancer; Immunologic drugs; Combined immunotherapy; Clinical trials

肺癌是常见的癌症, 其中小细胞肺癌 (small cell lung cancer, SCLC) 占15%~20%^[1]。SCLC的发生率在中国更是逐年上升^[2], 因其具有高度侵袭性和隐匿性的特点, 约80%的患者在初诊时已为广泛期, 尽管其对放化疗敏感, 但极易复发耐药^[3]。广泛期小细胞肺癌 (extensive-

stage SCLC, ES-SCLC) 的全基因组分析显示, 大多数ES-SCLC患者 $p53$ (90%) 和 $Rb1$ (65%) 基因失活, 这些基因突变导致了基因组的不稳定性, 使肿瘤产生持久的相关抗原, 使得ES-SCLC具有较高的肿瘤突变负荷^[4-5], 既往研究表明, 免疫治疗在ES-SCLC患者中显示出持久

的抗肿瘤活性^[6-9]，然而，程序性死亡[蛋白]配体-1 (programmed death ligand-1, PD-L1) 和主要组织相容性复合体 (major histocompatibility complex, MHC) 抗原的低表达以及肿瘤浸润淋巴细胞 (tumor infiltrating lymphocyte, TIL) 的低水平和快速的肿瘤进展似乎限制了免疫治疗的功效^[10-11]。在过去的几十年里，一些临床试验已经评估了在标准化疗基础上增加免疫治疗对ES-SCLC患者的效果^[12-13]。免疫检查点抑制剂目前正在研究中^[14]，特别是细胞毒性T淋巴细胞相关抗原4 (cytotoxic T-lymphocyte-associated antigen 4, CTLA-4) 和程序性死亡[蛋白]-1 (programmed death-1, PD-1) /PD-L1抑制剂^[15]。目前，有证据表明，对于以往未接受过全身治疗的患者，在标准的化疗基础上联合atezolizumab可显著提高患者的总生存率^[16-17]。另外，免疫联合放疗、免疫联合免疫、免疫联合抗血管治疗ES-SCLC患者初显疗效。在此我们回顾和分析最近的文献，讨论ES-SCLC的免疫联合治疗方案和正在进行的临床试验，并就目前ES-SCLC免疫联合治疗模式的探索进行综述。

1 免疫联合化疗策略

1.1 Atezolizumab联合EC一线治疗策略

既往IMpower133试验表明，相较于标准化疗，atezolizumab联合EC方案一线治疗ES-SCLC可显著提高患者的无进展生存期 (progression-free survival, PFS)，延长近1个月，总生存期 (overall survival, OS) 显著改善达12.3个月，延长2个月，死亡风险降低30%^[16, 18]，IMpower133试验是首个在ES-SCLC一线治疗中显示出免疫治疗联合化疗较当前标准化疗可显著延长患者PFS和OS的临床试验；基于该项研究atezolizumab联合EC方案一线治疗ES-SCLC的适应证于2019年获美国食品药品监督管理局 (Food and Drug Administration, FDA) 正式批准，后于2020年2月13日获中国国家药品监督管理局 (National Medical Products Administration, NMPA) 适应证审批。

1.2 Nivolumab联合EC一线治疗策略

2020年美国临床肿瘤学会 (American Society

of Clinical Oncology, ASCO) 公布了美国东部肿瘤协作组 (Eastern Cooperative Oncology Group, ECOG) —美国放射学会影像网络 (American College of Radiology Imaging Network, ACRIN) EA5161这一项随机对照Ⅱ期临床研究，旨在评估nivolumab联合EC一线治疗ES-SCLC的疗效和安全性^[19]。共入组160例患者，按照1:1随机分组，A组为nivolumab 360 mg+EC方案 (每21 d为1个周期，共4个周期)，随后采用nivolumab 240 mg，每2周1次的维持治疗，直至肿瘤进展或治疗满2年；B组为EC方案，每21 d为1个周期，共4个周期。期间，预防性脑照射 (prophylactic cranial irradiation, PCI) 被允许选择使用。两组之间的基线特征均衡，研究的主要终点是意向性治疗 (intention-to-treat, ITT) 患者的PFS，次要终点包括OS、客观缓解率 (objective response rate, ORR) 和安全性。结果显示，在ITT人群中，A组相比B组可明显延长患者的PFS，两组的中位PFS (median PFS, mPFS) 分别为5.5个月和4.6个月 (HR=0.65; 95% CI: 0.46~0.91; P=0.012)。A组OS也显著优于B组，两组的中位OS (median OS, mOS) 分别为11.3和8.5个月 (HR=0.67; 95% CI: 0.46~0.98; P=0.038)。在开始研究治疗的患者群体中，A组相比B组同样显著延长了患者的PFS，并改善了OS，两组的mPFS为5.5和4.7个月 (HR=0.68; 95% CI: 0.48~1.00; P=0.047)，两组mOS分别为11.3和9.3个月 (HR=0.73; 95% CI: 0.49~1.11; P=0.14)；两组的ORR分别为52.29%和47.71%，缓解持续时间 (duration of response, DOR) 分别为5.6和3.3个月。在安全性方面，A组和B组中3~4级不良反应事件发生率分别为77%和62%，因此导致治疗中断的患者比例分别为6.21%和2.07%。目前，10例患者仍然使用nivolumab进行维持治疗。与治疗相关的致死性不良事件在两组中发生例数相似，A组为9例，B组为7例。Nivolumab联合EC方案一线治疗，可以显著延长ES-SCLC患者的PFS和OS，但是不良反应率会更高，在采用此方案时应该重点关注不良反应。

1.3 Pembrolizumab联合EP一线治疗策略

Pembrolizumab联合化疗在NSCLC患者中取得了不菲的成就^[20]。在ES-SCLC患者中的疗效令人拭目以待。

2020年ASCO报道了KEYNOTE-604这一项双盲的Ⅲ期临床研究,旨在评估pembrolizumab (200 mg q3w)+EP方案 vs 安慰剂+EP方案,一线治疗ES-SCLC的疗效和安全性^[21]。初治ES-SCLC且未接受过中枢神经系统转移治疗的合格患者转移按1:1比例随机分配,接受pembrolizumab (200 mg q3w)或安慰剂治疗,最多35个周期+4个周期标准剂量依托泊苷+铂类药物。治疗4个周期后,完全缓解(complete response, CR)或部分缓解(partial response, PR)的患者可根据研究者的诊断接受PCI。分层因素包括铂类的选择(卡铂 vs 顺铂)、ECOG PS评分(0 vs 1)和乳酸脱氢酶(lactate dehydrogenase, LDH)(\leq ULN vs $>$ ULN)。主要终点为ITT人群的OS和PFS。次要终点为ORR、DOR和安全性。研究预设了第2次中期分析和最终分析。试验共入组453例患者(pembrolizumab+EP方案组228例,EP方案组225例),pembrolizumab+EP方案组中基线时合并脑转移的患者比例更高,两组分别为14%和10%。最终分析时(中位随访时间21.6个月),pembrolizumab+EP方案组尚有9%的患者持续治疗,而EP方案组仅为1%;两组接受PCI的比例为12%和14%。中期分析时(中位随访时间13.5个月),pembrolizumab+EP方案相比EP方案显著改善ITT人群的PFS,mPFS分别为4.5个月 vs 4.3个月(HR=0.75;95% CI: 0.61~0.91;P=0.002 3)。最终分析时,pembrolizumab+EP方案组ITT人群的OS得到延长,两组mOS为10.8和9.7个月,但是P值未达到显著性阈值(HR=0.80;95% CI: 0.64~0.98;P=0.016 4)。在接受治疗人群的事后OS分析中,P值也小于显著性阈值(HR=0.78;95% CI: 0.63~0.97;P=0.012 4)。最终分析时,pembrolizumab+EP组的ORR为70.6%,而EP组为61.8%,两组mDOR分别为4.2和3.7个月。安全性方面,未发现新的不良

反应,两组间3~4级不良反应发生率为77%和75%,5级不良反应发生率为6%和5%。两组间因不良反应停药的比例分别为15%和6%。因此,pembrolizumab+EP方案相比EP方案一线治疗,可以显著延长ES-SCLC患者的PFS,但在OS方面,仅延长了数值,差异无统计学意义。由此可见,在化疗的基础上联合pembrolizumab,只能给患者带来仅0.2个月的PFS获益,但PFS的获益没有转化为OS的获益,表明pembrolizumab联合化疗在ES-SCLC患者中疗效不甚理想,需多中心的进一步研究予以验证。

1.4 Durvalumab联合EP一线治疗策略

既往CASPIAN研究显示durvalumab联合EP方案一线治疗ES-SCLC疗效较为显著^[22]。

2020年ASCO报道了CASPIAN研究的更新结果,一项全球、随机、开放、多中心的Ⅲ期临床试验,旨在评估抗PD-L1抑制剂durvalumab±抗CTLA-4抗体tremelimumab联合EP方案在ES-SCLC一线治疗中的疗效和安全性^[23]。入组患者按1:1:1的比例随机分配至durvalumab 1 500 mg+EP方案q3w,durvalumab 1 500 mg+tremelimumab 75 mg+EP方案q3w或EP方案q3w。在免疫治疗组,患者接受4个周期的EP方案+durvalumab±tremelimumab,然后维持durvalumab 1 500 mg q4w,直到疾病进展。在durvalumab+tremelimumab+EP方案组,患者在EP方案后再接受tremelimumab 75 mg。在EP方案组中,患者最多可以接受6个周期的EP方案和可选PCI。研究的两个主要终点是durvalumab+EP方案 vs EP方案和durvalumab+tremelimumab+EP方案 vs EP方案的OS。之前的中期分析(截至2019年3月11日,63%成熟度)显示,durvalumab+EP方案(durvalumab+EP方案)相比EP方案,在OS上具有显著性优势(HR=0.73;95% CI: 0.59~0.91;P=0.004 7)^[24]。本次更新截至2020年1月27日,中位随访时间为25.1个月,durvalumab+EP方案 vs EP方案的OS数据(82%成熟度),以及初次公布了durvalumab+tremelimumab+EP方案 vs EP方案的数据。相比EP方案,durvalumab+EP方案表现出显著且持续的OS获益(HR=0.75,

95% CI: 0.62~0.91; $P=0.0032$), 中位OS分别为12.9和10.5个月。Durvalumab+EP方案组的2年OS率为22.2%, 而EP方案组中仅为14.4%。CASPIAN研究的次要终点为PFS和ORR, durvalumab+EP方案和EP方案组的更新的PFS结果分别为5.1和5.4个月(HR=0.80, 95% CI: 0.66~0.96), durvalumab+EP方案和EP方案组确认的ORR分别为67.9%和58% (OR=1.53, 95% CI: 1.08~2.18), durvalumab+EP方案相比EP方案更具优越性。Durvalumab+tremelimumab+EP方案与EP方案相比, 仅从数据上看似乎延长了患者的OS, 然而差异并未达到本研究预设的差异有统计学意义的要求[HR=0.82, 95% CI: 0.68~1.00; $P=0.0451$ (要求 $P\leq 0.0418$)]。Durvalumab+tremelimumab+EP方案组患者的mOS为10.4个月, 2年OS率为23.4%。与EP方案相比, durvalumab+tremelimumab+EP方案经研究者确认的ORR和PFS相近, 两组的ORR分别为58.4%和58.0%, 两组的mPFS分别为4.9和5.4个月(HR=0.84, 95% CI: 0.70~1.01)。然而在12和24个月的PFS率方面, durvalumab+tremelimumab+EP方案在数值上更高, 两组12个月PFS分别为16.9%和5.3%, 24个月PFS两组分别为11.5%和2.9%, mDOR分别为5.2和5.1个月。针对脑转移患者进行亚组分析, 基线有脑转移和整个病程中出现脑转移患者, 接受durvalumab治疗OS的HR分别为0.73 (95% CI: 0.42~1.29) 和0.78 (95% CI: 0.64~0.95), 显示出有获益的趋势。两组首次疾病进展时, 颅脑进展的比例分别为8.3%和9.5%。结果表明, 基线及病程中出现脑转移的患者, 联合durvalumab治疗均有获益趋势。安全性方面, 在durvalumab+EP方案、durvalumab+tremelimumab+EP方案和EP方案组中, 3~4级的不良反应发生率分别为62.3%、70.3%和62.8%, 因不良反应而停药的患者比例分别为10.2%、21.4%和9.4%, 因不良反应导致死亡的患者比例为分别4.9%、10.2%、5.6%。ES-SCLC的一线治疗已进入免疫治疗时代, CASPIAN试验本次更新, 再一次证明了durvalumab+EP方案可显著延

长ES-SCLC患者的OS, 支持该方案作为ES-SCLC的一线治疗新标准, 并且在铂类药物的选择上相对灵活。而在此基础之上, 再联合tremelimumab, 患者并无更多获益。因此, durvalumab+EP方案足以成为ES-SCLC的一线标准治疗方案。事实上, durvalumab+EP方案化疗已被美国FDA批准用于ES-SCLC一线治疗。

Durvalumab+EP方案在ES-SCLC的一线标准治疗中呈现出较好的疗效, 而在此基础之上, 再联合tremelimumab并未使患者获益更多。最近一项随机多中心的Ⅲ期临床研究拟评估ES-SCLC放疗后durvalumab联合或不联合tremelimumab维持治疗的疗效^[25], 其结果令人拭目以待。

2 免疫联合放疗策略

放射疗法和免疫疗法的结合代表了另一种有前途的方法。既往研究证明局部NSCLC的放射疗法联合免疫疗法策略具有显著的临床获益^[26]。近期一项单臂Ⅰ期临床试验(NCT02402920)评估了在ES-SCLC诱导化疗后将pembrolizumab与胸腔放疗(thoracic radiation therapy, TRT)联合应用的安全性^[27]。研究入组了已完成化疗的ES-SCLC患者接受pembrolizumab联合TRT治疗, 采用3+3剂量递增法评估pembrolizumab的最大耐受剂量, 剂量从100 mg开始, 以50 mg的增量增加到200 mg, 每3周注射1次, 持续16个周期, TRT被规定为15 d每日45 Gy。采用不良事件通用术语标准v4.0评估毒性, 依据治疗开始后35 d内的剂量限制毒性(dose-limiting toxicity, DLT)发生率, 主要终点是联合治疗的安全性。结果显示, 2015年9月—2017年9月, 共纳入38例ES-SCLC患者(中位年龄65岁, 范围37~79岁), 33例患者接受了按方案治疗, 所有患者在接受100~200 mg pembrolizumab治疗的35 d窗口期内均耐受, 无DLT, 没有4~5级的毒性, 2例(6%)发生3级事件(1例皮疹, 1例虚弱/感觉异常/自身免疫性疾病), 中位随访时间7.3个月(范围1~13个月); mPFS和OS分别为6.1个月(95% CI: 4.1~8.1)和8.4个月(95% CI: 6.7~10.1)。总之, pembrolizumab+TRT的耐受性良好, 短期内

严重不良事件较少; 由于存在异质性很难得出确切的无进展生存率和总体生存率。

虽然随机试验已经证明了单一TRT和单一免疫治疗的效果, 但联合方案的疗效需要进一步研究。同时放化疗后LS-SCLC患者的前期免疫治疗和维持免疫治疗的效果仍在研究中 (NCT03703297、NCT03585998、NCT02046733、NCT03540420和NCT03811002)。

3 免疫联合免疫, 双免疫治疗

既往研究CheckMate 227表明无论是PD-L1阳性 ($\geq 1\%$) 或阴性 ($< 1\%$), nivolumab+ipilimumab的一线治疗EGFR/ALK阴性的晚期NSCLC的OS都优于传统化疗^[28]。目前nivolumab+ipilimumab已经被美国FDA批准用于PD-L1 $\geq 1\%$ 的晚期NSCLC一线治疗, 其疗效值得期待^[29]。

3.1 CheckMate 032: nivolumab联合ipilimumab多线治疗ES-SCLC策略

Nivolumab单药疗法基于CheckMate 032研究结果^[30]已在美国FDA获批用于三线或以后的转移性SCLC。在CheckMate 032的队列II中评估了nivolumab联合ipilimumab在SCLC复发患者中的疗效, 值得期待的长期OS率终于更新出炉^[31]。既往经过1~2线化疗治疗后疾病进展的SCLC患者被随机分配为3:2, 每2周1次nivolumab 3 mg/kg, 或每3周1次nivolumab 1 mg/kg联合ipilimumab 3 mg/kg, 持续4个周期, 随后每2周1次nivolumab 3 mg/kg。根据先前的化疗方案对患者予以分层, 并进行治疗, 直到疾病进展或出现不可接受的毒性, 主要终点是ORR。结果显示, 总共147例患者接受了nivolumab和96例nivolumab联合ipilimumab, 各自随访时间为11.9和11.2个月, nivolumab联合ipilimumab的ORR更高 [21.9% vs 11.6% (HR=2.12, 95% CI: 1.06~4.26, $P=0.03$)]。OS方面, nivolumab组最小随访时间为29.0个月, 而nivolumab联合ipilimumab组为28.4个月, 各自mOS为5.7个月 vs 4.7个月, 2年OS率为17.9% vs 16.9%。3~4级TRAE分别为12.9% vs 37.5%, 与治疗相关的死亡比为1:3。尽管nivolumab联合

ipilimumab有更高的ORR, 但是并没有转化为OS获益, 并且给患者带来了更高的不良反应率。

3.2 CheckMate 451: nivolumab联合ipilimumab维持治疗策略

在CheckMate 451这项安慰剂随机对照的III期临床研究中^[32], 研究人员评估了nivolumab联合ipilimumab和nivolumab单药治疗作为诱导化疗后维持治疗对ES-SCLC患者的疗效, 并与维持期仅安慰剂进行了比较。结果显示, nivolumab联合ipilimumab和nivolumab单药治疗均未改善患者的mOS (9.2个月, HR=0.92; 95% CI: 0.75~1.12; 10.4个月, HR=0.84; 95% CI: 0.69~1.02; $P=0.369$)。接受免疫治疗的两组患者mPFS较安慰剂组有适度改善 (mPFS分别为1.7、1.9和1.4个月), 但差异无统计学意义。安全性方面, 所有级别和3~4级不良反应发生率nivolumab联合ipilimumab组为86% (52%), nivolumab单药为61% (12%), 安慰剂组为50% (8%)。由于治疗毒性而终止的比率nivolumab联合ipilimumab组为31%, nivolumab单药组为9%, 安慰剂组 $< 1\%$ 。与治疗相关的死亡nivolumab联合ipilimumab为7例 (2.5%), nivolumab为1例 ($< 1\%$), 安慰剂组为1例 ($< 1\%$)。诱导化疗后nivolumab单药或联合ipilimumab维持治疗ES-SCLC患者没有取得OS获益。但令人惊奇的是, 在对完成化疗5周内接受维持治疗的nivolumab患者数据的亚组分析中, OS得到了改善, 原因可能反映了nivolumab的作用机制不同或选择性偏差, 其疗效值得进一步验证。

4 免疫联合抗血管治疗

2020年美国癌症研究协会 (American Association for Cancer Research, AACR) 报道了一项一线铂类药物化疗失败后, camrelizumab联合apatinib在ES-SCLC中的II期PASSION研究, 属随机、开放标签、3组平行队列研究, 患者被随机分配 (1:1:1)。治疗方案为: ① Camrelizumab 200 mg q2w+apatinib 375 mg qd (apatinib每日连服) ($n=47$); ② Camrelizumab 200 mg q2w+apatinib 375 mg qd

(5 d用药, 2 d停药) ($n=6$); ③ Camrelizumab 200 mg q2w+apatinib 375 mg qd (7 d用药, 7 d停药) ($n=6$) 直到出现疾病进展, 不可接受的毒性反应, 或调查者决定退出。根据第1个周期28 d的耐受性和第1阶段的疗效数据, 选择一个队列将其扩展到45例患者的第2阶段。主要终点是依据实体瘤疗效评价标准 (Response Evaluation Criteria in Solid Tumors, RECIST) 1.1评估的ORR和安全性。结果显示, 所有患者 ($n=59$) 的ORR为33.9%, PR占33.9%, SD占35.6%, PD占30.5%; DCR为69.5%。第1、2和3组的ORR为34%、33.3%和33.3%, DCR为68.1%、100.0%和50.0%, PR占34.0%、33.3%和33.3%, SD占34.0%、66.7%和16.7%, PD占31.9%、0.0%和50.0%。化疗敏感患者 (一线化疗后 ≥ 90 d复发, $n=20$): 所有患者ORR为35.0%, DCR为80.0%; 第1、2组的ORR分别为37.5%和25.0%, DCR为75.0%和100.0%。化疗抵抗患者 (一线化疗后 < 90 天复发, $n=39$): 所有患者ORR为33.3%, DCR为64.1%; 第1、2和3组的ORR为32.3%、50.0%和33.3%, DCR为64.5%、100.0%和50.0%。第1组患者的PFS为3.6个月, 其中化疗敏感患者为3.6个月, 化疗抵抗患者为2.7个月。第1组OS为8.4个月, 6个月的OS率为63.3%; 12个月的OS率为36.3%。其中化疗敏感患者为9.6个月, 化疗抵抗患者为8.0个月。安全性方面, 有43例 (72.9%) 报告了 ≥ 3 级的治疗相关不良事件; 常见的不良反应为高血压 (25.4%)、手足综合征 (13.6%)、血小板计数降低 (13.6%)。5例 (8.5%) 的患者因治疗相关不良事件停药; 没有报道与治疗有关的死亡。基于铂类药物的化疗后, camrelizumab联合apatinib在化学敏感和化学抵抗的ES-SCLC患者中均显示出强大的抗肿瘤活性, 并且具有可接受的毒性。

5 总结与展望

总之, 目前免疫联合治疗在ES-SCLC领域取得了不菲的成就, IMpower、CASPIAN等研究提供了有力的证据来支持在ES-SCLC中使用免疫检查点抑制剂^[16, 22-24, 33]。但是, 关于抗PD-1/PD-L1与其他免疫检查点抑制剂的组合是否可以

进一步提高OS率^[30-32]以及在ES-SCLC中是否应将放疗与免疫疗法相结合^[27], 目前的临床试验略显证据不足, 仍需进一步开展大规模多中心的研究加以证实^[34-36]。再者, 目前免疫联合治疗给患者带来的获益有限, OS的改善普遍在3个月以内, PFS改善的绝对值也鲜有超过2个月的。考虑到联合治疗带来的安全性及卫生经济学的可行性, 这些治疗方案能在多大程度上改变中国的临床诊疗实践有待于进一步探索^[37-39]; 此外, 免疫治疗在NSCLC领域, 已有TMB和PD-L1两个应用较为广泛的标志物和一些探索性的标志物可以辅助筛选患者^[40-42], 而在ES-SCLC领域, 目前仍缺乏特异性标志物进行指导, 免疫联合治疗反应的预后生物标志物仍有待探索^[43-48]。

未来ES-SCLC免疫联合治疗的发展应积极探索免疫联合疗法的最佳组合方案, 进一步探讨免疫联合疗法的理想时机, 此外, 应积极寻找免疫联合的预测因子, 筛选获益人群, 实施个体化精准治疗^[49], 进一步研发新一代免疫治疗药物^[50], 重点关注免疫联合治疗的不良反应, 寻找最有效的解决方案^[51]。

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