工藤正俊業績

分子標的治療および免疫療法に関する開発研究

進行肝癌に対する分子標的薬は 2007 年に SHARP 試験および Asia Pacific 試験にてソラフェニブがプラセボに対して survival benefit があることが初めて証明され世界的には承認となった。日本においても 2009 年 5 月に同薬剤が承認となりそれ以降 10 年間唯一の肝癌に対する分子標的薬として使用されてきた。ソラフェニブに加えて薬剤選択肢を増やすためあるいはソラフェニブを超える薬剤開発のため 2007 年から 2016 年の間､肝細胞癌に対する一次治療薬の臨床試験､二次治療薬の臨床試験、TACE 併用試験、アジュバント試験などが約 20 試験以上と多数行われた。工藤正俊はこれらの殆どの臨床試験の Global Steering Committee もしくは Global PI として臨床試験を主導した。中でもポジティブ試験となった RESORCE 試験(Regorafenib)、REFLECT 試験(Lenvatinib)、REACH-2 試験(Ramcirumab)などの Global Steering Committee Member (REFLECT 試験は Global PI)として臨床試験をポジティブに導き、現在日本において承認されている一次治療薬 (Lenvatinib)、二次治療薬(Regorafenib, Ramucirumab)の 3 剤の開発試験に貢献した。

また世界では認められているもう一つの二次治療薬である､Cabozaitinib の第 3 相 CELESTIAL 試験の global 試験には日本全体としては参加できなかったが、ブリッジング Phase 2 として行われた日本の臨床試験の National PI として日本での治験を主導し、2020 年末に承認予定となっている。

これ以外にも、医師主導型臨床試験として肝動注化学療法とソラフェニブとの組み合わせがソラフェニブを上回る効果を示すかどうか、すなわち肝動注がソラフェニブに上乗せ効果があるかどうかを検証する SILIUS 試験を国内の 33 施設と共同で行い､Lancet Gastroenterology and Hepatology (2019 年)に発表した。この結果については Primary endpoint である肝動注化学療法の上乗せ効果こそ示せなかったものの、最終的なサブ解析も含め肝動注化学療法は両葉多発結節の BCLC B の肝細胞癌にはソラフェニブ以上の効果は無い事、及び VP4 などの Major Vascular Invasion に対して肝動注化学療法は明らかに効果がある事を前向き比較試験(RCT)において証明することができた。更には､TACE と Sorafenib の併用の有効性を示す TACTICS 試験を TACE + Sorafenib 対 Sorafenib 群で前向き比較試験を行い、独自に設定した time to unTACEable progression を主体とした PFS において TACE 単独よりも圧倒的に有意な差をもって PFS を延長させる事を示し Gut (2019)に発表した。これまでネガティブな臨床試験が 5 本 (Sorafenib との併用では Post TACE 試験、SPACE 試験、TACE-2 試験の 3 試験、及び Brivanib との併用の BRISK-TA 試験ならびに Orantinib との併用の ORIENTAL 試験)のいずれの試験も失敗した中で失敗した原因から学んで Trial Design を熟考することにより新たな trial design で行った RCT で試験を成功に導いた。結果的に分子標的薬をできるだけ長く TACE と併用する事により TACE と TACE との間隔を短くし、肝予備能を維持することにより患者の Outcome を良好にすることを前向き比較試験にて世界で初めて証明した。ちなみに Post-TACE 試験(Eur J Cancer 2011), BRISK-TA 試験(Hepatology 2014), ORIENTAL 試験(Lancet GH 2019)の全ての試験の global PI を工藤正俊が勤め 1st author としてこれらの雑誌に発表した。工藤正俊はこれらの業績により日本肝臓学会織田賞(2018 年)ならびに SGH がん特別賞(2019 年)を受賞した。

また免疫療法に関してはニボルマブの CheckMate040 試験(Phase 1/2 試験)の cohort 1 (単剤試験)、Cohort 4 (Nivolumab +Ipilimumab=PD-1 Ab + CTLA-4 Ab), cohort 5 (Child-Pugh B)に関しても

Steering committee として参画し、さらに Phase 3 CheckMate459 試験にも参画しそれぞれ論文発表している（Lancet, Lancet Oncology, JAMA Oncology, J Hepatology など）。また Pembrolizumab の開発においても Phase 1/2 試験の KEYNOTE-224 試験や Phase 3 の KEYNOTE-240 試験に Global Steering Committee Member として開発に参画した。また Pembrolizumab と Lenvatinib 併用の Phase 1b 試験にも参画しこれらの結果は Lancet, Lancet Oncology, J Clin Oncology などに共著者として掲載されている。2019 年に ESMO Asia で発表となった Atezolizumab + Bevacizumab の併用試験にも Global Steering Committee として参加し試験を positive に導き肝細胞癌においては初の免疫療法として確立した（New Engl J Med 2020）。

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