Selected Summaries

Trastuzumab and lapatinib in *HER2*-positive metastatic colorectal cancer

Sartore-Bianchi A, Trusolino L, Martino C, Bencardino K, Lonardi S, Bergamo F, Zagonel V, Leone F, Depetris I, Martinelli E, Troiani T, Ciardiello F, Racca P, Bertotti A, Siravegna G, Torri V, Amatu A, Ghezzi S, Marrapese G, Palmeri L, Valtorta E, Cassingena A, Lauricella C, Vanzulli A, Regge D, Veronese S, Comoglio PM, Bardelli A, Marsoni S, Siena S. (Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milano; Istituto di Candiolo, Fondazione del Piemonte per l'Oncologia-IRCCS, Candiolo; Oncologia Medica 1, Istituto Oncologico Veneto–IRCCS, Padova; Seconda Università degli Studi di Napoli, Napoli; Azienda Ospedaliero-Universitaria Città della Salute e della Scienza, Torino; Istituto Mario Negri IRCCS, Milano; Dipartimento di Oncologia, Università degli Studi di Torino, Torino; Dipartimento di Oncologia e Emato-Oncologia Università degli Studi di Milano, Milano, Italy.) Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, *KRAS* codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): A proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016;**17**:738–46.

SUMMARY

The results of this phase 2 trial show promise of dual anti-*HER2* therapy with trastuzumab and lapatinib in *HER2*-amplified, *KRAS* wild-type metastatic refractory colorectal cancer (mCRC). In the era of precision medicine and high throughput molecular oncology, this landmark study provides an effective therapy in the refractory setting and establishes a new standard of care in this subset of patients with mCRC. Anti-epidermal growth factor receptor (EGFR) therapy with monoclonal antibody, cetuximab and panitumumab is the frontline targeted therapy in *KRAS* wild-type mCRC though *EGFR* abnormality is an infrequent phenomenon in mCRC and not a specific molecular target for efficacy of these antibodies.[1] Previous studies[2,3] detected *HER2* gene amplification in cetuximab-resistant all-*RAS, BRAF* wild-type colorectal xenograft model and showed that combination therapy (trastuzumab with pertuzumab or lapatinib) showed sustained tumour shrinkage while monotherapy with anti-*HER2* monoclonal antibody or a *HER2* tyrosine kinase inhibitor was ineffective.

This proof-of-concept phase 2 single-arm study included *KRAS* exon 2 (codon 12 and 13) wild-type mCRC patients older than 18 years who progressed on or after firstline standard treatment with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The authors screened 914 *KRAS* wild-type previously treated mCRC and only 5% (*n*=48) patients had *HER2*-positive tumours defined by colorectal cancer-specific diagnostic criteria[4] and only 27 patients were eligible for the trial. After a median follow-up of 94 weeks, 30% patients achieved overall response (complete and partial) whereas another 12 patients achieved stable disease, and the median progression-free survival was 21 weeks with manageable and acceptable toxicity.

COMMENT

This study had few limitations, some mentioned in an accompanying commentary and some acknowledged by the authors, which would certainly impact the clinical implications. We wish to make a few points.

First, the authors used pre-validated colorectal cancer-specific *HER2*-positivity criteria, which was different from the standardized criteria of *HER2* testing in breast cancer.[5] *HER2* staining was required in >50% of cells as compared to >10% in breast cancer-specific criteria by the American Society of Clinical Oncology.[5] These stringent criteria would have missed many patients as *HER2*-negative who may have lost the opportunity of benefiting from the effect of anti-*HER2* therapy. It is known that *HER2* non-expressed but amplified patients (in fluorescence *in situ* hybridization [FISH]) have benefited from trastuzumab in advanced gastric cancer due to underlying discordance of immunohistochemistry (IHC) and FISH along with intra-tumour heterogeneity.[6] As refractory mCRC usually has a dismal outcome with no effective therapy, tumours with *HER2* 0 or 1+ by IHC should have been considered for FISH analysis and if amplified included in the trial.

Second, the *HER2* status was not known for many patients (37%) at the time of randomization though the authors cited a high concordance rate of *HER2* status at baseline and at progression or metastatic site in a small previous retrospective series.[4] It needs further validation in a larger sample and if high concordance rate is proved, then a liquid biopsy can get rid of intra-tumour heterogeneity and replace an invasive procedure such as re-biopsy.

Third, did the authors perform any mutation analysis for *KRAS* and *NRAS* during randomization? As most of the evaluable patients failed to show any response to prior anti-EGFR therapy (cetuximab or panitumumab), they may have acquired mutation in the *RAS* gene and biased the patient selection criteria.

The previous two studies[7,8] (non-selective for *KRAS* status) did show some clinical activity of trastuzumab with chemotherapy. If *HER2* amplification or overexpression is a specific genetic/molecular alteration for tumorigenesis of mCRC then why did trastuzumab alone or in combination with chemotherapy fail to show activity in *KRAS* wild *HER2*-amplified mCRC in preclinical model or in clinical setting? The authors do not explain this in the discussion.

Colon cancer is ranked as the eighth and ninth most common cancer in men and women in India, respectively.[9] With the high incidence of new cancer cases and a population of more than 1.2 billion, the total number of new mCRC is a huge burden with its associated morbidity, mortality and treatment-related cost. This study offers hope and a new standard of therapy as there is no effective salvage therapy in refractory mCRC.

In conclusion, the HERACLES trial provides promising results of anti-*HER2* therapy in *HER2*-amplified *KRAS* wild-type mCRC in the relapsed setting and show resistance to upfront anti-EGFR therapy. The results need further validation in a larger prospective study. If proven so, then anti-EGFR therapy should be offered upfront to all *RAS*-wild, *BRAF*-wild and *HER2*-negative mCRC.

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BIVAS BISWAS
SAMEER RASTOGI
ATUL BATRA
Department of Medical Oncology
Dr B.R. Ambedkar Institute Rotary Cancer Hospital
All India Institute of Medical Sciences
New Delhi
bivasbiswas@gmail.com

SANDIP GANGULY
Department of Medical Oncology
Tata Medical Centre
Kolkata
West Bengal

Medical marijuana laws and marijuana use in the USA: Any lessons?

Hasin DS, Wall M, Keyes KM, Cerdá M, Schulenberg J, O'Malley PM, Galea S, Pacula R, Feng T. (Departments of Epidemiology, Psychiatry and Biostatistics, Mailman School of Public Health, Columbia University, New York; New York State Psychiatric Institute, New York, NY; Institute for Social Research, University of Michigan, Ann Arbor; Institute for Social Research, University of Michigan, Ann Arbor, MI; RAND Corporation, Santa Monica, California; National Bureau of Economic Research, Cambridge, Massachusetts; Research Foundation of Mental Hygiene, New York, NY, USA.) Medical marijuana laws and adolescent marijuana use in the USA from 1991 to 2014: Results from annual, repeated cross-sectional surveys. *Lancet Psychiatry* 2015;**2:**601–8.

SUMMARY

Since the mid-2000s, there has been an increase in marijuana use amongst adolescents in the USA. Such use has been reported to be associated with impairment in memory, coordination and judgement in the short term and cognitive impairment, unemployment, psychiatric symptoms and substance addiction in the long term. It has been widely debated that legalization of marijuana use for medical purposes is one of the key reasons for increased marijuana use among adolescents. Since 1996, medical marijuana law has been passed by 23 states of the USA. It is feared that such laws may convey a message that marijuana use is acceptable, thus leading to an increase in its prevalence.

This study addressed two questions: first, whether adolescents were generally at a higher risk for marijuana use in states that ever passed a medical marijuana law by 2014 than adolescents in other states and second, whether adolescents in states that had passed medical marijuana laws were at a higher risk of marijuana use in the years immediately after the passage of the law than adolescents in those states before the passage of the law. The data were taken from the 'Monitoring the Future' study.[1] More than one million (1 098 270) adolescents were recruited in repeated cross-sectional surveys from 1991 to 2014 using a multistage, random sampling design with replacement. The various stages included schools within selected geographical areas (with probability proportionate to school size), and students within school. Up to 350 students per grade from VIII, X and XII grades were recruited. Students randomly selected within the schools, from over 400 schools in 48 contiguous US states (23 of which had passed medical marijuana laws) were asked to fill up self-administered questionnaires (containing questions on drug behaviour, attitude and related factors, background variables, and school experiences, role behaviour and satisfactions) in classrooms or larger group administrations using standardized procedures to maintain confidentiality. Primary outcome was taken as any 'marijuana use within previous 30 days'. Main exposure was 'state level medical marijuana laws'. Multilevel logistic regression modelling of adolescents nested within states was done by calculating adjusted odds ratio and prevalence. Further, a sensitivity analysis was done at various levels, such as fitting the multilevel model 48 times, replacing binary variables with ordered variables, using time varying variable, etc., which made the study more robust. The response rate of students was 81%–91%.

Twenty-one states had passed the medical marijuana law by 2014. The prevalence of marijuana use amongst adolescents in the previous 30 days was higher in the states that had passed such a law (adjusted prevalence 15.87% *v*. 13.27%; adjusted odds ratio 1.27, 95% CI 1.07–1.51; p=0.0057). However, further analysis revealed that states with a medical marijuana law had an increased prevalence of marijuana use even before the law was passed. Overall, the effect of medical marijuana laws on risk of marijuana use among adolescents before versus after passage of the law was not significantly different (adjusted prevalence 16.25% *v*. 15.45%; adjusted odds ratio 0.92, 95% CI 0.82–1.04; p=0.185). Sensitivity analysis did not affect the results. However, there was an unexpected finding that marijuana use was significantly reduced in VIII graders unlike X and XII graders after passage of the medical marijuana law. The authors attributed this to the possibility of more modifiable attitudes towards marijuana as well as more parental check against use in youngest adolescents after passage of the law. However, the authors did not examine additional variations in state medical laws (e.g. approved illnesses, amount of