Japanese Journal of Cancer and Oncology Research

Short Communication
Published: 19 Mar, 2018

Future Prospective of Delivery of Targeted Cancer Therapy for Improvement of Patients Survival

Stefan Mrdenovic[1] and Leland WK Chung[2]*

[1]*Department of Internal Medicine, University Hospital of Osijek, Croatia*

[2]*Department of Medicine, Cedars-Sinai Medical Center, USA*

Short Communication

Cytotoxic agents although effective in slowing progression in some tumors do not discriminate between normal and cancer cells and cannot produce effective therapeutic effects without doing extensive harm to healthy tissues. Treatment with cytotoxic drugs also inevitably leads to tumor resistance. Striving for new agents prolonging survival and curing cancer patients much effort was invested in targeted therapy. Monoclonal antibodies and small molecule tyrosine-kinase or serine/threonine kinase inhibitors have shown an increased advantage in treatment of numerous types of tumors. Efficacy of these agents is determined by numerous clinical measures. Most surrogate measures used in clinical testing of novel cancer agents are not actually reliable in predicting patient overall survival [1]. Cancer drugs are approved on the base of some proof of efficacy or benefit for the patient but recent data has shown that most novel cancer drugs approved in the European Union from 2009 to 2013 showed a minor benefit on improving median overall survival ranging from 1 to 5.8 months [2]. We must take into account that certain patients on the far end of the survival interval in these studies have a substantial benefit in overall survival. This is usually the case for less than 10 % of the patients and it's hard to predict whether their prolonged survival is solely due to the drug of interest or related to specific tumoral clonal evolution behavior. This also does not mean that these drugs are not effective but rather that their efficacy is probably limited to small selected groups of patients with specific tumor molecular alterations. We have presented a table regarding overall survival and overall survival gain for novel agents selected based on NCCN (National Comprehensive Cancer Network) recommendations given highest category of evidence and U.S. National Library of Medicine Clinical trials database for second-line/subsequent line of treatment for selected metastatic/relapsed/refractory tumors. We can see that selected agents provide median overall survival gain from 0 to 5. 4 months compared to prior considered *gold standard* agents or regimens in these settings. Only one study has shown a clear benefit in overall survival gain in treatment of patients with advanced melanoma with an anti PD-L1 monoclonal antibody pembrolizumab who had or had not received up to one previous systemic therapy (excluding anti-CTLA-4, PD-1, or PD-L1 agents) (median overall survival not reached) [3]. This fairly represents the today's state of cancer treatment regarding progress in prolonging survival. If striving for agents with curable effects these results seem rather discouraging. We must add that clinical breakthroughs in autologous chimeric antigen receptor (CAR)-T cell therapy in prolonging overall survival is not yet reported. Overall, it seems that drugs considered small molecule *targeted therapy* have many intracellular protein targets and are showing many side effects [4]. Additionally, intra- and inter-cellular redundant survival cell signaling network could present a formidable challenge to the intended targeted therapy. On the other hand, most, monoclonal antibodies and checkpoint inhibitors although marketed as remarkable breakthrough drugs seem only to impact a minority of patients in a subset of cancers and in most cases have no clear benefit to other conventional agents. Exception to this rule could be the immense impact of rituximab on B-cell lymphomas and chronic lymphocytic leukemia and trastuzumab on breast cancer in prolonging significant survival of these patients [5-7]. For majority of cancer patients, it remains unclear how best to mount clinically meaningful immune responses. It is despairing that most cancer patients with relapsed/refractory/metastatic disease that did not respond to some sort of cancer treatment have very limited survival ranging from one to two years, probably less in settings out of clinical trials, with a poor quality of life regardless to received novel highest category of evidence recommended drugs.

How to further proceed in finding more effective cancer agents? What we can see from the current *status quo* in cancer drug treatment is that most agents do not possess strong enough antitumor properties; they are not selective enough and are not thorough enough to eliminate all

OPEN ACCESS

Correspondence:
Stefan Mrdenovic, Department of Internal Medicine, University Hospital of Osijek, Osijek, Croatia,
E-mail: mrdenovic@gmail.com

Received Date: *27 Feb 2018*
Accepted Date: *12 Mar 2018*
Published Date: *19 Mar 2018*

Citation:
Mrdenovic S, Chung LWK. Future Prospective of Delivery of Targeted Cancer Therapy for Improvement of Patients Survival. Jpn J Cancer Oncol Res. 2018; 1(1): 1001.

Table 1: Overall survival and overall survival gain for novel cancer agents.

Tumor	Drug	Mechanism of action	Indication	Comparator	OS	OS gain	Study	Year
ALL	blinatumumab	Bispecific anti-CD3 and anti-CD19 mAb	patients with relapsed or refractory Ph- acute lymphoblastic	standard intensive chemotherapy	7.7	3.7	DOI: 10.1056/NEJMoa1609783	2017
	Inotuzumab ozogamicin	anti-CD22 mAb conjugated to calicheamicin	patients with relapsed or refractory Ph- acute lymphoblastic leukemia	standard intensive chemotherapy (standard-therapy group)	7.7	1	DOI: 10.1056/NEJMoa1509277	2016
Bladder cancer	Pembrolizumab	Anti PD-1 mAb	Reocurence or progression after platinum based chemotherapy	Paclitaxel, docetaxel, vinflunine	10.3	2.9	DOI: 10.1056/NEJMoa1613683	2017
	Atezolizumab	Anti PD-L1 mAb	Locally advanced or metastatic after platinum based chemotherapy	Paclitaxel, docetaxel, vinflunine	11.1	0.5	DOI: http://dx.doi.org/10.1016/S0140-6736(17)33297-X	2017
Breast cancer	Trastuzumab emtansine	Anti-HER2/neu conjugated to emtansine (DM1)	patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane.	capecitabine plus lapatinib	29.9	4	DOI: 10.1016/S1470-2045(17)30312-1.	2017
CNS tumors	bevacizumab	Anti-VEGF-A mAb	patients with recurrent glioblastoma	None	9.2	N/A	DOI: 10.1200/JCO.2008.19.8721	2009
Colorectal cancer	regorafenib	Multi-kinase inhibitor (VEGFR2-TIE2)	Patients with metastatic colorectal cancer and progression during or within 3 months after the last standard therapy	Best supportive care	6.4	1.4	DOI: http://dx.doi.org/10.1016/S0140-6736(12)61900-X	2012
	panitumumab	Anti-EGFR mAb	patients with metastatic colorectal cancer who had progressed after standard chemotherapy	Best supportive care	6	0	DOI: 10.1200/JCO.2006.08.1620	2007
Gastric cancer	Ramucirumab + paclitaxel	Anti VEGFR-2 mAb + taxane	progression for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma	paclitaxel	9.6	2.2	DOI: http://dx.doi.org/10.1016/S1470-2045(14)70420-6	2014
Head and neck cancer	Afatinib	HER2 and EGFR inhibitor	Patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (HNSCC) progressing after first-line platinum regimens	methotrexate	6.8	0.8	DOI: http://dx.doi.org/10.1016/S1470-2045(15)70124-5	2015
	Cetuximab + cisplatin/carboplatin + fluorouracil	Anti-EGFR mAb + platinum based ageent + thymidilate syntahse inhibitor	patients with untreated recurrent or metastatic squamous-cell carcinoma of the head and neck	cisplatin/carboplatin + fluorouracil	10.1	2.7	DOI: 10.1056/NEJMoa0802656	2008
Hepatobilliary cancer	regorafenib	Multi-kinase inhibitor (VEGFR2-TIE2)	patients with hepatocellular carcinoma (HCC) whose disease progresses during sorafenib treatment.	Best supportive care	10.6	2.8	DOI: http://dx.doi.org/10.1016/S0140-6736(16)32453-9	2017
Kidney cancer	Cabozatinib	MET, VEGFR, AXL inhibitor	Progression after VEGFR inhibitor Clear cell histology ccRCC	everolimus	21.4	4.9	DOI: http://dx.doi.org/10.1016/S1470-2045(16)30107-3	2016
	Nivolumab	Anti PD-1 mAb	Progression after VEGFR inhibitor ccRCC	everolimus	25	5.4	DOI: 10.1056/NEJMoa1510665	2015
	Sunitinib	PDGFR, VEGFRs, CD117, RET inhibitor	Patients with metastatic disease non-ccRCC	everolimus	16.2	1.3	DOI: 10.1016/j.eururo.2015.10.049.	2016
Lung cancer	Osimertinib + pemetrexed + carboplatin/cisplatin	EGFR inhibitor + folate antimetabolite + platinum based agent	patients with T790M-positive advanced non–small-cell lung cancer, who had disease progression after first-line EGFR-TKI therapy	pemetrexed + carboplatin/cisplatin	ongoing	ongoing	DOI: 10.1056/NEJMoa1612674	2017
	Atezolizumab + docetaxel	Anti PD-L1 mAb + taxane	patients with previously treated non-small-cell lung cancer	docetaxel	13.8	4.2	DOI: http://dx.doi.org/10.1016/S0140-6736(16)32517-X	2017
Melanoma	pembrolizumab	Anti PD-1 mAb	patients with advanced melanoma and up to one previous systemic therapy (excluding anti-CTLA-4, PD-1, or PD-L1 agents)	ipilimumab	Not reached	Not reached	DOI: http://dx.doi.org/10.1016/S0140-6736(17)31601-X	2017

Ovarian cancer	Bevacizumab + either liposomal doxorubicin, paclitaxel or topectan	Anti-VEGF-A mAb + either liposomal alkylating agent, taxane drug or a topoisomerase inhibitor	Patients with platinum-resistant recurrent ovarian cancer	Liposomal doxorubicin, paclitaxel or topectan	16.6	3.3	DOI: 10.1200/ JCO.2013.51.4489	2014
Pancreatic cancer	Albumine bound paclitaxel + gmecitabine	Protein bound taxane + pyrimidine nucleoside analouge	patients with advanced pancreatic cancer	Gemcitabine	8.5	1.8	DOI: 10.1056/ NEJMoa1304369	2013
	Erlotinib + gemcitabine	EGFR inhibitor + pyrimidine nucleoside analouge	patients with unresectable, locally advanced, or metastatic pancreatic cancer.	Gemcitabine	6.2	0.3	DOI: 10.1200/ JCO.2006.07.9525	2007
Prostate cancer	enzalutamide	Nonsteroidal antiandrogen	men with metastatic castration-resistant prostate cancer after docetaxel therapy	placebo	18.4	4.8	DOI: 10.1056/ NEJMoa1207506	2012
	Abiraterone acetate + prednisone	steroidal CYP17A1 inhibitor	men with metastatic castration-resistant prostate cancer after docetaxel therapy	Placebo + prednisone	15.8	4.2	DOI: 10.1056/ NEJMoa1014618	2011

cancer cells regardless of their resistance or *stemness* properties. We clearly have to further enhance drug delivery to reduce toxicity to normal cells and increase cancer cell killing capabilities by finding ways to effectively remove the complete tumor population, inducing complete remissions and preventing relapses. An emerging idea to achieve this is by repurposing the already effective conventional cytotoxic agents with a wide variety of specific cancer cell targeting moieties like antibodies, aptamers, small protein scaffolds, peptides and low-molecular-weight non-peptidic ligands [8]. While antibody-drug conjugates are dominating the field, and have shown some promising clinical results, like brentuximab vedotin in Hodgkin lymphoma and anaplastic large cell lymphoma, trastuzumab emtansine in breast cancer and inotuzumabozogamicin in ALL their mechanism for proper and completely effective drug delivery is still under development [9]. There is a focus in development of small molecule ligand drug conjugates. Agents using delivery strategies like σ2-opioid receptor [10], folate receptor [11], carbonic anhydrase IX inhibitor [12], PSMA [13]or HSP90 [14] ligands and cytotoxic drugs have shown great results and some have or are in process of entering clinical trials.

σ2-opioid receptor ligand-SMAC mimetic conjugate SW IV-134 has shown increased survival *in vivo* mouse pancreatic cancer xenograft models increasing median overall survival for 36 days compared to vehicle (88 *vs*. 52 days) [10]. Combining the drug with gemcitabine there was no evidence for increased survival but combining the two drugs presented with an increased median overall survival compared to gemcitabine alone (60 *vs*. 46 days) [15]. STA-8666, a novel HSP90 inhibitor/SN-38 drug conjugate has showed increased overall survival *in vivo* mouse Ewing sarcoma and osteosarcoma xenograft models, with median overall survival not reached with STA-8666 compared to irinotecan and ganetespib and increased overall survival in Ewing sarcoma mouse PDX model with median overall survival not reached with STA-8666 compared to irinotecan and irinotecan + ganetespib(14). Furthest evidence was provided with vinca alkaloid DAVLBH-folic acid derivative conjugate vintafolide in folate receptor expressing tumors. In preclinical studies human nasopharyngeal carcinoma and murine B-cell lymphoma mouse models were tested with complete curative results in both models [11]. The drug was subsequently evaluated in two clinical trials. In a PROCEED phase III trial for the treatment of platinum-resistant ovarian cancer there was no difference in PFS and OS in combination of vintafolide with pegylated liposomal doxorubicin (PLD) or PLD alone. In the ongoing TARGET trial comparing vintafolide as second-line treatment with vintafolide plus docetaxel and docetaxel alone in patients with non-small cell lung cancer (NSCLC) who have FR++ tumors there is evidence for increased overall survival in the vintafolide + docetaxel arm (11.5 *vs*. 8.8 months) [16].

These results encourage use of small molecule drug conjugates as a new path in cancer drug development but there is still a need in increasing drug killing capabilities with agents able to produce rapid cell death in all tumor cells employing mechanisms bypassing either intrinsic or acquired tumor drug resistance. This could be achieved by conjugating delivery of multiple effective drug molecules specifically to cancer cells to eliminate their ability to survive through targeting cancer cell organelles such as mitochondria and lysosomes that could subject cancer cells to metabolic starvation.

References

1. Prasad V, Kim C, Burotto M, Vandross A. The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses. JAMA Intern Med. 2015;175(8):1389-98.
2. Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ. 2017;359.
3. Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017;390(10105):1853-62.
4. Caldemeyer L, Dugan M, Edwards J, Akard L. Long-Term Side Effects of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia. Curr Hematol Malig Rep. 2016;11(2):71-9.
5. Salles G, Barrett M, Foa R, Maurer J, O'Brien S, Valente N, et al. Rituximab in B-Cell Hematologic Malignancies: A Review of 20 Years of Clinical Experience. Adv Ther. 2017;34(10):2232-73.
6. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant

chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-205.

7. Mendes D, Alves C, Afonso N, Cardoso F, Passos-Coelho JL, Costa L, et al. The benefit of HER2-targeted therapies on overall survival of patients with metastatic HER2-positive breast cancer – a systematic review. Breast Cancer Res. 2015;17(1):140.
8. Srinivasarao M, Galliford CV, Low PS. Principles in the design of ligand-targeted cancer therapeutics and imaging agents. Nat Rev Drug Discov. 2015;14(3):203-19.
9. Beck A, Goetsch L, Dumontet C, Corvaia N. Strategies and challenges for the next generation of antibody-drug conjugates. Nat Rev Drug Discov. 2017;16(5):315-37.
10. Hashim YM, Spitzer D, Vangveravong S, Hornick MC, Garg G, Hornick JR, et al. Targeted pancreatic cancer therapy with the small molecule drug conjugate SW IV-134. Mol Oncol. 2014;8(5):956-67.
11. Reddy JA, Dorton R, Westrick E, Dawson A, Smith T, Xu LC, et al. Preclinical evaluation of EC145, a folate-vinca alkaloid conjugate. Cancer Res. 2007;67(9):4434-42.
12. Krall N, Pretto F, Decurtins W, Bernardes GJ, Supuran CT, Neri D. A small-molecule drug conjugate for the treatment of carbonic anhydrase IX expressing tumors. Angew Chem Int Ed Engl. 2014;53(16):4231-5.
13. Kumar A, Mastren T, Wang B, Hsieh JT, Hao G, Sun X. Design of a Small-Molecule Drug Conjugate for Prostate Cancer Targeted Theranostics. Bioconjug Chem. 2016;27(7):1681-9.
14. Heske CM, Mendoza A, Edessa LD, Baumgart JT, Lee S, Trepel J, et al. STA-8666, a novel HSP90 inhibitor/SN-38 drug conjugate, causes complete tumor regression in preclinical mouse models of pediatric sarcoma. Oncotarget. 2016;7(40):65540-52.
15. Hashim YM, Vangveravong S, Sankpal NV, Binder PS, Liu J, Goedegebuure SP, et al. The Targeted SMAC Mimetic SW IV-134 is a strong enhancer of standard chemotherapy in pancreatic cancer. J Exp Clin Cancer Res. 2017;36(1):14.
16. Vergote I, Leamon CP. Vintafolide: a novel targeted therapy for the treatment of folate receptor expressing tumors. Ther Adv Med Oncol. 2015;7(4):206-18.