Chapter

Cancer Management by Tyrosine Kinase Inhibitors: Efficacy, Limitation, and Future Strategies

Venice Wing Tung Ho, Hor Yue Tan, Ning Wang and Yibin Feng

Abstract

Tyrosine kinase inhibitors are taking up an increasingly significant role in treating cancers. There are different types of TKIs currently used in clinical settings. However, TKI-associated limitations such as resistance and adverse effects are frequently reported. In this chapter, we would comprehensively review the clinical efficacy of current TKIs using the currently available clinical trial data. Significant limitations of TKIs on cancer treatment will be further summarized and discussed. The strategies on overcoming the limitations of TKIs to maximize their clinical effectiveness and efficiency, such as complementary use of Chinese medicine or development of novel TKIs, will be proposed. In conclusion, an overall picture of the clinical use and limitation of the current TKIs will be drawn and the prospective development in overcoming the limitations will be discussed. Evaluation of clinical efficacy of TKIs, evaluation of limitations of TKIs, strategies in overcoming the limitations of TKIs, and conclusion (including prospective development of TKIs) are discussed below.

Keywords: tyrosine kinase inhibitors, targeted therapy, cancer management, clinical efficacy, limitations, future strategies

1. Introduction

The development of tyrosine kinase inhibitors (TKIs) is revolutionary in treating cancers, as they act much more specifically toward malignant cells when compared to conventional cytotoxic chemotherapy [1]. In the past two decades, a plenty of novel compounds under this category have been discovered and are taking up an increasingly significant role in cancer treatment, especially for metastatic carcinomas. Many are proven with great efficacy. They showed significantly better results in progress-free survival rate with fewer side effects [1]. Looking back at the short but eventful history of this drug class, this book chapter intends to do an evaluation on clinical efficacy and effectiveness of TKIs, basing on the currently available clinical trial data. Significant limitations of TKIs on cancer treatment will be further summarized and discussed. Finally, strategies in overcoming the limitations will be proposed. With an overall picture of clinical use and limitations of current TKIs, prospective developmental directions will then be discussed.

Tyrosine kinases are a subclass of protein kinases, which are enzymes that catalyze the transfer of gamma phosphate group from a nucleoside triphosphate donor (e.g., ATP) to targeted proteins, hence resulting in a conformational change of the protein, which alters its function [2]. Tyrosine kinases are frequently involved in the cellular response to various growth factors, cytokines, and hormones (e.g., EGF, PDGF, VEGF, ABL, and JAK) [3, 4]. These molecules are, in many cases, responsible for the various mechanisms of tumor growth such as cell growth, cell proliferation, stromal growth, angiogenesis, and tissue invasion [4, 5]. In neoplasms, there are often gene mutations resulting in activation of the above pathways [6, 7]. It could be an excessive expression of growth factors/hormones, an excessive expression of their receptors (i.e., increased sensitivity to receptor tyrosine kinases), or intrinsic activation of tyrosine kinases receptors, etc. [7]. Thus, by inhibiting them, we may be able to control or even regress tumor growth.

Tyrosine kinases inhibitors (TKIs) inhibit these growth factor signaling pathways by various mechanisms. They compete with ATP, substrate or for sites for dimerization, and could also act allosterically [8]. By targeting these mutated pathways, TKIs are able to act specifically to cells with malignant changes and disrupt their malignant growth without causing much disturbance to other physiological functioning.

Imatinib was the first tyrosine kinase inhibitor developed, and also the first to be approved by the U.S. Food and Drug administration (FDA) in May 2001. It was approved initially for the use on patients with chronic myeloid leukemia. Shortly after, other tyrosine kinase inhibitors are discovered. There are currently at least 26 FDA-approved tyrosine kinase inhibitors [9] and more going down the pipeline. TKIs were initially only used as second-/third-line therapies, but nowadays, it is increasingly used as primary therapy, especially in selected patients with known mutations.

Tyrosine kinase inhibitors can be classified according to their acting target [10]. Major target classes include BCR-ABLTKIs (e.g., imatinib, dasatinib, and nilotinib), EGFR TKIs (e.g., gefitinib and erlotinib), and VEGFR TKIs (e.g., sunitinib and sorafenib) [10]. Another way to classify them would however be according to their generations. There are up to three, and even four, generations of TKIs. They differ not only by the period they are discovered, but also by their working mechanisms. The first-generation TKIs (e.g., imatinib and gefitinib) are reversible/competitive inhibitors (mostly ATP-competitive inhibitors) and are mostly single-targeted, whereas the second-generation TKIs (e.g., afatinib and dasatinib) and other newer generations of TKIs (e.g., osimertinib) are mostly irreversible/covalent binding and multitargeted [11]. Comparison of approaches used in first and newer generations will be made in later sections.

When compared to traditional chemotherapy and radiation therapy, which simply targets fast-growing cells, TKIs, along with many other targeted drugs, have a much higher specificity toward tumor cells. Thus, they provide a broader therapeutic window with less general toxicity. They are taking up a large role in treating cancers by showing significant improvements in progression-free survival rate and tolerability in patients.

2. Evaluation of clinical efficacy/effectiveness of TKIs

Numerous studies have been conducted to evaluate the clinical efficacy and effectiveness of TKIs. Different TKIs are found to have different clinical performances on different cancers. Most of them showed significant efficacy, especially in improving progression-free survival (PFS), when used as first-line or non–first-line therapies. Therefore, a lot of studies are trying to expand the use of these TKIs to other

cancers, yet results are not always promising. However, overall survival was not improved in many cases. A lot of the studies discovered a high percentage of users progressing to drug resistance eventually. In the following, the clinical efficacy and effectiveness of a number of TKIs will be discussed individually. And in the end of this section, a brief comparison is drawn.

2.1 Clinical efficacy/effectiveness of first-generation TKIs

2.1.1 Imatinib (BCR-ABL TKIs)

Imatinib is an orally administered small molecule tyrosine kinase inhibitor, which inhibits tyrosine kinases, specifically BCR-ABL, c-KIT, and PDGFRA [12]. Its marketing name is Gleevec (USA) or Glivec (Europe/Australia), also referred to as CGP57148B or STI571 in some literature [13]. It was invented in 1990s and first approved by FDA in 2001. It has been a huge success and was a revolutionary discovery in combating cancer. Up till today, Imatinib is well known for its efficacy with CML and GIST, and other tumors. A summary on its clinical efficacies will be provided as follows:

2.1.1.1 Chronic myeloid leukemia (CML)

Imatinib is first developed against chronic myeloid leukemia (CML). CML is characterized by the presence of a Philadelphia chromosome [14], which is a product of reciprocal translocation between chromosome 9 and 22. BCL-ABL tyrosine kinase is overexpressed in these CML patients and is a driving force for leukemogenesis [15]. By inhibiting the BCL-ABL tyrosine kinase, Imatinib is found to be able to control the disease effectively. Imatinib has proven significant clinical efficacy and effectiveness, both as a single agent or in combination therapy in chronic phase as well as accelerated phase/blast crisis in CML.

Imatinib, as a single agent, outperformed combined chemotherapy and interferon therapy with major cytogenic response induced in 87.1% (vs. 34.7%) at 18 months [16]. Imatinib also showed significant superiority, when combined with chemotherapy, against the combination of interferon therapy and chemotherapy. In a well-known International Randomized Study (IRIS) on 1106 newly diagnosed CML patients, complete hematological response was induced in 95.3% patients and complete cytogenic response in 73.8% patients [17]. The patients have an overall low risk of progressing to accelerated phase/blast crisis, and overall survival rate at 8 years remained as high as 85% [18] exceeding the reported survival rates in all previous CML therapies. Other studies trying to combine imatinib with other therapies, including chemotherapy and IFN, showed that MCR/CCR did tend to occur earlier, for example, rate of MCR at 3 months was 70% compared to 60% when combining imatinib with cytarabine. Yet the gap seemed to close after 12 months, with 84 and 83%, respectively. Combinations have however also resulted in more severe side effects, and are thus in general not preferred [19]. Other studies echo their results and have shown that imatinib in combination with chemotherapy does not display superiority against imatinib as a monotherapy in CML-chronic phase, but instead yielded more toxicity [20, 21].

Imatinib is proved effective in accelerated phase/blast crisis as well [19, 22]. However, there are also studies reporting that its effects are only transient, and can only produce palliative function to those patients at this stage [23]. Acquired resistance developed in a large portion of the cases treated with imatinib. Acquired resistance was defined as a progression of disease or loss of response with a 5- to 10-fold increase in BCL-ABL transcripts. These patients are subsequently treated

with higher dosage of imatinib, or a second-generation BCR-ABL TKI. Yet, allogenic hematopoietic cell transplantation remains the ultimate solution.

Response rate of imatinib in unselected CML patients is high only due to the high occurrence (91%) of the presence of Philadelphia chromosome [24, 25]. Its clinical efficacy in Philadelphia chromosome negative patients is however very low.

2.1.1.2 Gastrointestinal stromal tumors (GIST)

Gastrointestinal stromal tumor is the most common neoplasm of the mesenchymal cells of the digestive system and is thought to arise from the interstitial cells of Cajal [26]. C-KIT and PDGFRA tyrosine kinase mutations are present in a vast majority (85%) of these tumors [27–29]. Imatinib is able to inhibit the mutant C-KIT and PDGFRA tyrosine kinases. Imatinib has high efficacy against GIST in patients with these two mutations, both as an adjuvant therapy after surgery in non-metastatic GISTs, and as a palliative treatment for advanced non-resectable GISTs. For primary resectable GISTs, recurrence rate after surgery is extremely high. Studies have found that adjuvant therapy of imatinib can prolong relapse free survival (RFS), especially in those patients with great risks of relapse [30, 31]. Absolute relapse rate was 19 vs. 47% in imatinib treated patients and non-treated patients, respectively [30, 32]. Other studies have shown that imatinib displays similar promising results in GISTs in advanced stages as well. Approximately 80% of GIST patients with advanced disease receive some benefit from imatinib therapy [33], with median overall survival of 57 months, compared to 18 in chemotherapy. Yet, a significant proportion eventually became resistant with a median time to progression of 2 years [33]. Primary resistance was found in around 12% of the patients [34]. It was also found that, higher dosage of Imatinib showed no superiority over lower dosage [35, 36]. In GIST patients, side effects arose in 99% of the case [37]. The most common adverse events were diarrhea (29% of patients), nausea (27%), eyelid edema (23%), peripheral edema (22%), muscle cramps (15%), and fatigue (13%) [38]. Luckily, most patients found the side effects tolerable [37].

2.1.1.3 Others

Imatinib was also approved by the FDA and has now become the first-line treatment for patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph + ALL), which accounts for approximately 30% of all ALL cases [39]. Patients treated with imatinib early are found to have higher overall survival, event-free survival, and relapse-free survival [40]. Studies have also justified the efficacy of imatinib in dermatofibrosarcoma protuberans [41, 42], chronic eosinophilic leukemia [43], systemic mastocytosis [44, 45], aggressive fibromatosis [46], malignant melanoma [47], AIDS-related Kaposi's sarcoma [48], chordoma [49, 50], recurrent epithelial ovarian cancer [51], and anaplastic thyroid cancer [52]. The use of imatinib in these cancers is not yet approved, but lots of clinical trials have already been conducted and their use in the future is expected.

2.1.1.4 Tolerability of side effects

Clinical trials have shown that the side effects of imatinib are generally well-tolerated by the patients. Common side effects include edema, rash, nausea, diarrhea, muscle cramps, and more severely, myelosuppression [53]. Luckily, most side effects were mild to moderate, and in more than 95% of the patients, side effects could be managed with standard concomitant treatments [38].

2.1.2 Gefitinib and erlotinib (EGFR TKIs)

Gefitinib (Iressa, ZD1839) and erlotinib (Tarceva, OSI774) are the two first-generation EGFR-TKIs and are used mostly against non-small cell lung cancer (NSCLC), which accounts for 85% of all lung cancers [54]. As competitive antagonists of the ATP-binding site of EGFR, gefitinib and erlotinib were approved by the FDA in May 2003 and November 2004, respectively. As many cancers involve the hyperactivity of EGFRs, numerous studies have been conducted on drug repurposing of these two TKIs.

2.1.2.1 Non-small cell lung cancer

Gefitinib and Erlotinib are most established in treating non-small cell lung cancer (NSCLC) and are currently the first-line treatment for EGFR-mutated NSCLC patients [55]. EGFR mutations are commonly found in NSCLC patients, particularly in Asian populations, female gender, and nonsmokers [56, 57]. EGFR mutations are associated with the activation of antiapoptotic pathways as well as proliferation induction, thus leading to uncontrolled growth of cells. Among all the types of NSCLC, adenocarcinoma takes up the largest proportion, and is also the most commonly associated with EGFR mutations. Gefitinib was initially approved against NSCLC, but was then withdrawn from the market due to various studies showing its lack of benefit in overall survival in unselected patients. However, it was later found that EGFR mutation is a huge positive predicting factor for drug response to gefitinib, and was thus approved again. Gefitinib has well established clinical efficacy against advanced NSCLC when compared to chemotherapy [58, 59]. Progression-free survival was 10.8 vs. 5.4 months and mean overall survival was 30.5 vs. 23.6 months [59]. Combination of gefitinib with chemotherapy showed no superiority over gefitinib monotherapy [60]. Similarly, Erlotinib showed significant superiority over chemotherapy in EGFR mutation positive advanced NSCLC (PFS 13.1 vs. 4.6 months) [61]. However, its overall survival was reported to be lower than that of chemotherapy (24.68 vs. 26.16 months) [62]. Erlotinib plus chemotherapy is superior to chemotherapy alone with an improved PFS but not OS [63]. A meta-analysis revealed that the efficacy between gefitinib and erlotinib are comparable with erlotinib reported of more adverse drug effects [64].

Clinical effectiveness in unselected NSCLC patients were low as the frequency of EGFR gene mutation is 47.9% in Asians but only 19.2% in Western patients [65]. About only 10–35% of the NSCLC patients have EGFR mutations which are sensitive to the EGFR TKIs [66]. Progression-free survival in rare EGFR mutations was also lower than that of common EGFR mutations, yet the overall survival was similar [67, 68].

2.1.2.2 Other

There are currently some researches conducted on the use of gefitinib and erlotinib on other cancers, yet most are currently not approved yet. Gefitinib is reported to show effect on pancreatic cancer [69] and is approved to treat metastatic pancreatic cancer in combination with chemotherapy in 2005. The effects of gefitinib and erlotinib on other cancers are also being investigated, such as nasopharyngeal cancer [70], gastric cancer [71], esophageal cancer [72], cervical cancer [73], renal cell carcinoma [74], and hepatocellular carcinoma [75]. Yet most studies are still in preclinical stages, and those limited clinical trials were often with disappointing results.

2.1.2.3 Tolerability of side effects

Gefitinib has better tolerability than many cytotoxic drugs [76]. Acne-like rash was reported as the most common side effect, others include nausea, diarrhea, anorexia, stomatitis, dehydration, etc. Side effects were in general well-tolerated and few withdraw from gefitinib due to intolerability [76]. Erlotinib is in general well tolerated as well. Yet it was reported to have more severe side effects than that of gefitinib and was more frequently involved with dosage reduction due to side effect intolerance [77]. Significantly higher rates and severity of skin rash, nausea, vomiting, fatigue, and stomatitis were also reported.

2.1.3 Sunitinib and sorafenib (VEGFR TKIs)

Sunitinib (Sutent, SU11248) and sorafenib (Nexavar) are first-generation VEGFR-TKIs and are well established in the use against renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC), respectively. The VEGF family are frequently overexpressed in various solid tumors and bind to vascular endothelium and induce angiogenesis. Sunitinib and sorafenib are both multitarget ATP-competitive TKIs. Sunitinib inhibits tyrosine kinases such as VEGFR2, PDGFRβ, KIT, RET, CSF1R, and FLT3. Sorafenib inhibits tyrosine kinases including VEGFRs, PDGFRs, B-RAF, MEK, and ERK. They are both FDA approved for RCC, GIST and RCC, HCC, respectively. Their clinical efficacies are discussed below.

2.1.3.1 RCC

VEGF overexpression and high vascularization is a common feature of RCC. Both sunitinib and sorafenib were approved for renal cell carcinoma as first- and second-line therapies. Sunitinib was approved for metastatic RCC (mRCC) in 2006 after a phase III trial showing its superiority over IFN therapy [78]. Sunitinib displayed well clinical efficacy and effectiveness with median OS 26.4 months and PFS 11.0 months, especially in clear cell RCC, compared to OS 21.8 months in IFN therapy [78]. However, study also showed that median PFS and OS are not significantly different in poor-risk group [79]. Finally, a large scaled clinical trials conducted on unselected heterogeneous RCC patients confirmed the effectiveness of sunitinib [80]. Combination of sunitinib with chemotherapy was not explored after phase I trials showing its poor safety profile [81]. Trials combining sunitinib with other therapies have also shown no improved efficacy, yet increased toxicity [82]. On the other hand, Sorafenib was also proven to have high clinical efficacy against mRCC, both as first- and second-line therapy [83]. It was found to prolong PFS when compared to placebo after the failure of immunotherapy [84]. Yet there is no statistically significant difference in OS. Studies comparing efficacy of sunitinib and sorafenib showed no significant difference, with sorafenib slightly superior in elderly patients [85]. Sequence of use of sunitinib and sorafenib also has no significant difference [86].

2.1.3.2 HCC

Preclinical studies have demonstrated that MEK and ERK pathways play a role in hepatocellular carcinoma [87]. VEGF pathway also plays a significant role in angiogenesis in HCC [88]. This provides a window of opportunity of prolonging survival through TKIs targeting these pathways, including sorafenib. For unresectable HCC, especially in cases where potential curative methods or transarterial chemoembolization (TACE) are not available, Sorafenib is highly recommended as it demonstrates high clinical efficacy [89]. Sorafenib was reported with 3 months

longer in median overall survival (10.7 vs. 7.9) when compared to placebo [90]. Yet there was no significant difference in the median progression time to symptomatic progression [91]. Sorafenib, when combined with chemotherapy, also showed superiority over chemotherapy alone, with PFS 6.0 vs. 2.7 months and OS 13.7 vs. 6.5 months [92]. Yet it has poor effectiveness in generalized HCC patients and many argue that its efficacy is questionable [93].

2.1.3.3 GIST

Sunitinib is used against GIST as well and has been approved for usage following failure/intolerance of imatinib in 2006 [94]. The median time to progression was 27.3 weeks compared to 6.4 weeks in placebo [95]. There was no overall survival benefit of sunitinib over placebo, but the results were not reliable due to crossing over of placebo patients to sorafenib group. Studies have been conducted to modify the patient selection procedure in attempt to further raise its effectiveness, but are all in vain [96]. On the other hand, sorafenib also showed certain efficacy toward GIST. Yet its efficacy was lower than that of imatinib, and was thus only used as third/fourth line, after failure of initial therapy [97].

2.1.3.4 Differentiated thyroid cancer (DTC)

Sorafenib is also approved for use against advanced thyroid cancer which are resistant to radioactive iodine. Prior to the discovery of sorafenib, there was no effective treatment for this group of patients and overall survival was poor [98]. With sorafenib, a phase III trial showed that their PFS is greatly improved when compared to placebo (10.8 vs. 5.8 months) and thus provides a new treatment option for radioactive iodine resistant advanced DTC patients [99].

2.1.3.5 Tolerability of side effects

Compared to other TKIs, the tolerability of sunitinib is lower. Adverse events of any grade are reported in up to 95% of patients with one-third drug interruption due to intolerability in metastatic RCC [100]. Most common grade 3/4 adverse events include thrombocytopenia (10%), fatigue (9%), and asthenia, neutropenia and hand foot mouth syndrome (each 7%) [80]. It is commonly associated with various side effects including hypertension, hypothyroidism, diarrhea, fatigue, and nausea. Therefore, studies have recommended a special schedule for the administration for this reason, with 2-week drug use followed by a 1-week drug holiday alternatively, which offers a similar efficacy but with higher tolerability [101–103]. Sorafenib has a slightly better safety profile [104]. Safety profile agrees with what is previously reported, with hand–foot skin reaction (58.0%), lipase elevation (57.3%), and diarrhea (42.7%) as the most frequent drug-related adverse events. Neither unknown adverse event nor cumulative toxicity was observed over the long-term use of sorafenib [105]. Yet intolerability remains one of its greatest limitations.

2.2 Clinical efficacy/effectiveness of second-generation TKIs

2.2.1 Dasatinib, nilotinib, bosutinib, and radotinib (BCR-ABL TKIs)

Following the success of Imatinib, many second-generation TKIs targeting BCR-ABL have also been developed. These include dasatinib, nilotinib, bosutinib, and radotinib, and also a few more that will not be included in this discussion, including

ON012380, MK0457, PHA739358, etc. They are much more potent than imatinib and showed promising efficacy in treating patients who have failed imatinib treatment [106].

Dasatinib (Sprycel, DB01254) was the first FDA approved among them and is a dual Src and ABL kinase inhibitor. Besides binding to these two kinases, it also has inhibitory effect on PDGFRβ, c-KIT, and EPHA2 [107]. By targeting more kinases than those of imatinib, dasatinib is able to tackle multiple types of resistant mechanisms against imatinib, including secondary BCR-ABL mutation, alternative Src signaling pathway activation, and multidrug resistance gene overexpression. Study showed durable results of treatment with dasatinib following imatinib. Imatinib resistant/intolerant patients showed early (3–6 months) complete cytogenic response and major molecular response, and were associated with better PFS and OS rates [108, 109]. When compared to imatinib as first-line treatment to newly diagnosed CML, dasatinib showed even better response. It was able to achieve higher percentage of complete cytogenic response and major molecular response with a higher rate [110].

Nilotinib (Tasigna, AMN107), on the other hand, is more structurally similar to imatinib, but is 20–50 folds more potent. Nilotinib was another huge success. It was able to induce complete hematological response in 92% of the patients who were resistant/intolerant to imatinib [111]. Similarly, it was also found to be superior as first-line treatment than imatinib for newly diagnosed Ph + CML [112]. Both Dasatinib and Nilotinib are found to give similar results in large community settings as well. When compared to first-generation TKI imatinib, dasatinib and nilotinib performed significantly better as first-line treatment to newly diagnosed CML patients. They achieve higher Complete Cytogenic Response (CCyR) or Major Molecular Response (MMR) at 6, 12, and 18 months, respectively. By 12 months, 61% patients achieved CCyR or MMR compared to only 38% treated with imatinib. Time to MMR is also significantly higher in dasatinib and nilotinib than imatinib [113].

Bosutinib (Bosulif, SKI606) was initially approved in CML-AP/BC, and is later expanded to CML-CP. Trials prove improved rates of MMR at 12 months when compared to imatinib (47.2 vs. 36.9%) [114]. Soon it was also used as first-line therapy against CML.

Radotinib (Supect, IY5511) also showed significant superiority over imatinib. With minimum 12 months follow-up, radotinib demonstrated significantly higher and faster rates of CCyR and MMR than imatinib in patients with newly diagnosed CML-CP [115].

2.2.1.1 Tolerability of side effects

The second-generation BCR-ABL TKIs seem to have significantly higher efficacy than imatinib. Yet, their side effects are also more severe than that of imatinib. This is likely due to the increased potency as well as multi-targeting of the drugs. For example, when comparing bosutinib to imatinib, patients taking bosutinib have higher rates of increased liver enzyme values (24 vs. 4%), thrombocytopenia (13.8 vs. 5.7%), neutropenia (6.7 vs. 12.1%), and diarrhea (7.8 vs. <1%). 77.9% patients experienced severe Grade 3/4 adverse events and 24% patients had to discontinue bosutinib therapy due to emergence of adverse events in a study [116]. Radotinib's side effects are also more severe than that of imatinib. Grade 3/4 ALT/AST elevations caused 68% dosage reduction/interruption in radotinib patients, but only 19% in imatinib patients.

2.2.2 Afatinib and dacomitinib (EGFR TKIs)

Second-generation EGFR TKIs are irreversible inhibitors and are designed to target other ErbB family members, including HER2, to have more potent inhibition.

They target not only the T790M mutation of EGFR, but also other EGFR-activating mutations as well as wild-type EGFR [117].

Afatinib (Gilotrif, BIBW2992) is an irreversible inhibitor for the ERBB family, including HER1(EGFR), HER2, and HER4. Studies have proven that afatinib was effective in prolonging PFS when compared to chemotherapy (median PFS 11.1 vs. 6.9 months) [118]. When compared to erlotinib, afatinib can also significantly increase PFS by 18%, improve OS by 19% and improve disease control rate (51 vs. 40%) in NSCLC patients after failure of chemotherapy. It was eventually approved by FDA as another first-line therapy for NSCLC.

Dacomitinib (PF299804) is also an irreversible inhibitor of the ERBB family, including HER1(EGFR), HER2 and 4. It is currently still in the preregistration stage and is not approved yet in any country. Findings have shown superiority over gefitinib: PFS 14.7 months with dacomitinib vs. 9.2 months with gefitinib as first-line therapy [119, 120].

Second-generation EGFR-TKIs exhibit many dose-limiting toxicities, mainly skin and GI toxicities, as they inhibit WT-EGFRs as well [117].

2.2.3 Pazopanib, tivozanib, axitinib, and regorafenib (VEGFR TKIs)

Pazopanib (Votrient, GW786034B) was compared to sunitinib and showed superiority. It was shown to significantly improve PFS when compared to placebo in both treatment naïve and cytokine-pretreated patients of RCC [121]. Similar to the first-generation VEGFR-TKIs, Pazopanib inhibits a large number of pathways, including VEGFR, c-KIT, FGFR, PDGFRβ. The lack of specificity accounts for its multiple side effects. Yet, its tolerability is higher than that of sorafenib and sunitinib [122, 123].

Tivozanib and axitinib on the contrary, are well-known for their higher selectivity. Tivozanib (Fotivda, AV-951) is highly selective for VEGFR. In a study conducted on metastatic RCC, Tivozanib outperformed sorafenib as first-line treatment in prolonging PFS [124]. The study revealed that Tivozanib improved PFS in RCC by 3 months (30%) when compared to sorafenib, yet has an inferior overall survival [124, 125]. For this reason, it is unable to obtain approval from FDA. It was however approved by the European Medicines Agency (EMA). Axitinib (Inlyta, AG13736) is also highly selective for VEGFR. Axitinib was proved to be better than sorafenib in treating RCCs by giving longer PFS (6.8 vs. 4.7 months) in pretreated patients and are thus approved as second-line use.

Regorafenib (STIVARGA) is approved by the FDA in 2012 for its use in metastatic colorectal cancer (mCRC) and GIST. Regorafenib monotherapy was found to significantly improve OS (6.4 vs. 5.0 months) in mCRC when compared to placebo following failure of standard therapy [126]. Soon after, its efficacy in GIST was also found. A clinical trial compared patients treated with regorafenib monotherapy vs. placebo after acquiring resistance against imatinib and sunitinib [127]. PFS was way higher in regorafenib group (4.8 vs. 0.9 months) and is thus approved by the FDA. OS was however not determined as the patients in the placebo group were crossed over to the regorafenib group after disease progression.

2.2.3.1 Tolerability of side effects

Their tolerability is significantly better than sorafenib, especially with tivozanib. Drug dosage reduction due to intolerance was 11.6% in tivozanib, but 42.8% in sorafenib [125].

2.3 Clinical efficacy/effectiveness of third-generation TKIs

2.3.1 Ponatinib (BCR-ABL TKIs)

Ponatinib (Iclusig, IY5511) is a multitargeted TKI including BCR-ABL. It was specifically designed for T315I mutation-caused imatinib resistance. Studies have proven its high clinical efficacy of inducing cytogenic response in 66% CML-CP patients, which include all of the T315I mutation positive patients. Yet, in generalized CML-CP patients, ponatinib did not show significantly superior efficacy than the previous second- and first-generation TKIs [128]. Thus, it is suggested for first-line use only in the setting of detected T315I mutation, otherwise, merely as a second-line treatment following first- and second-generation TKIs.

2.3.1.1 Tolerability of side effects

Treatment-related side effects are moderately significant with ponatinib. Common adverse events include rash (47%), abdominal pain (46%), thrombocytopenia (46%), headache (43%), dry skin (42%), and constipation (41%). It is however associated with a severe adverse event, which is arterial occlusive events (AOE), which occurred in a cumulative of 31% patients.

2.3.2 Osimertinib (EGFR)

Due to the limited efficacy in tackling T790M resistance of EGFR of the second-generation TKIs, the third generation of EGFR-TKIs has been discovered. Third generation works significantly better against the T790M-mutated EGFR while sparing the wild-type EGFRs, making them very mutant selective. Various third-generation EGFR-TKIs are currently under clinical trials, including osimertinib, PF06747775, YH5448, avitinib, rociletinib, etc. Of them all, osimertinib is the only currently approved drug.

Osimertinib (Tagrisso, AZD9291) is a very promising third-generation EGFR-TKI. It is able to tackle gefitinib/erlotinib acquired resistance through T790M, exon 19 and 21, which accounts for a large portion of acquired resistant cases. In a FLAURA study, Osimertinib was compared to first-line EGFR-TKIs (erlotinib and gefitinib) as first line therapy [129]. It showed significantly higher efficacy against EGFR-mutated patients, with PFS 18.9 vs. 10.2 months. An extra feature of osimertinib is its ability to penetrate the blood-brain barrier and tackle patients with brain metastasis as well. CNS progression was lower in patients treated with osimertinib (6 vs. 15%). There is not yet data available on comparing overall survival between the two, yet osimertinib showed a trend of superiority. At 18 months of the FLAURA study, 83% of the patients in the osimertinib group were still alive vs. 71% in the first-generation EGFR-TKI group. Most third-generation EGFR-TKIs combat the T790M EGFR resistance mechanism selectively. Yet, the other 50% resistant mechanisms remain a challenge.

2.3.2.1 Tolerability of side effects

Side effects of third-generation EGFR-TKIs are rather mild and tolerable. Side effects of Osimertinib commonly include rash, nausea, and diarrhea. Grade 3 or 4 adverse events occurred in 24% of the patients, but only 2% of the patients required a dosage reduction, and only 4% discontinuation. However, there are also studies which disagree. In the FLAURA study, rate of permanent discontinuation due to adverse events of osimertinib was 13%. Yet it is still lower than that of those receiving first-generation EGFR-TKIs, which was 18% [129].

2.4 Comparison

2.4.1 Newer generations perform better than first generation

Viewed as a whole, TKIs of the later generations tend to outperform the first generation in terms of efficacy. This is mainly because the newer generations tend to target multiple pathways and also provide a more potent irreversible inhibition. This allows them to be effective in both first-line setting, as well as combatting heterogeneous resistant mechanisms arisen. Yet, their downside is the occurrence of more severe side effects. The third-generation TKIs thus aim at targeting multiple pathways while sparing physiological functions, e.g., third-generation EGFR-TKIs. VEGFR-TKIs are the exceptions. Their first-generation TKIs are multitargeted, and their newer generation TKIs are more specific, and thus offer a higher tolerability. Studies on newer generations of TKIs delineate promising results on both their efficacy as a potential first-line treatment and as a second-line treatment after acquired resistance of the initial therapy.

2.4.1.1 High efficacy but low effectiveness

Many TKIs seem to show merely improvement in progression-free survival, but not in overall survival rate. These include gefitinib in NSCLC [130], sunitinib, nilotinib and regorafenib in GIST [131], lenvatinib in differentiated thyroid cancer [132], and many other TKIs, regardless of whether they are of newer generations or not. Erlotinib even showed poorer overall survival rate than chemotherapy (24.68 vs. 26.16 months), despite a significantly higher progression-free survival [62]. The potential reasons shall be further discussed.

Response rate of TKIs are low in unselected patients. Various studies have shown that, in the absence of targeted mutation, targeted therapy performed worse than traditional chemotherapy. Presence of targeted mutation is a huge positive predicting factor for good tumor response [133, 134]. Response rate in unselected population is however high in a few cases, for example, in unselected CML patients. This is likely because the vast majority of them carry the same single mutation of BCR-ABL. It is also high in RCC for first-generation TKIs, since the first-generation VEGFR-TKIs are relatively nonspecific, and are able to target multiple mutation mechanisms.

3. Evaluation of limitations of TKIs

3.1 Development of resistance

The development of resistance has always been and will probably always be the greatest problem limiting the use of TKIs. The rate of developing acquired resistance (AR) is extremely high, and appears even to be inevitable in certain diseases. In EGFR-TKI therapy, a study showed the median time for patients developing AR is 8–10 months, and all responding patients developed AR eventually, with the inevitable consequence of disease progression [135, 136]. The case with imatinib is slightly better; around 7–15% is found to have secondary resistance, i.e., disease progression following initial achievement of cytogenic response [137, 138]. And this is the reason why the PFS, despite longer than chemotherapy, is still not very long, with most ranging from a few months to at most a few years, despite their high disease response rate and promptness in controlling the disease. Acquiring resistance and disease progression seem almost inevitable in many cancer lines using TKIs. This phenomenon occurs indiscriminately in all generations of TKIs and is a huge challenge.

The development of resistance comes in many ways, and many researches have been dedicated to finding out the mechanisms of resistance to TKIs. Studies have shown that cancer cells adapt to chronic therapy by through common mechanisms found include secondary mutations of target, activation of alternative signaling pathway, evading immune system and adaptive or cell fate changes, etc. Point mutation at site coding for TK resulting in decreased affinity for the TKI remains the most prevalent mechanism of acquired resistance [139]. Point mutations (esp. T315I mutation) in CML patients are a major cause in AR toward imatinib. Occurrence of these mutations reduces the life expectancy of chronic phase CML patients from 10 years to just 22 months [140]. Exon 20-T790M mutation is found in approximately half of the patients with progressed disease following initial EGFR-TKI use [141]. Any of the ways allow the tumor cells to regain its ability to grow and divide. The heterogeneity of resistance mechanisms poses huge difficulty for a single TKI to produce high response rate following AR to the initial TKI.

Newer generations of TKIs aimed at resolving acquired resistance toward the older generation TKIs. Yet, there are too many different types of resistance mechanisms that could arise between different patients, as discussed. Taking NSCLC AR to erlotinib and gefitinib as an example, AR mechanism could be T790M missense mutation, other secondary mutations of EGFR, MET amplification, HER2 amplification, small cell histological transformation, etc. And up to 30% of the NSCLC patients with AR to first gen TKIs have unknown resistance mechanism [135]. Its heterogeneity makes the development of new generation TKIs, especially one with high tumor response, very hard.

The management of post-TKI disease progression is a new therapeutic challenge. The ways to overcome include using multitargeted approach, in which the TKI is effective against a broad spectrum of resistance mechanisms, or perform genetic tests and learning the specific resistance mechanism of the individual patient and selecting the next TKI. Details are discussed in the next session.

3.2 Complexity and redundancy in tumor pathways and between tumor subclones

Multiple regulatory factors and multiple signaling pathways exist within a tumor, and they each share a role in supporting tumor growth [142]. Many elements of these pathways are redundant, and contribute toward the same function. With all these redundancy, inhibiting one factor or one pathway will often not be sufficient in inhibiting tumor growth [143]. This is part of the reason for the robustness of cancer cells, allowing them to survive through a diversity of treatments. Take angiogenesis as an example. Although VEGF is the most potent stimulatory regulator of angiogenesis, and human cancers often have an overexpression of VEGF, there are also many other stimulatory and inhibitory factors involved, which some are produced by tumor cells and some by the host cells. Therefore, simply administrating a single-target VEGFR-TKIs may not result in significant antiangiogenic effect. Besides, some of the factors, including VEGF, can exist in multiple isoforms, making it even harder to inhibit the angiogenic process [1, 144]. Moreover, many tumors have more than one mutated pathways, for instance, both VEGFR and PDGFR mutation [145]. It is only through multitargeting and combination therapy, or targeting more upstream pathways, could a more significant response be brought about [143]. Simply inhibiting one target is in many cases not effective enough to hinder cell growth.

With technology of next-generation sequencing of patient biopsies, it has been revealed that tumors contain vastly heterogeneous genetic alterations in multiple subclones. This is also called intratumor heterogeneity. This also includes geographical heterogeneity, in which the genetic makeup of metastatic tumors differs

from each other as well. As the neoplastic cells divide and undergo DNA replication, the clones are highly prone to genetic mutations, and the mutated cells continue to grow and give rise to their colony of cells. Thus within the same tumor, there could be multiple subclones each with their own variant of DNA makeup. This plays a huge role in the development of resistance toward TKIs. Heterogenic tumor subclones may exhibit different sensitivity toward the TKIs. Some tumors may have primary resistance, and with the TKI acting as the selecting pressure, the resistant subclones are selected and are able to continue growing. This accounts for the high rate of resistance toward TKIs. And research has also proven that high intratumoral heterogeneity predicts poorer prognosis and poorer response to treatment [146].

3.3 Poor patient selection

Low effectiveness of TKIs in studies may be due to poor patient selection. By knowing the mechanism of action of the TKIs, we know well that they could only work in a selected population of tumor cells, which contains the pharmacological target. They do not always work well in unselected populations. There are a certain portion of cancer cell lines which are innately resistant to the TKI therapy administered. In unselected NSCLC patients, only 15 in 58 in Japan and 1 in 61 in USA responded to the gefitinib treatment [147]. This is due to the heterogeneity of mutations of the same cancer in different individuals. This occurs not only with initial therapy option, but also newer generations of TKIs as well as non–first-line TKIs. Response rates of many newly developed EGFR-TKIs, targeting at patients with AR to first-line TKIs, were lower than 10%. These include neratinib, whose response rate is 3% [148] and IPI-504, whose response rate is 4% [148]. Therefore, poor patient selection will greatly limit the effectiveness of TKIs. Mechanisms for patient selection must be developed in order to increase TKI effectiveness in community settings.

3.4 Antagonistic drug interaction

Many studies found that combining TKI with traditional chemotherapy showed no significant benefit, but rather an additive effect of toxicity, resulting in disappointment. Concurrent administration may not be effective due to TKI induced G1 phase cell cycle arrest [149]. Although combination approach is believed to provide better outcome in many cases, practitioners must pay attention to antagonistic drug interactions in order to prevent this from limiting the effectiveness of TKI. Alternating administration schedule is proposed for many combination therapies in order to avoid this problem.

3.5 Side effects

Although TKIs are deemed to be relatively well tolerated, especially when compared to systemic cytotoxic chemotherapy, there are still many cases of side effects limiting the use of this drug. With variations from drug to drug, up to 50% report cases of skin toxicity and folliculitis with TKI use. EGFR TKIs display a broad spectrum of skin and hair adverse effects, including folliculitis, facial hair growth, facial erythema, paronychia, and varying forms of frontal alopecia, whereas VEGFR TKIs are more commonly associated with subungual splinter hemorrhages. Imatinib frequently causes periorbital edema. TKIs produce various hematological side effects (anemia, thrombocytopenia, neutropenia) and extra-hematological side effects, most commonly being edema, nausea, hypothyroidism, vomiting, and diarrhea. Regarding long-term effects, cardiac toxicity with congestive heart failure is discussed in patients receiving imatinib and sunitinib [150]. Adverse events have been reported in the use

of sorafenib against HCC, including Hand Foot Skin Reactions (HFSR), hyperbilirubinemia associated with heightened ALT. Adverse effects occurred in up to 40% of differentiated thyroid cancer patients, which are mainly hypertension, diarrhea, asthenia, or fatigue, nausea, decreased weight and appetite. This had resulted in dosage reduction despite good tumor response [151]. About 14% of the patients had to discontinue therapy due to intolerance of adverse events. Severity of side effects was found correlated with specificity of the TKIs. The newer generations are usually multitargeted, and thus yield more severe side effects. Luckily, third generations are more mutant selective, and thus showed improvement in this aspect.

3.6 Lack of follow-up and nonadherence

As TKI is a drug class that has to be administrated over a long period of time, the lack of follow-up during the course of treatment is a problem that could limit the effectiveness. In a study reporting effectiveness of TKIs in CML patients in a community setting, it is found that cytogenetic and molecular response monitoring assessments were conducted less frequently than recommended [113]. Poor monitoring may result in delay in adjustments in treatment plan. On the other hand, TKIs are mostly administrated orally, which may pose a challenge in patient adherence. Poor patient compliance plays a role in increasing rates of acquired resistance to TKIs. It is found that, as the treatment progresses, those with higher adherence did achieve better results in achieving CCyR and MMR [113]. While adherence to TKIs is critical in achieving durable responses, it is surprising that merely 56% patients in a study of 229 CML patients adhere to their dosage (which is defined as ³90% adherence) [113].

3.7 Financial burden on patients

There have been numerous studies conducted on cost-effectiveness of TKIs. But most work on merely the comparison between different TKIs or compare TKIs with other treatment. As TKIs are in many occasions not covered by the public health system, they are usually self-funded, unless the patient is covered by insurance, has successfully applied for external funding or is enrolled in a clinical trial. The average per person total cost of treatment with branded imatinib is (79,000 USD/year) and even higher for dasatinib and nilotinib (87,000–92,000 USD/year) [152]. The humongous financial burden complicates the patients' decision in drug choice. It may also affect their choice of continuation of treatment. Studies have shown that high costs of TKIs even lead to a delay in treatment for many patients with leukemia [153]. Some patients may resort to generic TKIs, which quality may not be always consistently good. For example, a study showed that generic Imatinib show suboptimal efficacy when compared to branded imatinib as first-line therapy in CML [154].

4. Strategies in overcoming the limitations of TKIs

Plenty studies have been coming up with all sorts of strategies in overcoming the limitations of TKIs. The big direction is to develop new inhibitors, use a combination approach, and improve patient selection.

4.1 Development of new inhibitors: specific approach and multitargeted approach

Following post-TKI disease progression, continuing the use of the initial TKI therapy does not improve PFS [155]. There is thus a desperate need for new

treatment options, or new TKIs. Various studies are working on drugs available for use after acquired resistance. A large number of new TKIs are working their way down the pipeline, in preclinical studies and clinical studies, a lot of which are very promising. The new inhibitors are either very specific toward a certain type of acquired mutation, or multitargeted to inhibit a broader spectrum of pathways, in order to overcome resistance.

With next-generation sequencing, we are able to identify the specific mutations and design molecules that specifically target them. The mutation mechanisms are however vast in diversity. Taking acquired resistance to imatinib in GIST as an example, in a study, among the 15 patients who acquired resistance to imatinib, 7 were found with secondary mutation at the KIT target, 6 of which occurred at the exon 17 (three were N822K, two were D820Y and one was Y823D) [156]. Luckily we were also able to identify some more common ones, e.g., T790M mutation in EGFR-TKI AR. One of the strategies is thus to develop drugs that target these mutations specifically. To facilitate this, however, there should be more research on mechanisms of acquired resistance against TKIs in different cancers. However, this would also be a very costly method.

Another approach of new inhibitors, also a more practical approach, would be the multi-targeted approach, as well as the inhibiting of upstream pathways. As stated previously, the vast heterogeneity within tumor subclones and the redundancy of cancer cell signaling pathways poses a huge challenge for targeted therapies. One of the strategies regarding is to have multiple targets. Network model suggests that partial inhibition of multiple targets may exhibit better effect than complete inhibition of a single target [157]. This has been the trend in many newly developed drugs. Many studies agree that multi-targeted TKIs should perform better than single-targeted ones in terms of efficacy and tumor response rate [145, 158–160]. When targeting a single molecule, the cancer cells can easily adapt and bend around the hindered pathway by activation of alternative pathways. By interacting with multiple targets simultaneously, it leaves less chance for cancer cells to do so [159, 161]. Multitargeted approach also eliminates the malignant cells faster as they inhibit multiple pathways, inhibiting the cancer cells at multiple levels.

Identifying convergent resistance mechanisms or targeting upstream pathways enables us to achieve something similar. Despite the large number of resistance mechanisms, a lot of them converge on reactivation of the driving pathway. For example, in BRAF-mutant melanomas, 89% of resistance mechanisms lie within the MAPK pathway [162]. Identifying these convergent resistance mechanisms could allow us to combat acquired resistance more effortlessly.

However, the multi-targeted approach is also with more severe adverse effects than the single-targeted [158]. It is thus important to be able to identify the suitable set of targets, which allows us to be specific enough to act selectively at the tumor cells only, not the normal body cells, yet not specific enough to prevent cancer cells from acquiring resistance too easily. Luckily, we are equipped with newer tools, including the network pharmacology approach, to aid us in the design of these new drugs [157].

4.2 Combination therapy

Combination approach with a similar mindset when that of developing multitargeted TKIs, it is believed that a combination of therapies would leave less chance for selection of resistant subclones, which allows the tumor to acquire resistance.

TKIs treatment could potentially combine with many different treatments. Many studies have already been conducted on the combination of TKIs with conventional therapies, including chemotherapy, radiation therapy, interferon therapy, etc. A study showed that combination of standard-dose imatinib and IF-therapy

yielded better results than standard-dose or high-dose imatinib alone, as well as standard-dose imatinib combined with chemotherapy [21, 163]. Icotinib, an EGFR-TKI is proved to improve radiosensitivity in lung cancer in vitro and in vivo, thus possibly allowing better radiotherapy effects [164]. They are extensively studied and are in many cases already put to clinical practice.

A TKI could also be combined with another TKI. For example, dual EGFR blockade by first and third-generation EGFR TKI combinations [165]. Or dual ALK and EGFR target inhibition in ALK translocated NSCLC with additional EGFR mutation [166]. Other ongoing clinical trials study the potential benefits of combining anti-angiogenic TKIs (e.g., apatinib, endostatin, and anlotinib) with EGFR-TKIs [167].

There are also studies proposing TKI combination with other target inhibitors including monoclonal antibodies. Researches are exploring possibilities of combinations of brigatinib and anti-EGFR antibodies, third-generation TKIs with MEK inhibitors, and osimertinib with oxidative phosphorylation inhibitors etc. [165]. For acute lymphocytic lymphoma, a WEE1 inhibitor AZD-1775 is proven to significantly enhance the efficacy of several tyrosine kinase inhibitors, such as imatinib, bosutinib, and ponatinib [168], or similarly, vitamin K1 with sorafenib in treating HCC [151] and antiestrogen fulvestrant with vandetanib in NSCLC.

Combination approach is promising, yet limited by potential toxicity. Combination of drug effects is true for both positive and side effects. Many studies echoed that concurrent chemotherapy and TKI therapy yielded no added benefits. Therefore, it is important to understand the mechanism of action of the two therapies and understand their interaction, thus design the best administration schedule. Taking TKIs and chemotherapy in an intercalated manner may reduce inhibitory drug interaction. A study compared synchronized administration and intercalated administration of the two therapies [101], and found that intercalated administration schedule improved PFS and OS [169]. More and more studies are thus conducted on the administration schedule and yielded similar results [63].

4.3 Wisdom from traditional Chinese medicine (TCM)

TCM has long been used to treat different cancers and are often shown with clinical efficacy. TCM herbs are able to stabilize tumor growth, control patient symptoms and alleviate side effects, and ultimately improve quality of life of patients [161]. Many researches are thus dedicated to discovering novel drugs by uncovering therapeutic potentials of various natural compounds.

Accumulating studies have been discovering tyrosine kinase inhibiting effects from natural compounds. Many TCM herbs contain natural compounds that are capable of interacting with multiple cellular targets [161]. Various molecules from traditional Chinese medicine are being discovered with tyrosine kinase inhibiting effects and these include 2-O-caffeoyl tartaric acid, emetine, rosmaricine, and 2-O-feruloyl tartaric acid, which are potential EGFR inhibitors [170]. Another meta-analysis identified another 24 kinase inhibitors from TCM [171]. Network pharmacology enables us to discover more of such molecules and their targets [161]. Using natural compounds as drugs is relatively safe and exhibit less side effects [161].

On the other hand, complementary use of TCM has been actively discussed in recent years. Many recent studies have been conducted. They appear to be able to increase efficacy as well as reduce toxicity when combined with TKI therapy [161, 172]. Some studies showed that TCM work synergistically with EGFR-TKI

and has additional effect of alleviating TKI induced toxicity [173]. They are able to significantly raise overall response rates, disease control rate, 1-year survival rate, 2-year survival rate, and improvement/stable Karnofsky Performance scores of tumors. Severe toxicity for rash was decreased, so were nausea, vomiting, and diarrhea [174, 175]. The strategy of minimizing or alleviating side effects of TKIs may be potential. This could help increase tolerability of patients and also reduce drug-related adverse events and subsequent possible drug reduction and discontinuation, which will have a toll on TKI therapy effectiveness.

4.4 Improve patient selection

The drug effects of TKIs can be drastically different in two patients. It can work miracles in one, but have no effect at all in another. The genetic makeup of a patient's tumor is a huge predicting value of the efficacy of the TKI. Various studies have shown the correspondence between genetic profiling and therapy response [176, 177]. Thus, it is vital to perform procedures to select the population of patients responsive toward the TKI. In the new era of personalized medicine, the most effective way of using TKIs to treat cancer is to consider each patient/tumor individually and to determine the strategy that specifically targets the consequences of altered genetics of the tumor. Not simply which TKI to use, but also which combination of TKIs and which combination of therapies.

4.5 Repeated monitoring, including repeated biopsy/ liquid biopsy

It was proposed that in order to overcome the limitation of AR in TKIs, repeated tumor biopsies should be done during the course of treatment. This is to give us the ability to spot mutations early and learn its resistance mechanism, thus allowing intervention prior to standard detection of radiographic signs of progression. The specific agent/combination against that particular resistance mechanism can thus be selected.

Yet multiple resistance mechanisms within a single patient, especially between multiple lesions in a patient, pose challenges for biopsy. Besides, biopsies are not accessible for all tumors and are also invasive to the patient. Studies have proposed repeated liquid biopsies as a solution [178]. Liquid biopsy checks for tumor DNA circulating in the blood, which is shed into the bloodstream by tumors all around the body, thus allowing us to peer into the tumor genome in distinct subclones in different metastatic lesions within the patient. It is more effective in learning the heterogeneity and multiple resistance mechanisms than performing a single lesion biopsy. It being less invasive (a simple blood draw will suffice), also allows a more frequent sampling.

4.6 Improve patient compliance

Patient compliance does make a big difference in treatment outcome. Studies have proven that those with higher adherence did achieve better results in achieving CCyR and MMR [113]. Since many TKIs are orally administered, of long-term usage, and in some cases, self-administered in an out-patient setting, patient compliance could pose a serious challenge, especially with irregular drug schedule, such as one with drug holidays. Patient education is one of the ways we could improve patient compliance. Perhaps systems for patient monitoring could also be developed, including system like DOTs therapy for TB patients, where out-patients are required to come to the clinic and take the medicine in front of the healthcare workers and official record is made. Other suggestions include designing phone apps for patients to keep track of their drug schedule.

4.7 Generic drug use

Generic drug use could be a possible solution to high cost of TKIs [179]. Researches on generic versions of various drugs have been conducted [180]. Studies have shown that generic imatinib and Brand named imatinib (Gleevec) showed no difference in efficacy [181]. Aside from imatinib, many TKIs are currently available in generic form, including dasatinib and sorafenib. Yet the quality of generic drugs is not always certified and has to be judged case by case.

4.8 Exploring the potential of TKI therapy termination

Many TKIs are believed to be required to be administered a lifetime. This has posed certain difficulties, including inconvenience to the patients, accumulative side effects, financial burden to the hospital and patient etc. Many studies are thus working on the possibility of discontinuing TKI therapy after a certain response is achieved. Some researches have identified specific subsets of patient populations which could consider discontinuation of TKIs [182].

5. Conclusion

Although TKIs have a very high clinical efficacy upon initial administration, the frequency of acquired resistance is too high, making it not as effective in improving overall survival. There are however many ways we can resort to, in order to prolong the period of stable disease, before progression. These include using multi-targeted approaches, or combination approaches, although it is also accompanied with more severe side effects. Resorting to natural compounds, for example, those from TCM, could be a potential way. They are often multitargeted and not as potent, thus allowing multitarget inhibition without bringing about severe toxicities. Adequate monitoring of disease status and patient adherence is another simple yet effective way to improve the performance of TKIs. Being able to make timely adaptations to treatment plan can play a vital role in prolonging survival. Another direction would be to place more emphasis on patient selection. There are many factors that could help us predict the patient's sensitivity and response toward that TKI. TKI should not be used as an empirical treatment, which would be too cost-ineffective. Even for the same cancer same stage, the specific genetic constitution of each tumor differ from each other, and choice of TKI may vary dependently. Hence, personalized treatment is the key.

Acknowledgements

The study was financially supported by grants from the research council of the University of Hong Kong (Project Codes: 104004092, 104004460, and 104004746), the Research Grants Committee (RGC) of Hong Kong, HKSAR (Project Codes: 764708, 766211, and 17152116), Wong's Donation on Modern Oncology of Chinese Medicine (Project code: 200006276), and Gala Family Trust (Project Code: 200007008).

DOI: http://dx.doi.org/10.5772/intechopen.82513

Author details

Venice Wing Tung Ho, Hor Yue Tan, Ning Wang and Yibin Feng*
School of Chinese Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong, People's Republic of China

*Address all correspondence to: yfeng@hku.hk

References

[1] Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. Journal of Pharmacology and Experimental Therapeutics. 2005;**315**(3):971-979

[2] Cammack R, et al. Tyrosine Kinase. Oxford, England, UK: Oxford University Press; 2008

[3] Maruyama IN. Mechanisms of activation of receptor tyrosine kinases: Monomers or dimers. Cell. 2014;**3**(2):304-330

[4] Perona R. Cell signalling: Growth factors and tyrosine kinase receptors. Clinical & Translational Oncology. 2006;**8**(2):77-82

[5] Witsch E, Sela M, Yarden Y. Roles for growth factors in cancer progression. Physiology (Bethesda). 2010;**25**(2):85-101

[6] Aaronson S. Growth factors and cancer. Science. 1991;**254**(5035):1146-1153

[7] Goustin AS et al. Growth factors and cancer. 1986;**46**(3):1015-1029

[8] Posner I et al. Kinetics of inhibition by tyrphostins of the tyrosine kinase activity of the epidermal growth factor receptor and analysis by a new computer program. Molecular Pharmacology. 1994;**45**(4):673-683

[9] FDA Approved Drugs for Oncology. 2018. Available from: http://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology

[10] Cismowski MJ. Tyrosine kinase inhibitors. In: Enna SJ, Bylund DB, editors. xPharm: The Comprehensive Pharmacology Reference. New York: Elsevier; 2007. pp. 1-4

[11] Sequist LV. Second-generation epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. The Oncologist. 2007;**12**(3):325-330

[12] Iqbal N, Iqbal N. Imatinib: A breakthrough of targeted therapy in cancer. Chemotherapy Research and Practice. 2014;**2014**:357027

[13] Imatinib-Drugbank. 2018. Available from: https://www.drugbank.ca/drugs/DB00619 [cited: November 2, 2018]

[14] Nowell PC. The minute chromosome (Phl) in chronic granulocytic leukemia. Blut. 1962;**8**:65-66

[15] Sillaber C et al. Chronic myeloid leukemia: Pathophysiology, diagnostic parameters, and current treatment concepts. Wiener Klinische Wochenschrift. 2003;**115**(13-14):485-504

[16] O'Brien SG, Guihot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. New England Journal of Medicine. 2003;**348**(11):994-1004

[17] Hughes TP et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. The New England Journal of Medicine. 2003;**349**(15):1423-1432

[18] Deininger M et al. International randomized study of interferon vs STI571 (IRIS) 8-year follow up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib. Blood. 2009;**114**(22):1126

[19] Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood. 2005;**105**(7):2640-2653

[20] Thielen N et al. Preliminary results from a phase III trial of imatinib versus imatinib in combination with cytarabine in patients with first chronic phase myeloid leukemia. Blood. 2011;**118**(21):2758

[21] Guilhot F et al. Significant higher rates of undetectable molecular residual disease and molecular responses with pegylated form of interferon a2a in combination with imatinib (IM) for the treatment of newly diagnosed chronic phase (CP) chronic myeloid leukaemia (CML) patients (pts): Confirmatory results at 18 months of part 1 of the spirit phase III Randomized trial of the French CML Group (FI LMC). Blood. 2009;**114**(22):340

[22] Leis JF et al. Management of life-threatening pulmonary leukostasis with single agent imatinib mesylate during CML myeloid blast crisis. Haematologica. 2004;**89**(9):Ecr30

[23] Sawyers CL et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: Results of a phase II study. Blood. 2002;**99**(10):3530-3539

[24] Chauffaille MdLLF et al. Frequency and diversity of variant philadelphia chromosome in chronic myeloid leukemia patients. Blood. 2011;**118**(21):4903

[25] Ujjan ID et al. Cytogenetic and molecular analyses of philadelphia chromosome variants in CML (chronic myeloid leukemia) patients from Sindh using Karyotyping and RT-PCR. Pakistan Journal of Medical Sciences. 2015;**31**(4):936-940

[26] Min KW, Leabu M. Interstitial cells of Cajal (ICC) and gastrointestinal stromal tumor (GIST): Facts, speculations, and myths. Journal of Cellular and Molecular Medicine. 2006;**10**(4):995-1013

[27] Heinrich MC et al. PDGFRA activating mutations in gastro-intestinal stromal tumors. Science. 2003;**299**(5607):708-710

[28] Heinrich MC et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. Journal of Clinical Oncology. 2003;**21**(23):4342-4349

[29] Zhao X, Yue C. Gastrointestinal stromal tumor. Journal of Gastro-intestinal Oncology. 2012;**3**(3):189-208

[30] Dematteo RP et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: A randomised, double-blind, placebo-controlled trial. Lancet. 2009;**373**(9669):1097-1104

[31] Blackstein M. Risk assessment for tumor recurrence after surgical resection of localized primary gastrointestinal stromal tumor (GIST). North American Intergroup Phase III Trial ACOSOG Z9001. ASCO GI Cancer Symposium. 2010;**28** (Suppl 4):6

[32] Duffaud F, Salas S, Huynh T. Recent advances in the management of gastrointestinal stromal tumors. F1000 Medicine Reports. 2010;**2**:36

[33] Ksienski D. Imatinib mesylate: Past successes and future challenges in the treatment of gastrointestinal stromal tumors. Clinical Medicine Insights: Oncology. 2011;**5**:365-379

[34] Van Glabbeke M et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic

factors: A European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group Study. Journal of Clinical Oncology. 2005;**23**(24):5795-5804

[35] Blanke CD et al. Long-term results from a randomized phase II trial of standard-versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. Journal of Clinical Oncology. 2008;**26**(4):620-625

[36] Blanke CD et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. Journal of Clinical Oncology. 2008;**26**(4):626-632

[37] Verweij J et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: Randomised trial. Lancet. 2004;**364**(9440):1127-1134

[38] Schlemmer M et al. Activity and side effects of imatinib in patients with gastrointestinal stromal tumors: Data from a german multicenter trial. European Journal of Medical Research. 2011;**16**(5):206-212

[39] Liu-Dumlao T et al. Philadelphia-positive acute lymphoblastic leukemia: Current treatment options. Current Oncology Reports. 2012;**14**(5):387-394

[40] Yanada M et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: A phase II study by the Japan Adult Leukemia Study Group. Journal of Clinical Oncology. 2006;**24**(3):460-466

[41] Kerob D et al. Imatinib mesylate as a preoperative therapy in dermatofibrosarcoma: Results of a multicenter phase II study on 25 patients. Clinical Cancer Research. 2010;**16**(12):3288-3295

[42] Han A et al. Neoadjuvant imatinib therapy for dermatofibrosarcoma protuberans. Archives of Dermatology. 2009;**145**(7):792-796

[43] Qu S-Q et al. Long-term outcomes of imatinib in patients with FIP1L1/PDGFRA associated chronic eosinophilic leukemia: Experience of a single center in China. Oncotarget. 2016;**7**(22):33229-33236

[44] Alvarez-Twose I et al. Imatinib in systemic mastocytosis: A phase IV clinical trial in patients lacking exon 17 KIT mutations and review of the literature. Oncotarget. 2017;**8**(40):68950-68963

[45] Valent P et al. Long-lasting complete response to imatinib in a patient with systemic mastocytosis exhibiting wild type KIT. American Journal of Blood Research. 2014;**4**(2):93-100

[46] Penel N et al. Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): An FNCLCC/French Sarcoma Group phase II trial with a long-term follow-up. Annals of Oncology. 2011;**22**(2):452-457

[47] Hodi FS et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. Journal of Clinical Oncology. 2013;**31**(26):3182-3190

[48] Koon HB et al. Phase II trial of imatinib in AIDS-associated Kaposi's sarcoma: AIDS Malignancy Consortium Protocol 042. Journal of Clinical Oncology. 2014;**32**(5):402-408

[49] Hindi N et al. Imatinib in advanced chordoma: A retrospective case series analysis. European Journal of Cancer. 2015;**51**(17):2609-2614

[50] Casali PG et al. Imatinib mesylate in chordoma. Cancer. 2004;**101**(9):2086-2097

[51] Safra T et al. Weekly paclitaxel with intermittent imatinib mesylate (Gleevec): Tolerance and activity in recurrent epithelial ovarian cancer. Anticancer Research. 2010;**30**(9):3243-3247

[52] Ha HT et al. A phase II study of imatinib in patients with advanced anaplastic thyroid cancer. Thyroid. 2010;**20**(9):975-980

[53] Hensley ML, Ford JM. Imatinib treatment: Specific issues related to safety, fertility, and pregnancy. Seminars in Hematology. 2003;**40**(2 Suppl 2):21-25

[54] Molina JR et al. Non-small cell lung cancer: Epidemiology, risk factors, treatment, and survivorship. Mayo Clinic Proceedings. 2008;**83**(5):584-594

[55] Sebastian M, Schmittel A, Reck M. First-line treatment of EGFR-mutated nonsmall cell lung cancer: Critical review on study methodology. European Respiratory Review. 2014;**23**(131):92-105

[56] Tseng C-H et al. EGFR mutation, smoking, and gender in advanced lung adenocarcinoma. Oncotarget. 2017;**8**(58):98384-98393

[57] Graham RP et al. Worldwide frequency of commonly detected EGFR mutations. Archives of Pathology & Laboratory Medicine. 2018;**142**(2):163-167

[58] Mok TS et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. The New England Journal of Medicine. 2009;**361**(10):947-957

[59] Maemondo M et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. The New England Journal of Medicine. 2010;**362**(25):2380-2388

[60] Nakamura A et al. Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). Journal of Clinical Oncology. 2018;**36**(15_suppl):9005

[61] Zhou C et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. The Lancet Oncology. 2011;**12**(8):735-742

[62] Wen F et al. OPTIMAL and ENSURE trials-based combined cost-effectiveness analysis of erlotinib versus chemotherapy for the first-line treatment of Asian patients with non-squamous non-small-cell lung cancer. BMJ Open. 2018;**8**(4):e020128

[63] Xu JL et al. Chemotherapy plus erlotinib versus chemotherapy alone for treating advanced non-small cell lung cancer: A meta-analysis. PLoS One. 2015;**10**(7):e0131278

[64] Zhang W et al. Gefitinib provides similar effectiveness and improved safety than erlotinib for east Asian populations with advanced non-small cell lung cancer: A meta-analysis. BMC Cancer. 2018;**18**(1):780

[65] Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: A systematic review and global map by ethnicity (mutMapII). American Journal of Cancer Research. 2015;**5**(9):2892-2911

[66] Lovly C, Horn L, Pao W. Molecular Profiling of Lung Cancer. My Cancer Genome. Nashville, Tennessee: Vanderbilt-Ingram Cancer Center; 2018

[67] Krawczyk P et al. Comparison of the effectiveness of erlotinib, gefitinib, and afatinib for treatment of non-small cell lung cancer in patients with common and rare EGFR gene mutations. Oncology Letters. 2017;**13**(6):4433-4444

[68] Wu JY, Shih JY. Effectiveness of tyrosine kinase inhibitors on uncommon E709X epidermal growth factor receptor mutations in non-small-cell lung cancer. OncoTargets and Therapy. 2016;**9**:6137-6145

[69] Zhou X et al. Gefitinib inhibits the proliferation of pancreatic cancer cells via cell cycle arrest. Anatomical Record (Hoboken, NJ). 2009;**292**(8):1122-1127

[70] Chua DT et al. Phase II study of gefitinib for the treatment of recurrent and metastatic nasopharyngeal carcinoma. Head & Neck. 2008;**30**(7):863-867

[71] Dragovich T et al. Phase II trial of erlotinib in gastroesophageal junction and gastric adenocarcinomas: SWOG 0127. Journal of Clinical Oncology. 2006;**24**(30):4922-4927

[72] Wainberg ZA et al. Phase II trial of modified FOLFOX6 and erlotinib in patients with metastatic or advanced adenocarcinoma of the oesophagus and gastro-oesophageal junction. British Journal of Cancer. 2011;**105**(6):760-765

[73] Schilder RJ et al. A phase II trial of erlotinib in recurrent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group Study. International Journal of Gynecological Cancer. 2009;**19**(5):929-933

[74] Gordon MS et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. Journal of Clinical Oncology. 2009;**27**(34):5788-5793

[75] Llovet JM, Hernandez-Gea V. Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design. Clinical Cancer Research. 2014;**20**(8):2072-2079

[76] Forsythe B, Faulkner K. Overview of the tolerability of gefitinib (IRESSA) monotherapy: Clinical experience in non-small-cell lung cancer. Drug Safety. 2004;**27**(14):1081-1092

[77] Zhang W et al. Gefitinib provides similar effectiveness and improved safety than erlotinib for advanced non-small cell lung cancer: A meta-analysis. Medicine. 2018;**97**(16):e0460

[78] Ravaud A et al. Real-life patterns of use and effectiveness of sunitinib in patients with metastatic renal cell carcinoma: The SANTORIN study. Journal of Clinical Oncology. 2013;**31**(6_suppl):400

[79] Motzer RJ et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology. 2009;**27**(22):3584-3590

[80] Gore ME et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. British Journal of Cancer. 2015;**113**(1):12-19

[81] Bellmunt J et al. Phase I study of sunitinib in combination with gemcitabine and capecitabine for first-line treatment of metastatic or unresectable renal cell carcinoma. The Oncologist. 2014;**19**(9):917-918

[82] Schmid TA, Gore ME. Sunitinib in the treatment of metastatic renal cell carcinoma. Therapeutic Advances in Urology. 2016;**8**(6):348-371

[83] Guevremont C et al. Sorafenib in the management of metastatic renal cell carcinoma. Current Oncology. 2009;**16**(Suppl 1):S27-S32

[84] Escudier B et al. Sorafenib in advanced clear-cell renal-cell carcinoma. The New England Journal of Medicine. 2007;**356**(2):125-134

[85] Zhang H-L et al. Sorafenib versus sunitinib as first-line treatment agents in Chinese patients with metastatic renal cell carcinoma: The largest multicenter retrospective analysis of survival and prognostic factors. BMC Cancer. 2017;**17**(1):16

[86] Michel MS et al. SWITCH: A randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO)/sunitinib (SU) versus SU/SO in the treatment of metastatic renal cell cancer (mRCC). Journal of Clinical Oncology. 2014;**32**(4_suppl):393

[87] Li L et al. The Ras/Raf/MEK/ERK signaling pathway and its role in the occurrence and development of HCC. Oncology Letters. 2016;**12**(5):3045-3050

[88] Zhang L et al. VEGF is essential for the growth and migration of human hepatocellular carcinoma cells. Molecular Biology Reports. 2012;**39**(5):5085-5093

[89] Chaparro M et al. Review article: Pharmacological therapy for hepatocellular carcinoma with sorafenib and other oral agents. Alimentary Pharmacology & Therapeutics. 2008;**28**(11-12):1269-1277

[90] Bruix J et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: Subanalyses of a phase III trial. Journal of Hepatology. 2012;**57**(4):821-829

[91] Llovet JM et al. Sorafenib in advanced hepatocellular carcinoma. The New England Journal of Medicine. 2008;**359**(4):378-390

[92] Abou-Alfa GK et al. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: A randomized trial. JAMA. 2010;**304**(19):2154-2160

[93] Sanoff HK et al. Sorafenib Effectiveness in Advanced Hepatocellular Carcinoma. The Oncologist. 2016

[94] Younus J et al. Sunitinib malate for gastrointestinal stromal tumour in imatinib mesylate-resistant patients: Recommendations and evidence. Current Oncology. 2010;**17**(4):4-10

[95] Demetri GD et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: A randomised controlled trial. Lancet. 2006;**368**(9544):1329-1338

[96] Mulet-Margalef N, Garcia-del-Muro X. Sunitinib in the treatment of gastrointestinal stromal tumor: Patient selection and perspectives. OncoTargets and Therapy. 2016;**9**:7573-7582

[97] Kefeli U et al. Efficacy of sorafenib in patients with gastrointestinal stromal tumors in the third- or fourth-line treatment: A retrospective multicenter experience. Oncology Letters. 2013;**6**(2):605-611

[98] Durante C et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: Benefits and limits of radioiodine therapy. The Journal of Clinical Endocrinology and Metabolism. 2006;**91**(8):2892-2899

[99] Brose MS et al. Sorafenib in locally advanced or metastatic, radioactive iodine-refractory, differentiated thyroid cancer: A randomized,

double-blind, phase 3 trial. Lancet. 2014;**384**(9940):319-328

[100] van der Veldt AA et al. Predictive factors for severe toxicity of sunitinib in unselected patients with advanced renal cell cancer. British Journal of Cancer. 2008;**99**(2):259-265

[101] Zhang M, Liu M, Wang Y. Clinical efficacy of EGFR-TKIs in combination with chemotherapy in patients with advanced non-small cell lung cancer harboring EGFR mutations. Journal of Thoracic Disease. 2016;**8**(10):E1293-E1295

[102] Di Paolo A et al. Sunitinib in metastatic renal cell carcinoma: The pharmacological basis of the alternative 2/1 schedule. Frontiers in Pharmacology. 2017;**8**:523

[103] Najjar YG et al. A 2 weeks on and 1 week off schedule of sunitinib is associated with decreased toxicity in metastatic renal cell carcinoma. European Journal of Cancer. 2014;**50**(6):1084-1089

[104] Schuette K et al. Tolerability of sorafenib in the treatment of hepatocellular carcinoma (HCC) in patients with Child A and B liver cirrhosis. Journal of Clinical Oncology. 2009;**27**(15S):e15593

[105] Naito S et al. Overall survival and good tolerability of long-term use of sorafenib after cytokine treatment: Final results of a phase II trial of sorafenib in Japanese patients with metastatic renal cell carcinoma. BJU International. 2011;**108**(11):1813-1819

[106] Giles FJ. New directions in the treatment of imatinib failure and/or resistance. Seminars in Hematology. 2009;**46**(2 Suppl 3):S27-S33

[107] Aguilera DG, Tsimberidou AM. Dasatinib in chronic myeloid leukemia: A review. Therapeutics and Clinical Risk Management. 2009;**5**(2):281-289

[108] Shah NP et al. Long-term outcome with dasatinib after imatinib failure in chronic-phase chronic myeloid leukemia: Follow-up of a phase 3 study. Blood. 2014;**123**(15):2317-2324

[109] Hochhaus A et al. Dasatinib induces durable cytogenetic responses in patients with chronic myelogenous leukemia in chronic phase with resistance or intolerance to imatinib. Leukemia. 2008;**22**(6):1200-1206

[110] Kantarjian H et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. The New England Journal of Medicine. 2010;**362**(24):2260-2270

[111] Kantarjian H et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome–positive ALL. The New England Journal of Medicine. 2006;**354**(24):2542-2551

[112] Saglio G et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. The New England Journal of Medicine. 2010;**362**(24):2251-2259

[113] Di Bella NJ et al. The effectiveness of tyrosine kinase inhibitors and molecular monitoring patterns in newly diagnosed patients with chronic myeloid leukemia in the community setting. Clinical Lymphoma, Myeloma & Leukemia. 2015;**15**(10):599-605

[114] Cortes JE et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: Results from the randomized BFORE trial. Journal of Clinical Oncology. 2018;**36**(3):231-237

[115] Kwak J-Y et al. Efficacy and safety of radotinib compared with imatinib in newly diagnosed chronic phase chronic myeloid leukemia patients: 12 months result of phase 3 clinical trial. Blood. 2015;**126**(23):476

[116] Adverse Reactions. Pfitzer Canada Inc. 2018. https://www.pfizermedicalinformation.ca/en-ca/bosulif/adverse-reactions

[117] Sullivan I, Planchard D. Next-generation EGFR tyrosine kinase inhibitors for treating EGFR-mutant lung cancer beyond first line. Frontiers in Medicine. 2016;**3**:76

[118] Sequist LV et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. Journal of Clinical Oncology. 2013;**31**(27):3327-3334

[119] Wu YL et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. The Lancet Oncology. 2017;**18**(11):1454-1466

[120] Reckamp KL et al. A phase 2 trial of dacomitinib (PF-00299804), an oral, irreversible pan-HER (human epidermal growth factor receptor) inhibitor, in patients with advanced non-small cell lung cancer after failure of prior chemotherapy and erlotinib. Cancer. 2014;**120**(8):1145-1154

[121] Sternberg CN et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. Journal of Clinical Oncology. 2010;**28**(6):1061-1068

[122] van Geel RMJM, Beijnen JH, Schellens JHM. Concise drug review: Pazopanib and axitinib. The Oncologist. 2012;**17**(8):1081-1089

[123] Pazopanib outscores sunitinib on tolerability. Cancer Discovery. 2014;**4**(1):Of8. http://cancerdiscovery.aacrjournals.org/content/4/1/OF8, https://www.ncbi.nlm.nih.gov/pubmed/24402960

[124] Motzer RJ et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: Results from a phase III trial. Journal of Clinical Oncology. 2013;**31**(30):3791-3799

[125] Motzer RJ. AVEO and Astellas Announce Positive Findings from TIVO-1 Superiority Study of Tivozanib in First Line Advanced RCC. Astellas. 2012. https://newsroom.astellas.us/news-releases?item=136985

[126] Grothey A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. The Lancet. 2013;**381**(9863):303-312

[127] Demetri GD et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, phase 3 trial. The Lancet. 2013;**381**(9863):295-302

[128] Cortes JE et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: Final 5-year results of the phase 2 PACE trial. Blood. 2018;**132**(4):393-404

[129] Soria J-C et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. The New England Journal of Medicine. 2018;**378**(2):113-125

[130] Hsia T-C et al. Comparative effectiveness of concurrent chemoradiotherapy versus EGFR-tyrosine kinase inhibitors for the treatment of clinical stage IIIb lung adenocarcinoma patients with mutant EGFR. Thoracic Cancer. 2018;**9**:1398-1405

[131] Wu L et al. Clinical efficacy of second-generation tyrosine kinase

inhibitors in imatinib-resistant gastrointestinal stromal tumors: A meta-analysis of recent clinical trials. Drug Design, Development and Therapy. 2014;**8**:2061-2067

[132] Ferrari SM et al. Lenvatinib in the therapy of aggressive thyroid cancer: State of the art and new perspectives with patents recently applied. Recent Patents on Anti-Cancer Drug Discovery. 2018;**13**(2):201-208

[133] Archer K. What factors are predictive of survival in patients with non-small-cell lung cancer treated with gefitinib? Thorax. 2007;**62**(9):757

[134] Bonomi PD, Buckingham L, Coon J. Selecting patients for treatment with epidermal growth factor tyrosine kinase inhibitors. Clinical Cancer Research. 2007;**13**(15):4606s-4612s

[135] Stasi I, Cappuzzo F. Second generation tyrosine kinase inhibitors for the treatment of metastatic non-small-cell lung cancer. Translational Respiratory Medicine. 2014;**2**:2

[136] Hirsh V et al. A personalized approach to treatment: Use of egfr tyrosine kinase inhibitors for the treatment of non-small-cell lung cancer in Canada. Journal of Current Oncology. 2012;**19**(2):13

[137] Milojkovic D, Apperley J. Mechanisms of resistance to imatinib and second-generation tyrosine inhibitors in chronic myeloid leukemia. Clinical Cancer Research. 2009;**15**(24):7519-7527

[138] Bixby D, Talpaz M. Mechanisms of resistance to tyrosine kinase inhibitors in chronic myeloid leukemia and recent therapeutic strategies to overcome resistance. ASH Education Program Book. 2009;**2009**(1):461-476

[139] Chen Y-f, Fu L-w. Mechanisms of acquired resistance to tyrosine kinase inhibitors. Acta Pharmaceutica Sinica B. 2011;**1**(4):197-207

[140] Burke AC, Swords RT, Kelly K, Giles FJ. Current status of agents active against the T315I chronic myeloid leukemia phenotype. Expert Opinion on Emerging Drugs. 2011;**16**(1):85-103

[141] Tudor RA et al. Beyond disease-progression: Clinical outcomes after EGFR-TKIs in a cohort of EGFR mutated NSCLC patients. PLoS One. 2017;**12**(8):e0181867

[142] Logue JS, Morrison DK. Complexity in the signaling network: Insights from the use of targeted inhibitors in cancer therapy. Genes & Development. 2012;**26**(7):641-650

[143] Lavi O. Redundancy: A critical obstacle to improving cancer therapy. Cancer Research. 2015;**75**(5):808-812

[144] Parikh AA, Ellis LM. The vascular endothelial growth factor family and its receptors. Hematology/Oncology Clinics of North America. 2004;**18**(5):951-971, vii

[145] Potapova O et al. Contribution of individual targets to the antitumor efficacy of the multitargeted receptor tyrosine kinase inhibitor SU11248. Molecular Cancer Therapeutics. 2006;**5**(5):1280-1289

[146] Morris LG et al. Pan-cancer analysis of intratumor heterogeneity as a prognostic determinant of survival. Oncotarget. 2016;**7**(9):10051-10063

[147] Paez JG et al. EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science. 2004;**304**(5676):1497-1500

[148] Sequist LV et al. Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: Results of a phase II trial in patients with advanced non-small-cell lung

cancer. Journal of Clinical Oncology. 2010;**28**(18):3076-3083

[149] Perez-Soler R. The role of erlotinib (Tarceva, OSI 774) in the treatment of non-small cell lung cancer. Clinical Cancer Research. 2004;**10**(12 Pt 2): 4238s-4240s

[150] Hartmann JT et al. Tyrosine kinase inhibitors—A review on pharmacology, metabolism and side effects. Current Drug Metabolism. 2009;**10**(5):470-481

[151] Aravalli RN, Cressman ENK, Steer CJJAoT. Cellular and molecular mechanisms of hepatocellular carcinoma: An update. Archives of Toxicology. 2013;**87**(2):227-247

[152] Padula WV et al. Cost-effectiveness of tyrosine kinase inhibitor treatment strategies for chronic myeloid leukemia in chronic phase after generic entry of imatinib in the United States. JNCI - Journal of the National Cancer Institute. 2016;**108**(7):djw003

[153] Winn AN, Keating NL, Dusetzina SB. Factors associated with tyrosine kinase inhibitor initiation and adherence among medicare beneficiaries with chronic myeloid leukemia. Journal of Clinical Oncology. 2016;**34**(36):4323-4328

[154] Islamagic E et al. The efficacy of generic imatinib as first- and second-line therapy: 3-year follow-up of patients with chronic myeloid leukemia. Clinical Lymphoma, Myeloma & Leukemia. 2017;**17**(4):238-240

[155] Soria JC et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): A phase 3 randomised trial. The Lancet Oncology. 2015;**16**(8):990-998

[156] Antonescu CR et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. 2005;**11**(11):4182-4190

[157] Péter Csermely VÁ, Pongor S. The efficiency of multi-target drugs: The network approach might help drug design. Trends in Pharmacological Sciences. 2005;**26**(4):178-182

[158] Broekman F, Giovannetti E, Peters GJ. Tyrosine kinase inhibitors: Multi-targeted or single-targeted? World Journal of Clinical Oncology. 2011;**2**(2):80-93

[159] Petrelli A, Giordano S. From single- to multi-target drugs in cancer therapy: When aspecificity becomes an advantage. Current Medicinal Chemistry. 2008;**15**(5):422-432

[160] Medina-Franco JL et al. Shifting from the single to the multitarget paradigm in drug discovery. Drug Discovery Today. 2013;**18**(9-10):495-501

[161] Phani Krishna P, Khajapeer KV, Balakrishnan AP, Rajasekaran B. Multi-Targeted Approach to Treat Drug Resistant CML Using Natural Compounds: A Double Edged Sword. New York, USA: Crimson Publishers; 2018

[162] Johnson DB et al. Acquired BRAF inhibitor resistance: A multicenter meta-analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. European Journal of Cancer. 2015;**51**(18):2792-2799

[163] O'Dwyer M. First-line treatment of chronic myeloid leukaemia. Therapeutic Advances in Hematology. 2010;**1**(1):15-22

[164] Zhang S et al. Icotinib enhances lung cancer cell radiosensitivity in vitro and in vivo by inhibiting MAPK/ERK and AKT activation. Clinical

and Experimental Pharmacology & Physiology. 2018;**45**(9):969-977

[165] Tan CS et al. Third generation EGFR TKIs: Current data and future directions. Molecular Cancer. 2018;**17**(1):29

[166] Yamaguchi N et al. Dual ALK and EGFR inhibition targets a mechanism of acquired resistance to the tyrosine kinase inhibitor crizotinib in ALK rearranged lung cancer. Lung Cancer (Amsterdam, Netherlands). 2014;**83**(1):37-43

[167] ClinicalTrials.gov, Zhengtang Chen. Xinqiao Hospital of Chongqing-Identifier: NCT03461185. Anti-Angiogenesis Combine With EGFR-TKI in Advanced Non-Squamous Non Small Cell Lung Cancer. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03461185

[168] Ghelli Luserna Di Rora A et al. Targeting WEE1 to enhance conventional therapies for acute lymphoblastic leukemia. Journal of Hematology & Oncology. 2018;**11**(1):99

[169] Wu YL et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): A randomised, double-blind trial. The Lancet Oncology. 2013;**14**(8):777-786

[170] Yang S-C et al. Identification of potent EGFR inhibitors from TCM Database@Taiwan. PLoS Computational Biology. 2011;**7**(10):e1002189

[171] Liu M et al. Development of certain protein kinase inhibitors with the components from traditional Chinese medicine. Frontiers in Pharmacology. 2016;**7**:523

[172] Hu X-Q et al. Advances in synergistic combinations of Chinese herbal medicine for the treatment of cancer. Current Cancer Drug Targets. 2016;**16**(4):346-356

[173] Hung H-Y et al. The efficacy of traditional Chinese herbal medicine in the treatment of EGFR mutated stage IV pulmonary adenocarcinoma patients who received first-line EGFR-TKI treatment. Integrative Cancer Therapies. 2017;**16**(1):126-131

[174] He W, Cheng M. Meta-analysis on effectiveness and safety of traditional Chinese medicine combined with first-generation EGFR-TKI in treating advanced non-small cell lung cancer. Zhongguo Zhong Yao Za Zhi. 2017;**42**(13):2591-2598

[175] Liu ZL et al. Traditional Chinese medicinal herbs combined with epidermal growth factor receptor tyrosine kinase inhibitor for advanced non-small cell lung cancer: A systematic review and meta-analysis. Journal of Integrative Medicine. 2014;**12**(4):346-358

[176] Farber NJ et al. Renal cell carcinoma: The search for a reliable biomarker. Translational Cancer Research. 2017;**6**(3):620-632

[177] Manley BJ, Hakimi AA. Molecular profiling of renal cell carcinoma: Building a bridge towards clinical impact. Current Opinion in Urology. 2016;**26**(5):383-387

[178] Ahronian LG, Corcoran RBJGM. Strategies for monitoring and combating resistance to combination kinase inhibitors for cancer therapy. Genome Medicine. 2017;**9**(1):37

[179] Chen CT, Kesselheim AS. Journey of generic imatinib: A case study in oncology drug pricing. Journal of Oncology Practice. 2017;**13**(6):352-355

[180] Klil-Drori AJ et al. Comparative effectiveness of generic imatinib and

brand-name imatinib for the treatment of chronic myeloid leukemia. Blood. 2015;**126**(23):2778

[181] Kozaric AK et al. The comparison of efficacy between generic and branded imatinib in achievement of overall survival and cytogenetic responses in CML patients in Bosnia and Herzegovina. Blood. 2016;**128**(22):5451

[182] Dvorak P, Lysak D, Vokurka S. Discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia patients—Worldwide battlefield. Neoplasma. 2015;**62**(2):167-171