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REVIEW

Human topoisomerase II alpha as a prognostic biomarker in cancer chemotherapy

Yousaf Ali[1] · **Shafida Abd Hamid**[1]

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Abstract Topoisomerases are nuclear enzymes that regulate topology of DNA by facilitating the temporary cleavage and ligation cycle of DNA. Among all forms of topoisomerases, TOP-IIA is extensively associated with cell proliferation and therefore is an important therapeutic target in diseases that involved cellular proliferation such as cancers. Nearly half of present-day antitumor regimens contain at least one prescription that act as a topoisomerase inhibitor. Generally, tumor cells show divergent expression of TOP-IIA compared to normal cells. The remarkable expression of TOP-IIA in various carcinomas provides a significant biomarker toward understanding the nature of malignancy. TOP-IIA expression and amplification studies help in diagnosing cancer and to observe the disease progression, overall survival (OS) of patients, and response to therapy. This review highlights the research output and analysis in exploring the standing of TOP-IIA in various carcinomas. As some reports show contradiction within the same field of interest, the outline of that may help to induce researchers for further investigation and clarification. To the best of our knowledge, this is the first overview briefly summarizing the prognostic feature of TOP-IIA in various types of cancer.

Keywords Topoisomerase II alpha · Prognosis · Biomarker · Cancer

✉ Shafida Abd Hamid
shafida@iium.edu.my

[1] Kulliyyah of Science, International Islamic University Malaysia, Bandar Indera Mahkota, 25200 Kuantan, Pahang, Malaysia

Introduction

Topoisomerases (TOPs) are nuclear enzymes that facilitate temporary cleavage and ligation cycle of DNA [1–3]. Double helix structure of the DNA creates a barrier for hitch-free transcription, replication, recombination, or chromatin remodeling of the genetic material [4]. Tension develops during unaided separation of the DNA strands that blocks the continuation of genetic replication or transcription [5, 6]. Hence, in order to release the tension, topoisomerases transiently cut either single or double strand of the supercoiled DNA, change the topology by passage of the other strands, and realigning the ligation to form a tension-free non-helix double-stranded DNA [2, 5, 7, 8]. In other words, they convert the double helix DNA into another isomer by changing the topology of the DNA, as their name 'topoisomerase' reflects [2, 5]. Topoisomerase was first discovered in *Escherichia coli* in the 1971 by an American biochemist, James C. Wang, but enzymes of similar activities have been discovered by other researchers in other eukaryotic and prokaryotic organisms ranging from bacterium to human [5, 9].

Types of topoisomerases

There are two basic types of TOPs, TOP-I and TOP-II, classified based on their mode of action [7, 10]. During their transesterification process, TOP-I breaks a single-strand of DNA while TOP-II cuts two strands of DNA [1, 2, 10]. Each type is further classified into sub-types A and B [2, 10]. Irrespective of the origin of organism, topoisomerase sub-type A covalently attaches to the 3′ end of DNA and the sub-type B attaches to the 5′ end during their catalytic activity [8]. Both human and *E. coli* topoisomerase II alpha (TOP-IIA) are homodimers [3, 8]. Type I carries out its activity without any

co-factor, whereas type II activity is coupled with hydrolysis of ATP [9]. In mammals, there are two isozymes of TOP-IIA which only differs in molecular weight and are denoted as TOP-IIA (170 kDa) and TOP-IIβ (180 kDa). TOP-IIA has been proven to be distinctively associated with proliferating cells while TOP-IIβ is uniquely present in non-dividing cells and developing neuronal cells [1, 8, 9]. Therefore, TOP-IIA is an important therapeutic target in diseases that involved cellular proliferation such as microbial infection and cancers.

Topoisomerase inhibitions

Both TOP-I and TOP-II have been implicated in cancer treatment, and their resulting activities are reported to be modulated by the presence of some compounds [6, 11–13]. In research setting, such compounds that serve as anticancer drugs are referred to as topoisomerase-poisons but in the clinical setting, they are preferably called topoisomerase inhibitors [1]. All topoisomerase-targeted anticancer drugs are known to stabilize the cleavage-complex of the enzyme and DNA [1, 6, 12]. Meanwhile, some other compounds have been discovered to affect the activity of topoisomerase II in a way independent of cleavage-complex stabilization and are also called topoisomerase catalytic inhibitors [11]. This group should not be mistaken for the topoisomerase-poison group because normally, all topoisomerase anticancer drugs are tagged Top-poisons because they always convert topoisomerase to cellular toxins but some topoisomerase inhibitors tend to antagonize topoisomerase-poisons [11]. Thus, only in clinical setting that Top-poisons are called topoisomerase-inhibitor. To further distinguish these two groups of compounds, Top-poisons that facilitate DNA cleavage are called DNA cleavage-enhancing drugs [1]. Nearly half of present-day antitumor regimens contain at least one prescription that act as a topoisomerase inhibitor [14]. TOP-IIA has a major role in DNA replication, and research reports revealed that DNA damage made by TOP-IIA poisons is connected to their interaction with DNA replication fork progression [15].

Prognostic feature of topoisomerase II alpha in cancer

Regulated expression of normal genes has a key role in defining human health. Overexpression of normal genes contributes to several disorders including cancer. Knowing the mechanisms involved in the control expression of normal genes is helpful in understanding and preventing the disorders by genes therapeutic approach [16]. In all forms of topoisomerases, TOP-IIA is predominantly associated with proliferating cells [1, 2, 8], and therefore has been a common biomarker and target for many anticancer agents [17]. TOP-IIA overexpression is expressively related with changes in tumor behavior and responses to medication. Several reports proved that TOP-IIA expression in tumor cells is comparatively higher than normal cells [18]. The up-down regulation of TOP-IIA alone and sometimes in association with other genes predicted the nature of malignancy, therapeutic response, and overall survival of patients. Most of the published data about the prognostic aspect of TOP-IIA is related to breast cancer. However, the importance of this enzyme is not only confined to breast cancer, and its prognostic significance in other types of cancer is also part of the literature [19–26]. Here, we have assembled some of the reports recounting the prognostic part of TOP-IIA in various types of cancer.

Urinary bladder cancer

The prognostic assessment of TOP-IIA in primary non-muscle-invasive bladder cancer (NMIBC) was reported by Kim et al. [19]. They studied TOP-IIA mRNA levels in 103 tumor samples by using real-time polymerase chain reaction (PCR). Immunohistochemical (IH) staining was done on 39 matched specimens, and the expression levels of TOP-IIA mRNA were found more in high-stage ($p=0.041$) and high-grade ($p<0.001$) tumors samples. Kaplan–Meier analysis showed notable variation in tumor progression and recurrence, depending on the level of TOP-IIA expression (log-rank test, $p<0.05$). Furthermore, Cox regression analysis indicated that expression level of TOP-IIA could predict the recurrence and progression for NMIBC, with hazard ratios of 2.507; 95 % and 4.192; 95 %, and confidence intervals of 1.228–5.116; $p=0.012$ and 1.002–17.536; $p=0.049$ respectively. These findings suggested that higher expression of TOP-IIA has direct correlation with a high degree of recurrence and progression in primary NMIBC [19]. The results are actually in contrast with previously reported data of patients with superficial bladder cancer, where low levels of TOP-IIA mRNA in tumor tissue compared to biopsies of normal tissue were reported [20].

The prognostic potential of TOP-IIA in bladder carcinoma may be supported from the research report of Koren et al. [21] who investigated the IH expression of TOP-IIA in transitional cell carcinoma. They studied the correlation of TOP-IIA expression with grade, stage, and survival of patients. By IH staining of 57 urothelial neoplasms, positive TOP-IIA nuclear staining was found in 56 samples. The TOP-IIA index in death prediction or overall survival (OS) was quite significant but independent of grade and stage of cancer ($p=0.019$, hazard ratio 1.1). The higher TOP-IIA index directly showed more possibility of disease recurrence and poorer OS.

Human epidermal growth factor receptor 2 (HER2) amplifications were found to be correlated with alterations of the TOP-IIA gene. A total of 2317 bladder cancer samples were studied by fluorescence in situ hybridization (FISH) and IH.

Amplification frequencies, which were most often determined in advanced-stage tumors, were 13.8 % for HER2 and 3.4 % for TOP-IIA. In 56 % of HER2-amplified tumors, alterations of TOP-IIA were seen, including 33.3 % gains, 14.7 % co-amplifications, and 8 % deletions. Only 17.6 % of TOP-IIA amplifications took placed independently of HER2 alterations. The data showed significant association of TOP-IIA and HER2 amplifications with protein overexpression (for both $p<0.0001$), high grade (for both $p<0.0001$), and advanced stage of tumor (TOP-IIA $p<0.0218$, HER2 $p<0.0001$). Both TOP-IIA amplification ($p=0.0042$) and overexpression ($p=0.0077$) were associated with lower survival [22].

In a recent report, significant association between the expression of three genes, TOP-IIA, p53, and ki67, with World Health Organization (WHO) grade and recurrence has been explained statistically. The clinical relevance and prognostic standing of these three markers were assessed in 71 cases of non-muscle-invasive urothelial bladder biopsy specimens. Positive staining of TOP-IIA, p53, and ki67 was found in 39.5, 38, and 38 % cases respectively. The overexpression of TOP-IIA was associated with developed tumor stage. However, according to their report, none of these three genes was found to show predictive significance on recurrence [23]. It is worth to mention here that TOP-I elevation in transitional cell carcinoma (TSC) has also been reported by Monnin et al. [24] with 77 % (38 of 49) of the cases showing elevated expression of topoisomerase I.

Ovarian carcinoma

TOP-IIA is also a valuable prognostic factor for understanding the status of ovarian cancer. Zee et al. [25] reported that TOP-IIA expression was higher in advanced stage IV and grade III of ovarian carcinomas. Similarly, Fagged et al. [26] found that shorter survival of ovarian cancer patients has direct correlation with TOP-IIA expression. In the 133 cases examined, an elevated TOP-IIA mRNA expression was noticed in advanced stage of the disease ($p=0.011$) and high-grade tumors ($p=0.003$). Univariate Kaplan–Meier analysis also indicated that the overall survival of patients was reduced with high expression of TOP-IIA ($p=0.045$). On the same note, Ferrandina et al. [27] who worked on 96 primary untreated advanced ovarian cancer patients also supports the prognostic importance of TOP-IIA expression.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) stands as the third most common cause of cancer death and more prevalent in men than women [28]. The prognostic significance of TOP-IIA expression in HCC and assessment of TOP-IIA targeting agents was reported by Wong et al. [29]. TOP-IIA expression was found to be higher than other genes and was associated with microvascular invasion ($p=0.004$), advance histological grading ($p<0.001$), and an early age (≤40 years) onset of the malignancy ($p=0.007$). Evaluation on 148 patients (75 nonresistant and 73 chemoresistant) showed that TOP-IIA was positively associated with chemoresistance and shorter patients survival ($p=0.029$, $p<0.0001$, respectively). These findings are in accordance with earlier work by Watanuki et al. [30] who reported TOP-IIA overexpression association with a probably aggressive tumor phenotype, tumor recurrence, and death cases in HCC.

Most recently, the prognostic significance of TOP-IIA in HCC was elaborated by Panvichian et al. [31]. They studied gene aberrations of TOP-IIA and HER2 and protein expressions of TOP-IIA, HER2, Ki-67, and p53 in both tumor and corresponding non-tumor tissues. TOP-IIA overexpression was only discovered in tumor tissues while TOP-IIA gene amplification was neither detected in tumor nor in non-tumor tissues. The overexpression of TOP-IIA was associated with HCC tumor tissues ($p<0.001$), Ki-67 ($p=0.038$), and hepatitis B surface antigen in the serum ($p=0.004$). In contrast, HER2 overexpression and amplification were not observed in both tissues [31].

Prostate cancer

The association of TOP-IIA expression with prostate cancer was first reported by Sullivan et al. who discovered TOP-IIA at profound levels through the progression of the disease [32]. The expression of TOP-IIA was found to increase with Gleason score (GS, a common grading system for PC). Similar result was also reported by Willman et al. [33]. The elevated expression of enzyme in carcinomas was poorly distinguished and showed the highest GS. Hughes's group also reported the correlation of TOP-IIA elevation with GS and hormone insensitivity [34]. Further investigation on 100 cases of prostate cancer (PC) (59 advanced and 41 localized) and 42 cases of benign prostatic hyperplasia (BPH) found that 31 % of the advanced PC showed TOP-IIA overexpression and 26 % showed TOP-IIA low-level amplification. In addition, 16 % HER2 expression and 13 % of low-level amplification were noted. TOP-IIA co-amplification and co-expression was found in 66 and 75 % of HER2-positive cases, respectively. Localized PC and BPH presented neither gene amplification nor TOP-IIA overexpression. Gene amplification and overexpression were found correlated with high stage and GS, while low-level TOP-IIA amplification in PC showed correlation with HER2 duplication, decreased survival, and androgen resistance [35].

From another perspective, Resende et al. [36] carried out TOP-IIA digital assessment as well as fractal analysis in association with biochemical recurrence-free survival (BRFS). Out of 193 patients with PC, they analyzed the biochemical

and pathological data of those with $p<0.05$. TOP-IIA expression was found to be associated with higher GS ($p=0.018$) and higher levels of preoperative PSA ($p=0.011$). Shorter BRFS ($p=0.001$) was observed for patients with higher levels of TOP-IIA. Fractal analysis showed high levels of TOP-IIA expression association with angiolymphatic invasion ($p=0.033$) and higher GS ($p=0.025$) [36].

Furthermore, evaluation of the immunohistochemical expression of TOP-IIA and HER2/neu in PC and benign BPH found TOP-IIA expression to be higher both in moderately and poorly differentiated carcinoma cases compared to BPH ($p=0.005$ and $p=0.002$, respectively). The difference observed between the expression of well-differentiated carcinoma and BPH was statistically not significant ($p=0.171$). Within the spectrum of PC, a statistically significant upturn was noticed in TOP-IIA expression with increased GS ($p=0.001$) [37].

Soft tissue sarcoma

Soft tissue sarcomas (STSs) comprised of about 15 % malignant tumors in children and 1 % in adults. TOP-IIA expression as well as gene amplification was found in several cases of STS, which were declared helpful in the evaluation of different grades of STS cases [38]. On the same note, leiomyosarcomas (one of the forms of sarcoma) was reported to show TOP-IIA expression [39]. Similarly, the enzyme was also intensely expressed in most cases involving synovial sarcomas with no variation in gene amplification after treatment [40]. The use of TOP-IIA expression as a useful diagnostic marker of liposarcoma was also suggested by Endo et al. [41] based on their surgical specimen study of various liposarcomas.

Brain-related cancers

The prognostic feature of TOP-IIA in glioma was studied by Zhao et al. [42] whereby the correlation between the enzyme and PCNA was identified. On the same note, Hong et al. [43] explored the role of TOP-IIA in cell proliferation and cell survival in glioblastoma cancer stem cells. When TOP-IIA expression was quieted in U87 cell lines using a specific siRNA, they noticed a decline in cell proliferation and cell survival in cancer stem cells. In addition, the expression of TOP-IIA was found higher in cancer stem cells compared to non-cancer stem cells. Based on these evidences, they recommended TOP-IIA as a biomarker in glioblastoma cancer stem cells. Likewise, TOP-IIA expression score and its prognostic importance in overall survival of patients in oligodendroglioma patients were reported by Miettinen et al. [44]. TOP-IIA expression was found to be strongly linked with patient prognosis. The survival of patients with low TOP-IIA value was reported after 5-year follow-up ($p=0.03$), and the Cox regression analysis showed TOP-IIA as an independent prognostic score for overall survival ($p=0.034$) [44].

Oral squamous cell carcinoma and esophageal squamous cell carcinoma

Protein expression in 16 patients with oral epithelial dysplasia (OED), 22 oral squamous cell carcinoma (OSCC), and 20 normal oral mucosa was studied quite recently by Shamaa et al. [45]. TOP-IIA expression was observed in all the specimens and was found significantly high in tumors of low differentiation compared to corresponding tumors of high and moderate differentiation ($p<0.001$) [45].

In contrast to Hanagiri et al. [46] who reported that TOP-IIA overexpression had no impact on patient prognosis, a recent work by Xu et al. [47] explored the prognostic importance of TOP-IIA as biomarker in resectable esophageal squamous cell carcinoma (ESCC) patients. They conducted a large-scale study on 829 specimens of ESCC from those who underwent complete esophageal cancer resection, evaluated by using IH assay. TOP-IIA overexpression was identified as an independent prognostic factor for progression-free survival and overall survival ($p<0.001$ and $p=0.009$ respectively). In an earlier study, Ohashi et al. immunohistochemically studied the TOP-IIA expression in 136 cases of human ESCC, 10 foci of squamous dysplasia, and 10 non-pathologic squamous epithelium. The direct correlation between TOP-IIA and Ki67 labeling index (LI) in all specimens was examined, and the TOP-IIA LI/Ki67 LI (T/K ratio) was shown to be higher in carcinoma cases compared to normal epithelium. However, TOP-IIA LI alone showed no correlation with the clinicopathological parameters studied, although comparatively higher T/K ratio was observed in higher histological stages/lymph nodes metastasis. Carcinoma cases where T/K ratio >0.8 gave poorer prognosis than those with T/K ratio <0.8 [48].

Nasopharyngeal carcinomas and laryngeal squamous cell carcinoma

TOP-IIA was recently recognized as a differentially up-regulated gene in nasopharyngeal carcinoma (NPC) tissues by Lan et al. [49]. The biopsy specimens of 124 NPC patients, who were subjected to standard treatment and have no indication of metastasis at preliminary diagnosis, were studied. H-score method was used to analyze TOP-IIA immunohistochemistry, and cases where H-score was found higher than median score were considered as presenting TOP-IIA overexpression. The results were associated with the disease-specific survival, clinicopathological variables, and distant metastasis-free survival. The up-regulation of TOP-IIA was highly related with stages III and IV of the American Joint of Cancer

Committee ($p=0.019$). TOP-IIA overexpression was univariately prognostic of hostile outcomes for disease-specific survival ($p=0.0078$) and distant metastasis-free survival ($p=0.0003$). Multivariate analysis indicated that the overexpression of TOP-IIA stayed prognostically independent to show poorer disease-specific survival ($p=0.047$, hazard ratio=1.732) and distant metastasis-free survival ($p=0.003$, hazard ratio=2.569), along with advanced American Joint of Cancer Committee stages III and IV [49].

In another study, TOP-IIA protein up-regulation was compared between specimens of laryngeal carcinoma patients and healthy tissues. TOP-IIA expression was observed in about 71 % cases of laryngeal carcinoma tissues, correlated with advanced tumor T stage and tumor de-differentiation. In contrast, only 9 % of healthy tissues showed TOP-IIA expression. There was no indication of correlation between TOP-IIA expression and TOP-IIA amplification. However, TOP-IIA expression was found directly associated with aneuploidy of chromosome 17 ($p<0.05$). Abnormal chromosome 17 aneuploidy and TOP-IIA expression were found to give rise to laryngeal cancer development and progression. These findings lead to suggestion that TOP-IIA may be used as a target for the treatment of laryngeal carcinoma patients [50].

Acute leukemia

The use of TOP-IIA and p-glycoprotein (gp-170) expression as a combined parameter was found to be more suitable compared to their individual factor for the prognostic study of acute leukemia [51]. The prognostic feature of TOP-IIA expression in Hodgkin's lymphoma (a type of blood cancer) had also been studied. However, the adverse prognostic effect of elevated TOP-IIA expression was mostly restricted only to advanced-stage patients, while its effect in early stages was statistically insignificant. Furthermore, high TOP-IIA expression was predictive of adverse outcome in patients treated only with chemotherapy [52].

Wilms' tumor

The prognostic role of TOP-IIA in Wilms' tumorigenesis was indicated by Tretiakova et al. [53] by immunostaining samples of primary and metastatic Wilms' tumor. Over expression of TOP-IIA protein was observed in 97 % of Wilms' tumors, which was significantly correlated with proliferation, as assessed by Ki67 ($r=0.85$). Elevation of TOP-IIA expression was correlated with the existence of metastases, prominent apoptosis, vascular invasion, and adverse clinical outcomes ($p<0.05$). The high levels of TOP-IIA were also associated with tumor aggressiveness [53].

Pancreatic ductal adenocarcinoma

Tsiambas et al. [54] evaluated translation and gene status of TOP-IIA pancreatic ductal adenocarcinoma (PDA), showing the possible prognostic effect of gene alterations. Fifty sporadic, primary PDAs were subjected to tissue microarray analysis, and the overexpression of TOP-IIA was found in 64 % of tumor cells. Gene deletion and amplification, linked with overexpression of protein, was found in four and nine cases respectively. In 19 cases, aneuploidy was recorded in chromosome with high death rate (Cox regression analysis, $p=0.001$). The expression of TOP-IIA was strongly correlated with grade ($p=0.034$) and stage ($p=0.021$), and its amplification was associated with overexpression of protein, but not vice versa [54]. These findings may be compared with another study conducted by Liang et al. [55] on Chinese patients suffering from PDA. According to their report, the nuclear positive index of TOP-IIA varied from 0.5 to 70 % and the positive rate of HER2/neu in PDA was recorded in 46.2 %. By using fluorescence in situ hybridization (FISH), 9/10 TOP-IIA amplified adenocarcinomas indicated TOP-IIA and HER2/neu gene co-amplification. Only one case with HER2/neu gene amplification adenocarcinoma did not exhibit TOP-IIA amplification. The expression of TOP-IIA HER2/neu proteins and amplification of TOP-IIA and HER2/neu gene in adjacent non-neoplastic pancreatic tissues, chronic pancreatitis tissues, and in normal pancreas were not observed. Similarly, no relationship was detected between expression and amplification of TOP-IIA and HER2/neu ($p>0.05$). However, TOP-IIA gene amplification was found to be correlated with HER2/neu amplification ($p<0.01$) [55].

Papillary thyroid carcinoma

Manaios et al. [56] examined the possible alterations of enzymatic protein in papillary thyroid carcinoma and compared them with Ki67 expression. The overexpression of both TOP-IIA and Ki67 was associated to aggressive phenotype in papillary thyroid carcinoma.

Non-small cell lung cancer

Yan et al. [57] examined the prognostic role of TOP-IIA expression level in patients with non-small cell lung cancer (NSCLC) (stages I–III), who underwent surgery and received adjuvant chemotherapy. By immunohistochemistry procedure, the expression of Ki67 and TOP-IIA in paraffin-embedded tissues was investigated. The relationships between chemotherapy regimens, disease-free survival (DFS), the expression of biomarkers, and clinicopathological characteristics were evaluated. Ki67 and TOP-IIA was highly expressed in 36.4 and 22.5 % out of 151 patients, respectively. Univariate survival analysis demonstrated that non-adenocarcinoma,

over expression of TOP-IIA, male sex, pathological N stage, or earlier pathological TNM stage were linked with better DFS, while smoking history, age, T stage, diverse chemotherapy regimens, and Ki67 expression level were found of non-significant prognostic. The overall result concluded good correlation of high TOP-IIA expression with better DFS for those treated with adjuvant chemotherapy. Thus for NSCLC patients who were subjected to adjuvant chemotherapy after surgery, TOP-IIA may be utilized as an independent prognostic biomarker of DFS [57].

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a type of non-Hodgkin's lymphoma with 3–4 years of overall survival time. Schrader et al. [58] elaborated the expression of TOP-IIA as a central prognostic marker in MCL. High expression of TOP-IIA was found to be connected with shorten overall survival time. Examination of biopsy specimens of 95 patients showed that overall survival time for low TOP-IIA expression (<10 %) was 49 months compared to higher expression (>10 %) at 17 months [58].

Renal medullary carcinoma

Albadine et al. [59] performed immune-expression analysis of renal medullary carcinoma (RMC) tissue and found that TOP-IIA was overexpressed in 85 % (11/13) of RMC cases and therefore suggested that TOP-IIA probably be an effective molecular target in future research and trial. Similarly, Schaeffer et al. [60] also investigated the elevation of TOP-IIA expression and positive response was observed when topoisomerase II inhibitors were used in metastatic RMC.

Adrenocortical carcinoma

Jain et al. [61] investigated TOP-IIA expression in human adrenocortical neoplasm and adrenocortical carcinoma (ACC) cells to analyze the anticancer potential of some TOP-IIA inhibitors in ACC cells. TOP-IIA expression levels were assessed in 11 ACCs, 21 normal adrenal cortex, and 80 benign adrenocortical tumors tissues. In vitro siRNA knockdown of TOP-IIA in ACC cell lines (NCI-H295R and SW13) was used to know its effect on cell cycle, cellular proliferation, anchorage-independent growth, and also cellular invasion. A total of 14 TOP-IIA inhibitors were screened for their anticancer action in ACC cells. Higher expression of TOP-IIA was observed in ACC compared to benign ($p<0.008$) and normal adrenocortical tissue samples ($p<0.05$). Knockdown of TOP-IIA gene expression in ACC cell lines considerably reduced cell proliferation, anchorage-independent growth, and cellular invasion ($p<0.05$). A screening assay in NCI-H295R cells showed that 11/14 TOP-IIA inhibitors exhibited anti-proliferative activity, while 5/14 TOP-IIA inhibitors showed even higher anti-proliferative activity than mitotane and aclarubicin. Among the TOP-IIA inhibitors screened, aclarubicin was found more potent in future clinical trials for patients suffering from locally advanced and metastatic ACC [61].

Colon/colorectal cancer

Various studies are pointing the prospect of TOP-IIA expression in the diagnosis of colon and colorectal related cancers. In 1 study, 48 (22.3 %) biopsy samples out of 215 patients were diagnosed with colon cancer. TOP-IIA overexpression was discovered in both colon carcinoma and high-grade dysplasia samples. In addition, TOP-IIA overexpression exhibited correlation with Ki67 expression in all ranks of epithelial dysplasia and grades of tumor [62].

Kim et al. [63] demonstrated the importance of targeting overexpression of TOP-IIA by its inhibitors in colon and esophageal cancers. Analysis of 18 samples of tumor and nearby normal tissues of colon, esophageal, and gastric cancers for Top-I and TOP-IIA mRNA expression found that TOP-IIA gene mRNA expression was significantly higher in tumor tissues compared to the nearby normal tissues. Likewise, the expression showed correlation with S-phase population in cell cycle. A significant relationship of Top-I and TOP-IIA was observed between tumors and normal samples in colon and esophageal cancers ($p<0.05$) [63].

With the imperative role in occurrence and metastasis of the colorectal carcinomas, TOP-IIA may serve as a valuable indicator for the diagnosis, treatment, and the prognostic evaluation of the malignancy. Yang et al. [64] reported that the protein and mRNA expressions of TOP-IIA in the metastatic lymph nodes were considerably higher than those in matched primary lesions and normal tissues ($p<0.05$). No significant difference of TOP-IIA expressions was found between normal mucosa and colorectal carcinomas. The protein and mRNA expressions of TOP-IIA were significantly correlated to metastasis and invasion depth ($p<0.05$), but not to the differentiation of the tumor ($p>0.05$) [64].

Liming et al. [65] retrospectively assessed the status of HER2 and TOP-IIA in tumor specimens from 302 rectal cancer (RC) patients and compared the clinicopathological parameters. The overexpression of HER2 was recorded in 31 patients (10.3 %), while positive immunostaining for the TOP-IIA protein was detected in 272 patients (90.1 %). In another study, TOP-IIA overexpression in colorectal cancer was found to be related with prolonged overall survival ($p=0.022$) and disease-free survival ($p=0.036$) [66]. Moreover, lower expression of TOP-IIA ($p=0.017$) was found as an independent predictive factor for poor prognosis [66].

Gastric cancer

The expression and amplification of TOP-IIA, ERBB2, and DARPP32 genes in gastric cancer samples were characterized by Varies et al. [67]. These three genes were amplified in 17 % of the intestinal type of gastric adenocarcinoma. However, PCR quantitative studies showed that the expression levels of the genes were independent and the overexpression was recorded as 17 % in TOP-IIA, 48 % in DARPP32, and 3 % in ERBB2 [67].

The amplification of TOP-IIA in gastric cancer was studied by Kanta et al. [68] in their investigation of the effectiveness of its inhibitors. Amplification of TOP-IIA was observed in 13/38 cases. In all cases except one, no abnormality or divergence in the TOP-IIA gene was detected without HER2 overexpression. TOP-IIA amplification had no mutual relation with the TOP-IIA protein-labeling index, and they showed an independent relation with each other. The low prevalence of TOP-IIA amplification (2.4 %) revealed the minor advantage of anthracycline-type drugs in patients with gastric cancer [68].

In another study, co-amplification of TOP-IIA with HER2/neu amplification was present in gastric and esophagogastric junction cancers (63 and 68 % respectively) and was associated with low survival [69]. Similarly, Liu et al. [70] reported that high expression of HER2/neu and TOP-IIA (21.0 and 80.6 % respectively) was found in tissues of 62 gastric cancer patients compared to normal gastric tissue ($p<0.05$). However, they declared no correlation between TOP-IIA expression and HER2/neu.

Breast cancer

Sekine et al. [71] inspected the data of 6378 patients testified in 69 different investigations, and evaluated the role of 18 genes in breast cancer. Among the different selected markers, overexpression and amplification of TOP-IIA were more commonly noticed in breast cancer patients who responded to first-line chemotherapy [71]. In locally advanced breast cancer (LABC), the prognostic value and significance of TOP-IIA was reported by Rebey et al. [72]. The positive expressions of TOP-IIA and tissue inhibitor of metalloproteinases 1 (TIMP-1) in LABC samples were associated with factors of poor prognosis such as the presence of necrosis and low apoptotic count [72]. On the same note, Chen et al. [73] determined the expression of different biomarkers and found the co-expression of HER2/ TOP-IIA associated with chemotherapeutic response (logistic regression $p=0.042$). During neoadjuvant chemotherapy, 20 % alteration in the TOP-IIA levels was noticed, which may affect the sensitivity to therapy. Most recently, high level of *TOP-IIA* expression was reported in triple negative breast cancer (TNBC) study, involving 83 patients who underwent surgery [73]. The expression of TOP-IIA suggested the effectiveness of anthracyclines in TNBC therapy [74]. In early breast cancer, TOP-IIA gene amplification provided negative prognostic evidence [75].

TOP-IIA overexpression is also used as a prognostic marker for the response to chemotherapeutic agents [76]. Biesaga et al. [77] reported that, after surgery and anthracycline adjuvant chemotherapy, around 60 % of patients with breast cancer showed recurrence. The study of different markers clearly indicated that lower TOP-IIA expression and lower tumor grade are promising prognostic factors for the patients with early advanced breast cancer, after using anthracycline-based adjuvant chemotherapy [77].

Conclusion

In conclusion, prognostic value of TOP-IIA is pointed out by different researchers in various types of cancer. Understanding the overexpression, implication, and co-amplification of TOP-IIA with other genes help in determining the stage of cancer, which indicates the overall survival of patients and their response to treatment. This report is an attempt to combine some of the important scattered literatures about the prognostic aspect of TOP-IIA. Further investigations are required to know the exact role of TOP-IIA, its association with other biomarkers, and correlation of expression among different types of cancer. These may help in selective inhibition of TOP-IIA, which is next to targeted chemotherapy.

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Compliance of ethical standards

Conflicts of interest None

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