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Review

Meta-analysis of the prognostic role of p53: Playground for solution or source of confusion?

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Deregulation of the p53 gene is considered to be a prognostic marker in patients with tumours. In this review we are summarizing the results of meta-analyses dealing with the prognostic role of p53 status published in the literature. We found 7 studies examining 5 different tumours (osteosarcoma, ovarian carcinomas (OC), astrocytomas, urothelial bladder carcinomas and non-small lung cell carcinomas (NSCLC)). Significant results are reported in four of the studies (OC and NSLCC). However, most of the studies found significant heterogeneity, particularly those that reported significant results, whereas the majority used the results of univariate survival analysis for quantitative synthesis. Despite the significant information published the last decades regarding the role of p53 alterations in the clinical course of patients with malignant tumours, it could be argued that there is a huge amount of studies that cannot be combined in order to provide more valid and aggregated results.

Key words: Overexpression, tumours, p53 protein, immunohistochemistry.

INTRODUCTION

The tumour suppressor gene p53 is at the hub of a plethora of signaling pathways involved in cell cycle control and the maintenance of DNA integrity (Vousden and Prives, 2009). Even 30 years after its discovery, it is still somewhat of an enigma since it has multifaceted roles. Since the 1990s several studies have reported details regarding the basic structure of p53 protein, such as the DNA binding domain which indicates the effects of common p53 cancer mutants, namely apoptosis deregulation, cell cycle promotion, DNA repair impairment, overall inducing genetic instability. However, it should be noted that many aspects of the structural basis of p53 protein or its inactivation in cancer remain elusive.

Loss of p53 tumour suppressor function is one of the most frequent features of human cancer. p53 is inactivated directly in 50% of human cancers whereas in the remaining malignant neoplasms its apoptotic function seems to be impaired (Joerger and Fersht, 2010). The wild type p53 protein product has a dual role in the control of cell proliferation and apoptosis (Vogelstein et al., 2000) either arresting cells in G1 phase to allow replication of undamaged DNA or inducing apoptosis when DNA damage is irreversible. Moreover, phosphorylation of p53 protein, in contrast to what is seen in untransformed cells, is expected to alter the conformation of p53 and its corresponding association with other transcription factors such as MDM-2, thereby providing a mechanism by which p53 activities can be altered in human tumours that do not harbor mutant forms of p53 (Buschman et al., 2000). The latter may explain the increasing evidence for nonfunctional p53, despite its wild type form in human tumours. In addition to its complex pattern of phosphorylation, p53 is acetylated on at least three known residues, which is mediated by pCAF and CBP/p300 in response to DNA damage and stress, and is possibly dependent on its phosphorylation. Acetylation has been implicated in transcriptional activities of p53 and its association with members of the basal transcriptional machinery. The loss of p53 function in tumour cells results in impaired p53-mediated cell cycle arrest and apoptosis and therefore in a continuous growth of aberrant cells (Vogelstein et al., 2000). Overexpression of p53 in the cell nucleus detected by immunohistochemical techniques is regarded as a surrogate marker of p53 mutation and has been commonly used in practice in many tumours during the past 15 years. In this context, there is a huge amount of studies in the literature investigating the prognostic role of p53 immunosuppressor in several human tumours.

In this article, we provide a short systematic review of published papers dealing with meta-analysis of the prognostic role of p53 immunoexpression and TP53

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gene alterations in several human tumours in an effort to summarize all the attempts to synthesize published information in this regard (Table 1). In particular we are discussing the results of seven studies examining five different tumours (osteosarcoma, ovarian carcinomas (OC), astrocytomas, urothelial bladder carcinomas and non-small lung cell carcinomas (NSCLC)).

SEARCH STRATEGY AND SELECTION CRITERIA

We systematically reviewed all meta-analyses published between January 1990 and December 2010 in English language that analyzed the prognostic role of p53 immunoexpression and TP53 gene alterations in patients with malignant neoplasms. We identified twenty eight articles from a research of MEDLINE database using the key words “meta-analysis” and “p53” and “prognosis” or “survival”. Reviews analyzing the prognostic role of p53 alterations without performing data synthesis of the results of each individual study were excluded from our analysis. From this research we found seven meta-analysis dealing with the prognostic significance of p53 alterations in human malignancies (osteosarcoma, ovarian carcinomas (OC), astrocytomas, urothelial bladder carcinomas and non-small lung cell carcinomas (NSCLC)).

OSTEOSARCOMA

Several studies have tried to investigate the clinical significance of p53 alterations or TP53 protein over-expression in osteosarcoma based on the high frequency of p53 gene mutations observed in these tumours (Gokgoz et al., 2001; Gorlick et al., 1999; Junior et al., 2003). Many studies failed to show any relationship between p53 status, assessed by either protein expression or by the identification of gene alterations and response in chemotherapy (Gorlick, 1999; Serra 1999; Jensen et al., 1998; Yokoyama et al., 1998; Radig et al., 1998; Kakar et al., 2000; Ueda et al., 1993; Patino-Garcia et al., 2003; Junior, 2003) or disease progression, whereas other studies suggested associations with poor response to chemotherapy and decreased survival or reported inconclusive results. However, most of these studies had limited sample size. A few years ago Pakos et al. (2004) conducted a meta-analysis of all available studies relating TP53 expression and TP53 gene mutations with response to chemotherapy and/or clinical outcome as defined by 2 year survival, since all eligible studies had at least 2 years of follow-up. During enrollment to the analysis, four studies (4/23) were excluded due to lack of any informative clinical data and six were excluded because they reflected duplicate data. The eligibility criteria for inclusion in this meta-analysis are described in detail (Pakos et al., 2004). In the quantitative analysis 499 patients with osteosarcoma were enrolled. Nine studies (282 patients) had data for the histologic response to chemotherapy and 14 (436 patients) had data on 2 year survival. Nine of these studies used immunohistochemistry (IHC) to determine TP53 status, four studies used reverse transcription (RT)-PCR and three used both methodologies. Although separate analysis was performed for studies with IHC for p53, or those using molecular analysis of TP53 alterations, emphasis is given on analysis performed for the entire group of studies eligible for inclusion in meta-analysis, irrespectively of the method used for p53 status assessment. However, quantitative analysis did not show any statistical significance in the heterogeneity among various studies.

In summary, when synthetic analysis was performed (Pakos et al., 2004) p53 status had no discriminating ability to identify poor versus good response to chemotherapy. Interestingly, p53 positive status tended to be associated with a worse 2 year survival, although the overall results were not formally statistically significant.

Significant associations with prognosis were observed when analysis was restricted to studies that clearly stated blind assessment of p53 protein expression or to studies using RT-PCR for evaluating TP53 gene alterations. It is to be noted, however, that the hazard and risk ratios used in quantitative synthesis were not adjusted for other tumour determinants such as tumour size, type and grade, a fact that could account for the adverse effect of p53 status on survival and could lead to biased results.

OVARIAN CANCER

p53 is one of the most frequently studied putative molecular biological prognostic factors in ovarian cancer (OC), mostly due to the fact that it also holds considerable promise as a therapeutic target (de Graff et al., 2009). Systematic reviews in this regard have showed that p53 status might predict prognosis in ovarian cancer, suggesting also considerable methodological variability among published studies (de Graff et al., 2009; Crijns et al., 2003; Hall et al., 2004). de Graeff et al., (2009) recently conducted a meta-analysis on p53 status in OC, as determined by IHC, mutational analysis, in situ hybridization and immunoassays. Forty-two studies used IHC, using a wide range for defining positive immunostaining (from 5 to 90%) and applied a score system to classify studies as phase I-III prognostic marker studies, according to the classification proposed by Simon and Altman (Simon and Altman, 1994). Quantitative synthesis included all log-hazard ratios of a univariate regression analysis reported in the enrolled studies or extracted by the published data. There was no adjustment for already defined significant prognosticators for OC (such as histologic grade and type). Meta-analysis on the prognostic value of p53 status based on the 53 enrolled

Table 1. A summary of the meta-analyses of the prognostic role of p53 abnormalities in human neoplasms (NM = not mentioned, SCC = squamous cell carcinoma, IHC = immunohistochemistry, NSCLL = non small cell lung carcinoma).

Year of publication	Tumour investigated	Number of studies included	Number of patients investigated	Heterogeneity	Publication bias	Subgroup analysis	Adjustment for other factors	Results
2004	Osteosarcomas	19	499	No	NM	Yes	No	Combined HR = 1.47, p value 0.001
2009	Ovarian cancer	53	9448	Yes	No	Yes	No	Combined HR = 1.47, p value <0.0001
2010	Astrocytomas	14	1328	No	No	No	Yes	Combined HR = 1.034, p=0.531
1999	Urothelial bladder cancer	12 for recurrence 11 for progression 16 for mortality	NM	Yes	No	Yes	No	Combined HR = 1.6, 95% CI 1.2- 2.1 for recurrence, HR = 3.1, 95% CI 1.9 – 4.9 for progression HR=1.4, 95% CI 1.2-1.7 for mortality
2000	Non small lung cancer	30 for protein expression	3579	Yes	NM	Yes	No	Combined 3 and 5 year HR -11.4.5 (p = 0.0021) and -9.1% (p = 0.0091) for immunohistochemical studies
		11 for DNA alterations	1031					10.7% (p=0.0001) and -22% (p=0.0026) for molecular studies
2000	Non small lung cancer	8	829	Yes	NM	No	No	1.52 with 95% CI of 1.07-2.16
2001	Non small lung cancer	56 any stage, n=11 Stages I–II, n=19 Stages I–IIIB, n=5 Stages III–IV, n=9 Surgically resected NSCLC, n=20 SCC, n=9 Adenocarcinoma, n=9 For a positive IHC with Ab 1801, n=8 for a positive IHC with Ab DO-7, n=16 For molecular alterations, n=13	3944	Yes	NM	Yes – only subgroup analysis was performed	No	Any stage, combined HR = 1.44, 95% CI (1.20–1.72) In stages I–II, combined HR = 1.50, 95% CI (1.32–1.70) In stages I–IIIB, combined HR = 1.68, 95% CI (1.23–2.29) In stages III–IV, combined HR = 1.68, 95%CI (1.30–2.18) In surgically resected NSCLC, combined HR=1.48, 95% CI (1.29–1.70) In squamous cell carcinoma, combined HR= 1.37, 95% CI (1.02–1.85) In adenocarcinoma, combined HR= 2.24 , 95% CI (1.70–2.95) For a positive IHC with antibody 1801, combined HR = 1.57, 95% CI (1.28–1.91) For a positive IHC with antibody DO-7, combined HR = 1.25, 95% CI (1.09–1.43) For molecular alterations, combined HR= 1.65 (1.35–2.00)

studies showed that aberrant p53 status is associated with poor overall survival (combined HR=1.47, p value 0.001). Subgroup analysis revealed a prognostic impact for IHC studies with the DO-7 antibody, studies using mutational analysis and studies with a quality score of 6. This result was confirmed when meta-analysis was restricted to studies investigating only serous tumours (Bali et al., 2004; Terauchi et al., 2005; Ueno et al., 2006; Yakirevich et al., 2006; Kobel et al., 2008; Vartiainen et al., 2008). However, meta-regression analysis showed that the outcome was influenced by FIGO stage distribution. This is in accordance with the fact that in the six studies reporting results for stage III/IV prognostic ability of p53 did not hold true. However, there was considerable heterogeneity between studies (I^2 = 49.4%), indicating that not all sources of heterogeneity, such as methodological factors, were taken into consideration.

Taken together, this meta-analysis shows that p53 seems to have a modest effect in survival and is unlikely to be useful as a prognostic marker for OCs in clinical practice.

BRAIN TUMOURS

Astrocytic tumours

p53 immunoexpression has been one of the most broadly investigated markers in human astrocytomas in the past 15 years (Louis et al., 2007). Molecular techniques have shown that secondary glioblastomas are strongly associated with p53 mutations, in contrast to primary ones that are usually marked by epidermal growth factor (EGFR)-amplification and loss of heterogeneity (LOH) in chromosome 10 (Louis et al., 2007). The challenge of p53 expression as a prognostic factor in gliomas has been reviewed by several studies (Ishii and de Tribolet, 1998; Nieder et al., 2000) concluding a relative low impact of p53 mutations on the survival of malignant astocytomas, as compared to other established parameters, such as grade and age. A confirmation of this suggestion came recently from our group (Levidou et al., 2010) in which we reviewed 44 publications (including 3627 patients) and a performed a meta-analysis based on 14 of the studies that fulfilled the criteria for inclusion in this quantitative synthesis. In particular, this meta-analysis enrolled original articles focusing on the prognostic role of p53 immunoexpression in diffuse astrocymomas (grade II-IV) adjusted for histologic grade and patients' age, excluding those studies analyzing gliomas other than those of pure astrocytic origin or duplicate publications. This analysis showed that p53 expression is not a significant prognostic factor (combined HR = 1.034, p=0.531) in human astrocytomas, a result that was also repeated when analysis was restricted only to glioblastomas. Although there were not significant between- study heterogeneity and publication bias, the descriptive analysis of 44 studies showed that most of the studies did not contain information on important variables, such as patients' sex and age, whereas there was a wide variation of the definition of positive p53 staining among studies. Meta-analysis included only those estimates (HR and 95% CIs) derived from multivariate Cox regression models in which the prognostic value of p53 expression status was adjusted for tumour grade and patients' age.

In conclusion, synthetic analysis showed that p53 immunoexpression when adjusted for tumour grade and patients' age is not correlated with prognosis in patients with diffuse astrocytomas.

Ependymomas

Mutations of the TP53 tumour suppressor gene have been occasionally observed in ependymomas (Louis et al., 2007). Von Haken et al. (1996) reported a 50% incidence of allelic losses or the short arm of chromosome 17 in 18 paediatric ependymomas, but TP53 gene was rule out as a candidate. Although the information regarding the prognostic role of p53 status in ependymomas is limited, its higher expression has been reported to correlate with shorter progression free and overall survival. This observation, however, reflects the results of cohorts (published in 5 studies, 4 of which were duplicate reports (Zamecnik et al., 2003; Verstegen et al., 2002; Zamechnik et al., 2004; Korshunov et al., 2001). Due to inadequate published data (only 3 groups of researchers investigating the effect of p53 alterations on survival in ependymomas, total number of examined patients rising to 185) the attempt of Kuncova et al. (2009) to perform a meta-analysis in this regard was unsuccessful and therefore the authors just reported the results of individual studies.

UROTHELIAL BLADDER CANCER (BLADDER UC)

The first important report which showed that p53 changes were predictive of outcome in patients with bladder cancer undergoing cystectomy was published by Esrig et al., (1999, 1994). Since then there have been several studies focusing on the prognostic role of p53 expression or mutational status in bladder UC. In the same context, a few reviews tried to summarize published results, which concluded that more or less in p53 staining is not sufficient to stratify patients with bladder UC in terms of aggressiveness (Schimtz-Drager et al., 2000; Zlotta and Schulman, 2000; Olumi, 2000; Masters et al., 2003; Goebell et al., 2004). A quantitative approach of summarization was performed by Malats et al. (2005), who performed a meta-analysis on 117 studies focusing on the correlation of p53 expression with recurrence, progression and mortality. Twelve studies (12/34) dealing with recurrence, eleven studies dealing with progression

(11/24) and 16 (16/35) dealing with mortality were eligible for inclusion in meta-analysis. From these investigations seven reported a significant association with progression, five with recurrence and six with mortality. Meta-analysis included only those estimates (HR and 95% CI) derived from Cox regression, irrespectively of the cofactors used in the multivariate models. All three analysis showed that overexpression of p53 is correlated with an adverse outcome (combined HR =1.6, 95% CI 1.2 to 2.1 for recurrence, HR = 3.1, 95% CI 1.9 to 4.9 for progression and HR=1.4, 95% CI 1.2 to 1.7 for mortality). However, all three analysis displayed significant heterogeneity (p=0.010, p=0.009 and p=0.001, respectively) attributed to different methodologies applied in several studies that were included in the meta-analysis. In this context, there is an extensive comment on the differences as well as the information missing in the most of the published investigations. It is worthy of note that the authors report the limitations of these meta-analyses, such as the small number of the included studies and suggest that their interpretation should be made with caution.

Despite the significant heterogeneity that emerged among the enrolled studies, this meta-analysis actually correlates p53 alterations with patients' recurrence, progression and survival.

LUNG CANCER

Lung cancer has been the leading cause of cancer death in North America and in Japan in 1998 (Mitsudomi et al., 2000). It is divided into two morphological types, namely: small cell carcinoma and non-small cell carcinoma (NSCLC). Recent literature focuses on the assessment of possible tools in the discrimination of cases that could predict relapse or unfavourable prognosis. The p53 gene is the most exclusively investigated in this context because its genetic alterations are common and usually present as a qualitative alteration that is, point mutations (Mitsudomi et al., 2000). However, there is a great controversy as to whether p53 adversely affects survival of NSCLC cases, since there are studies reporting that p53 alterations have a significant prognostic role in NSCLC whereas others suggesting the absence of such a role, as revised by Mitsudomi et al. (2000). Several authors have published extensive reviews on this issue (Brambilla and Bramcilla, 1997; Komiya et al., 1999). Moreover, respective literature contains three meta-analyses dealing with the same issue, published almost simultaneously.

Mitsudomi et al. (2000) performed a systematic review on the prognostic role of p53 status in NSCLC, assessed either by immunohistochemistry or molecular studies. The incidence of p53 alteration in molecular studies was 37% and was found to be lower than the one observed in protein studies (48%) (Mitsudomi et al., 2000). Inclusion criteria are described in detail and there is an extensive discussion of the studies excluded from the present meta-analysis. Combined 3 and 5 year survival differences were -11.45 (p=0.0021) and -9.1% (p=0.00-91) for immunohistochemical studies and -10.7% (p=0.0001) and -22% (p=0.0026) for molecular studies. It seems that the effect of p53 alterations detected as p53 mutation was stronger than those detected as p53 protein overexpression. Subgroup analysis for histological types was also performed showing that the results in adeno-carcinomas were significant whereas in squamous cell carcinomas they failed to attain statistical significance. The authors (Mitsudomi et al., 2000) attribute these results to the fact that studies with adeno-carcinomas were more homogenous than those with squamous cell carcinomas. In this regard, tests for heterogeneity were significant in both DNA and protein studies, a result that hampers the validity of the results of this analysis and raises the question for potential sources of variability.

At the same time, Huncharek and colleagues (Huncharek et al., 2000) performed a meta-analysis on the prognostic significance of p53 mutations in NSCLC. The authors describe in detail the reasons for excluding 2 studies from their analysis, especially referring to one using both IHC and molecular techniques for the assessment of p53 status (Mitsudomi et al., 1993). The observed incidence of p53 mutations (36%) was comparable to the one reported in the meta-analysis of Mitsudomi et al. (2000). In agreement with the previous combined analysis the authors found substantial between-studies heterogeneity, whereas qualitative analysis showed a relative risk of 1.52 with 95% CI of 1.07 to 2.16 (favouring a negative prognostic role for p53 mutations). Moreover, trying to reveal possible causes for heterogeneity a sensitivity analysis was performed by dropping 2 studies dealing with adenocarcinomas from the meta-analysis. However, the exclusion of these studies did not largely affect the observed variability. Despite these results, the authors did not perform subgroup analysis.

Almost one year later, Steels et al. (2001) performed a similar meta-analysis on NSCLC, recruiting all studies that investigated the prognostic role of p53 status assessed either by IHC or by molecular methods. In this analysis the eligible studies were evaluated according to the European Lung Cancer Working Party (Steels et al., 2001). Fifty-six identified studies provided sufficient data from univariate survival analysis allowing survival results aggregation. Because of the important heterogeneity of the cohorts of the 56 selected trials only subgroup analysis was performed. In particular, the studies were categorized according to histology, disease stage, treatment and laboratory technique. In all the examined subgroups combined hazard ratios suggested that an abnormal p53 status has an unfavourable effect on survival. However, even by doing this stratification the issue of heterogeneity could not be addressed completely, since in two of the ten subgroups there remained

significant between-study heterogeneity (those performed for stage III-IV and those for surgical resected tumours).

It is to be noted that none of these three meta-analyses used adjusted hazard ratios extracted from multivariate survival models for the prognostic role of p53 status in NSCLC, whereas none of these analyses mentions the smoking behaviour of the enrolled patients, although smoking behaviour is a definite factor correlated with NSCLC prognosis. Despite these possible limitations, it should be noted in that all these three meta-analyses deregulated p53 status is correlated with patients' adverse survival.

DISCUSSION

Although, there are several meta-analyses and original articles investigating the prognostic role of p53 alterations in several human cancers, contemporary literature is lacking any summary and comparison of these individual attempts. This fact prompted as to perform a systematic review of the published meta-analysis, summarizing and comparing the existing data on this issue. This review has largely confirmed what is already well known among pathologists, the studies on prognostic markers, particularly, but not exclusively those regarding immunohistochemical assays, often give rise to contradictory or inconsistent results. Moreover, all meta-analyses performed on the prognostic role of p53 status, assessed either by IHC or by mutational analysis, included a small number of investigations, mostly due to the small number of articles that fulfilled the eligibility criteria. More published studies did not report important factors regarding the methodology, the evaluation or the statistical analysis performed, a fact that limited their quality and excluded them from combined analysis. Therefore, the results of each published meta-analysis should be interpreted with caution since not all sources of bias seem to have been ruled out. Importantly, most of the attempts to quantitatively synthesize data did not include adjustment for previously validated clinical and pathological prognosticators, such as histologic grade and stage in each case, possibly due to the fact that each study included in meta-analysis did not report the co-variates included in the multivariate model or had not performed multivariate survival analysis. Additionally, in many meta-analyses the authors included in the same analysis studies dealing with the immunohistochemical assessment of p53 protein expression and those focusing on the mutational status of p53 gene (Pakos et al. 2004; de Graff et al., 2009; Steels et al., 2001), plausibly in an attempt to increase the sample size of studies including in meta-analysis, yet hampering the heterogeneity observed in the performed quantitative synthesis. In addition, a possible drawback of these analyses is that in none of the ethnicity of the patients included in each study is mentioned, a factor that has been suggested to influence disease progression especially in breast carcinoma (Bowen et al., 2006).

It could be argued that more than a decade of research on the prognostic implications of p53 has not improved our ability to draw conclusions relevant to the clinical course of patients. This issue has become urgent as oncology is entering the dawn of personalized medicine with targeted treatments, for example, in gastrointestinal stromal tumours where transcriptomic data permit treatment quantification (McShane et al., 2005; Ochs et al., 2009). A few years ago, the statistics subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics has published the reporting recommendations on tumour marker prognostic studies (REMARK) guidelines (McShane et al., 2005). These guidelines could possibly reduce the variation in the study design factors that may contribute in the inconsistencies and contradictions in the results they are reporting. In the same context, there are several suggestions in the evaluation and publication of immunohistochemical prognostic markers, in order to avoid publication biases and caveats regarding the limited data reported in each publication (Zhu et al., 2006). Based on these guidelines, meta-analyses on markers for which more than 10 studies could be eligible for inclusion can provide important insights on whether these markers are worthy of further investigation.

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